July 2015

CCHCS Care Guide: Anticoagulation

SUMMARY | **DECISION SUPPORT** | **PATIENT EDUCATION / SELF MANAGEMENT**

GOALS

- ✓ Monitor INR in every warfarin patient at least monthly
- ✓ Designate a sole provider responsible to adjust warfarin for each patient
- ✓ Achieve therapeutic INR within 30 days of warfarin initiation
- ✓ Identify a single target INR value as goal (e.g., target INR 2.5)

ALERTS

- High risk of serious bleeding
- INR outside desired range
- Significant drug-drug interactions
- Extremity pain or swelling
- Altered level of consciousness
- Skin Necrosis / Purple Toe Syndrome
- Acute Rash, Hepatitis, Diarrhea / Nausea
- Pregnancy

DIAGNOSTIC CRITERIA / EVALUATION

IDENTIFY THROMBOTIC CONDITION OR RISK	VENOUS THROMBOEMBOLISM (VTE) (e.g., DVT or PE)	ARTERIAL THROMBOEMBOLISM (ATE) (e.g., cerebral infarction, MI, Peripheral arterial occlusive disease, Threatened ischemia [GI, GU, limb])
DETERMINE THROMBOTIC RISK (SEE PAGES 3-4)	High thrombosis risk = active thrombotic process (e.g., DVT or PE) Lower thrombosis risk = e.g., atrial fibrillation without recurrent thromboembolism	
EVALUATION	H&P, identify events associated with thrombotic event: (e.g., recent surgery, bleeding, pregnancy, immobility, trauma, mechanical heart valve)	
DIAGNOSTIC STUDIES	Lab: CBC including platelets, PT/INR, PTT, chemistry panel, UA	

TREATMENT OPTIONS

HIGH THROMBOSIS RISK	COMBINATION ANTICOAGULANT THERAPY: WARFARIN AND LMWH Start both, administer simultaneously for at least 5 days and until INR > 2. See page 3-4 for conditions requiring combination therapy, page 7 for dosing recommendations.
LOWER THROMBOSIS RISK	CONSIDER WARFARIN ALONE. See warfarin alone indications pages 3-4, dosing recommendations page 7.

MONITORING

WARFARIN

- Baseline: CBC with platelets, creatinine, PT/INR ,PTT, albumin and liver enzymes (ALT, AST).
- After 2 days of warfarin therapy, repeat INR on day 3. If > 2.0 after the first 2 doses, consider decreasing the dose by half. (Measure INR 16 hours after warfarin dose.)
- Adjust dose as indicated and order subsequent INR tests based on initial response.
- When desired level reached, test INR weekly for 1-2 weeks.
- At goal INR, test INR every 4 weeks.
  - ✓ If INR < ± 0.5 out-of-range: repeat INR within 7-14 days.
  - ✓ If INR more than 0.5 out of range, see dosing adjustment recommendations on page 5.
  - ✓ If INR unexpectedly out of range, consider ASAP repeat of test and review handling of specimens/lab procedures.

Consider causes of rapid INR rise such as:

- · Drug interactions
- · Poor nutritional status
- · Infection
- · Systemic disease process

ENOXAPARIN (LMWH)

- Baseline: CBC with platelets, creatinine, PT/INR, PTT
- Ongoing monitoring:
  - ✓ Not routinely indicated.
  - ✓ Consider platelet monitoring in patients at risk for heparin induced thrombocytopenia (HIT).
  - ✓ Heparin anti-Xa level monitoring not routinely required (sometimes used in patients w/ obesity and/or renal insufficiency and in pregnant women receiving therapeutic doses).

TABLE OF CONTENTS

CCHCS Care Guide: Anticoagulation

EVALUATION AND MANAGEMENT OF ANTICOAGULATION CANDIDATE

EVALUATION

- ✓ Establish the diagnosis of thrombotic disorder
- ✓ Perform history and physical examination
- ✓ Look for acquired causes of hypercoagulability:
  - Malignancy (lung, colon, ovary, prostate)
  - Surgery, especially orthopedic
  - Hormone replacement therapy
  - Antiphospholipid antibody syndrome
  - Congestive heart failure
  - Myeloproliferative disorders
  - Inflammatory bowel disease
  - Oral contraceptives
  - Trauma
  - Pregnancy
  - Immobilization
  - Nephrotic syndrome
- ✓ Initial laboratory studies: CBC with platelets, PT/INR, PTT, chemistry panel
- ✓Consider inherited cause of hypercoagulability based on clinical suspicion and patient's thrombophilic status:
  - WEAKLY thrombophilic: First episode of idiopathic venous thromboembolism (VTE) ≥ age 50 and no family history VTE
  - STRONGLY thrombophilic:
    - First idiopathic venous thrombosis prior to age 50, or
    - Recurrent thrombotic episodes, or
    - First degree relative with thromboembolism prior to age 50
  - Work-up for inherited causes of hypercoagulability includes:

LABS TO ORDER	WEAKLY THROMBO-PHILIC	STRONGLY THROMBO-PHILIC	COMMENTS
Factor V Leiden	YES	YES	Factor V Leiden is the most common clotting factor mutation in the US, most frequent in Caucasians.
Prothrombin mutation	YES	YES	Prothrombin mutation most common after Factor V Leiden.
Antiphospholipid Antibodies	YES	YES	Antiphospholipid antibodies may be present temporarily or permanently May be measured during thrombotic event.
Antithrombin	NO	YES	Antithrombin function and quantity are measured to determine deficiency. The test should not be performed in presence of thrombosis or during treatment for thrombosis.
Protein C / Protein S	NO	YES	Protein C and Protein S should not be measured while patient is on warfarin or within 10 days of thrombotic event.

TREATMENT

VENOUS THROMBOSIS

Identify contraindications for anticoagulation:
- Active/ severe bleeding
- Platelets <20,000
- Neurosurgery, ocular surgery, or intracranial bleed within the past 10 days
- Pregnancy (absolute contraindication for warfarin)

Contraindications present

Consider referral to interventional radiology for vena cava filter

Contraindications not present

Initiate treatment ASAP with heparin or LMWH, and warfarin

ARTERIAL THROMBOSIS

- Generally managed in acute care setting
- Embolectomy, thrombolytics, and/or surgical treatment
- Heparin/LMWH initially with warfarin for long term anticoagulation

CCHCS Care Guide: Anticoagulation

THROMBOTIC RISK OR CONDITION	RECOMMENDED ANTICOAGULATION/DURATION	INR GOAL (range)
ATRIAL FIBRILLATION (AF) - CHRONIC AND PAROXYSMAL *evaluate for the risk-benefit ratio of long-term therapy including if anticoagulant monitoring is possible*		
Patients with: • History of prior ischemic stroke, transient ischemic attack, or systemic embolism. • One or more of the following risk factors for ischemic stroke: – Age > 75 years, history of HTN or DM – Moderately or severely impaired left ventricular function or CHF – Valvular heart disease such as mitral stenosis	Warfarin - lifetime	INR 2.5 (2.0 to 3.0)
Patients without the associated conditions or risk factors noted above.	Initiation of lifetime anticoagulation is controversial. Consultation recommended, see references below[1-3].	
Before cardioversion for Atrial Fibrillation lasting > 48 hours:	Warfarin-3 weeks before cardioversion and 4 weeks after (if successful and no other indication for ongoing anticoagulation)	INR 2.5 (2.0 to 3.0)
DEEP VENOUS THROMBOSIS (DVT)		
DVT prophylaxis	Short term use of heparin or LMWH indicated along with mechanical methods of DVT prevention. Warfarin indicated only for long term use in patients with known VTE risk factors.	
DVT treatment (see below):		
PROVOKED (reversible risk factor) UNPROVOKED and DISTAL and first DVT	Warfarin - 3 months	INR 2.5 (2.0 to 3.0)
UNPROVOKED and DISTAL and recurrent DVT UNPROVOKED and PROXIMAL	Warfarin - Consider lifetime	INR 2.5 (2.0 to 3.0)
CANCER patient	Warfarin or LMWH - Indefinitely or until cancer is resolved	INR 2.5 (2.0 to 3.0)
PULMONARY EMBOLISM (PE)		
PROVOKED (reversible risk factor)	Warfarin or LMWH for at least 3 months	INR 2.5 (2.0 to 3.0)
UNPROVOKED: First PE:	Warfarin or LMWH for at least 3 months Recommend lifetime treatment	INR 2.5 (2.0 to 3.0)
UNPROVOKED: Recurrent PE	Warfarin - lifetime	INR 2.5 (2.0 to 3.0)
CANCER patient	LMWH for 3-6 months, then warfarin or LMWH indefinitely or until cancer is resolved*	INR 2.5 (2.0 to 3.0)
ACUTE MYOCARDIAL INFARCTION (MI)		
High risk: large anterior MI, significant CHF, intracardiac thrombus	Warfarin - 3 months	INR 2.5 (2.0 to 3.0)
LEFT VENTRICULAR DYSFUNCTION		
Ejection fraction < 30%	Warfarin - lifetime	INR 2.5 (2.0 to 3.0)

[1]Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182,678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J 2012; 33:1500.
[2]Antithrombotic and Thrombolytic Therapy – 9th ed.: American College of Chest Physicians (ACCP) Guidelines. Feb, 2012.
[3]Manning, Warren J., MD, Singer, Daniel E., MD, Lip, Gregory YH, MD, FRCPE, FESC, FACC, "Atrial fibrillation: Anticoagulant therapy to prevent embolization" -UpToDate. 1/20/2015.

*specialist input recommended

CCHCS Care Guide: Anticoagulation

THROMBOTIC RISK OR CONDITION	RECOMMENDED ANTICOAGULATION AND DURATION	INR GOAL (range)
VALVULAR HEART DISEASE		
Rheumatic mitral valve disease:		
Alone or with AF History of systemic embolism, Left atrial thrombus Normal sinus rhythm with left atrial diameter > 55 mm	Warfarin - lifetime	INR 2.5 (2.0 to 3.0)
Rheumatic mitral valve disease at target INR (2.5) with AF who develops systemic embolism or left atrial thrombus	Warfarin and low dose aspirin (50-100 mg daily) - both lifetime OR	INR 2.5 (2.0 to 3.0)
	Warfarin alone - lifetime. Increased INR goal	**INR 3.0 (2.5 to 3.5)**
(BIOPROSTHETIC) TISSUE HEART VALVES		
Mitral valve, sinus rhythm, no other risk factors:	LMWH until therapeutic on warfarin— Warfarin 3 months post-op then ASA 75-100 mg daily	INR 2.5 (2.0 to 3.0)
Aortic valve, sinus rhythm, no other risk factors:	ASA 50-100 mg daily for 3 months is superior to vitamin K Analog (VKA), Add clopidogrel (75 mg) in patients with *transcatheter* aortic valve replacement.	N/A
Mitral or Aortic valve AND additional risk factors: AF, hypercoagulable state, low ejection fraction (EF)	LMWH until therapeutic on warfarin Warfarin - lifetime	INR 2.5 (2.0 to 3.0)
MECHANICAL PROSTHETIC VALVES		
Aortic mechanical valve sinus rhythm and no other risk factors	LMWH until therapeutic on warfarin Warfarin - lifetime	INR 2.5 (2.0 to 3.0)
There is no evidence that higher INR for mechanical AVR results in fewer thrombotic events.		
Mitral mechanical valve with or without aortic mechanical valves	LMWH until therapeutic on warfarin Warfarin - lifetime	**INR 3.0 (2.5 to 3.5)**
In patients with mechanical valves at low risk of bleeding (caution if history of GI bleeding)	Consider adding antiplatelet agent such as low dose aspirin (50-100 mg daily) in addition to the warfarin	**INR 3.0 (2.5 to 3.5)**

Antithrombotic and Thrombolytic Therapy – 9th ed.: American College of Chest Physicians (ACCP) Guidelines. Feb, 2012.

CCHCS Care Guide: Anticoagulation

Consider medical hold for any patient with INR above 4.0

WARFARIN DOSE ADJUSTMENT

USE ONLY FOR PATIENTS ALREADY TAKING WARFARIN. DO NOT USE FOR INITIATION OR DURING FIRST ONE TO TWO WEEKS OF WARFARIN THERAPY.
THERE IS NO UNIFORMLY ACCEPTED PROTOCOL FOR WARFARIN DOSE ADJUSTMENT.

Goal INR 2.5 (Range 2.0–3.0)		Goal INR 3.0 (Range 2.5–3.5)	
If INR Result Is:	**Action**	**If INR Result Is:**	**Action**
≤1.5*	• Increase weekly dose by 15% • Repeat INR in 7 - 14 days	**≤1.5***	• Increase weekly dose by 20% • Repeat INR in 7 - 14 days
1.51–1.99*	• Continue same dose warfarin • Repeat INR within 7 - 14 days • If still 1.5-1.99, increase weekly dose by 10% and repeat INR in 7 - 14 days	**1.51–1.99***	• Increase weekly dose by 15% • Repeat INR in 7 - 14 days
2.00–3.00	• Continue same dose warfarin • Repeat INR in no later than 4 weeks	**2.00–2.49***	• Continue same dose warfarin • Repeat INR within 7 - 14 days • If INR still 2.0 - 2.49, increase weekly dose by 10% and repeat INR in 7 - 14 days
		2.50–3.50	• Continue same dose warfarin • Repeat INR in no later than 4 weeks

Goal INR 2.5 (Range 2.0–3.0) **OR** Goal INR 3.0 (Range 2.5–3.5)	
If INR Result is:	**Action**
Greater than goal INR, but < 4.5 (between 3.0-4.5 and no bleeding)	• Option 1: Decrease or hold dosage, increase frequency of monitoring, and resume at lower dosage once INR is within desired range • Option 2: May continue current dosage if INR is minimally elevated (0.5 or less above therapeutic range in a previously stable patient)
4.5–9 and no bleeding	• Consider possible cause (new medication, acute illness, etc.) • Hold next 1-2 warfarin doses • Increase frequency of INR monitoring (every 24 hours as long as INR ≥ 5) • Resume warfarin when INR is within therapeutic range; restart at a dosage that reflects a 10% decrease in the total weekly warfarin dose • Repeat INR in 7–14 days • Vitamin K is not recommended
>9 and no bleeding	• Consider possible cause (new medication, acute illness, etc.) • Hold warfarin • Administer vitamin K 2.5 - 5 mg orally** once • Increase frequency of INR monitoring (every 24 hours as long as INR ≥ 5) • If INR remains > 9, repeat vitamin K** 2.5 - 5 mg orally** once • Resume warfarin when INR reaches < 3.0; restart at a dosage that reflects a 15% decrease in the total weekly warfarin dose
Serious bleeding regardless of INR	• Hold warfarin and transfer to higher level of care • If elevated INR, hold warfarin, give vitamin K 2.5-5 mg orally**, and transfer to a higher level of care

INR: International Normalized Ratio.
*Clinical and professional judgment may allow variation in the application of the algorithm.
**Oral vitamin K administration is preferred in non-emergency situations.
Avoid subcutaneous or intramuscular administration of vitamin K.

Holbrook, A et al. Evidenced-Based Management of Anticoagulant Therapy. Chest 2012; 141(2) (Suppl):e152s-e184s, e326s-e350s.
Valentine, Karen A, MD, PhD, and Hull, Russell D, MBBS, MSc, "Correcting excess anticoagulation after warfarin" -UpToD ate. 11/10/2014.
Valentine, Karen A, MD, PhD, and Hull, Russell D, MBBS, MSc, "Outpatient management of anticoagulation with warfarin" - UpToDate. 10/16/2013.
Valentine, Karen A, MD, PhD, and Hull, Russell D, MBBS, MSc, "Therapeutic use of warfarin and other vitamin K antagonists" - UpToDate. 10/16/2013.

CCHCS Care Guide: Anticoagulation

PROCEDURES IN ANTICOAGULATED PATIENTS

RISK ASSESSMENT

Determine risk of bleeding during procedure if anticoagulation is not interrupted.
Determine the perioperative risk of thrombosis if anticoagulant therapy is interrupted.
Adjust anticoagulant therapy as indicated based on risk of bleeding and risk of thrombosis.

LOW BLEEDING RISK PROCEDURES THAT CAN BE PERFORMED WITHOUT DISCONTINUING OR CHANGING WARFARIN/ VITAMIN K ANALOG (VKA)			
DENTAL	Teeth cleaning Uncomplicated extractions Periodontal therapy	Endodontics Prosthetics Restorations	For most dental procedures no change in warfarin dosing is needed. It may be reasonable to allow the patient to "drift" to the low end of his/her therapeutic INR prior to a dental procedure with a higher risk of bleeding.
DERMATOLOGIC	Mohs surgery Simple excisions Skin biopsy		Continue VKAs around the time of the procedure and optimize local hemostasis
OPHTHALMIC	Cataract surgery Trabeculectomy		Continue VKAs around the time of the surgery
GASTROINTESTINAL	Diagnostic esophagogastroduodenoscopy (EGD) Colonoscopy without biopsy Endoscopic ultrasonography without biopsy Diagnostic endoscopic retrograde cholangiopancreatography (ERCP) Biliary stent without sphincterotomy Push enteroscopy		Continue VKAs around the time of the surgery

LOW BLEEDING RISK PROCEDURES FOR WHICH ANTICOAGULATION ADJUSTMENT IS RECOMMENDED	
Gynecologic	Reduce warfarin dose four to five days before surgery and the surgery performed at a lower INR (INR 1.3-1.5). The warfarin dose can be increased to the previous dose 12-24 hours postoperatively.
Orthopedic	Reduce warfarin dose four to five days before surgery and the surgery performed at a lower INR (INR 1.3-1.5). The warfarin dose can be increased to the previous dose 12-24 hours postoperatively.

ACCP'S* PERIOPERATIVE THROMBOEMBOLISM RISK STRATIFICATION (BRIDGING DECISION BASED ON THROMBOEMBOLIC RISK OF UNDERLYING CONDITION)		BRIDGING RECOMMENDATION
LOW THROMBOSIS RISK	< 4% / yr risk of Arterial Thromboembolism (ATE) or > 2% / mo risk of VTE •Bileaflet aortic valve without AF and no other risk factors for stroke •AF and CHADS** score of 0-2 (and no prior stroke or TIA) •Single VTE within past 3-12 mo and no other risk factors	Consider no bridging anticoagulation during VKA interruption
MODERATE THROMBOSIS RISK	4%-10% / yr risk of ATE or 4%-10% / mo risk of VTE •Bileaflet aortic valve and one of the following: AF, prior stroke/TIA, HTN, DM, CHF, age > 75 yr •AF and CHADS** score of 3 or 4 •VTE within past 3-12 mo •Recurrent VTE •Nonsevere thrombophilic conditions •Active cancer	Bridging or no bridging decision needs to be individualized based on the surgical risk of bleeding and patient risk factors.
HIGH THROMBOSIS RISK	10% / yr risk of ATE or >10% / mo risk of VTE •Any mechanical mitral valve •Older aortic valve •Mechanical heart valve and recent (< 6 mo) stroke or TIA •AF and CHADS** score of 5 or 6, recent (< 3 mo) stroke or TIA, or Rheumatic valvular heart disease •Recent (< 3 mo) VTE •Severe thrombophilia	Consider bridging anticoagulation with LMWH; stop VKA 5 days prior to surgery

*ACCP = American College of Chest Physicians; From Chest. Feb 2012; 141(2 Suppl): e326S–e350S.
**CHADS scoring system: one point for each factor: CHF, HTN, DM, age >75. Two points for prior stroke or TIA. Range 0-6 points

CCHCS Care Guide: Anticoagulation

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ANTICOAGULANTS

MEDICATION	DOSING	ADVERSE EFFECTS / INTERACTIONS*	COMMENTS
VITAMIN K ANTAGONIST (VKA) (ORAL)			
WARFARIN Coumadin® Jantoven, Marevan Lawarin, Waran **Formulary** Strengths: 1 mg-pink 2 mg-lavender 2.5 mg-green 3 mg- tan 4 mg-blue 5 mg-peach 6 mg-teal 7.5 mg-yellow 10 mg-white **$**	Initial daily dose is usually 5 mg orally every evening. **Avoid loading doses** Consider lower starting dose: 2.5 mg every evening if: • Age > 75 yrs • Multiple comorbidities • Hypoalbuminemia • Elevated pretreatment INR • Elevated LFTs • Changing thyroid status • CHF • Debilitated • Malnourished • Recent major surgery Consider higher starting dose: 7.5 mg every evening for patients > 80 kg Patients restarting warfarin can usually start at their previous dose. If stopped due to bleeding, assess risk of thrombosis vs. risk of rebleeding Recheck INR on day 3 after first two doses, if INR > 2.0, consider reducing dose by 1/2 (evaluate for cause of rapid rise in INR) (See page 4) Steady-state INR will take up to 3 weeks Dose adjustments at steady state (See page 5) • Assess variables affecting the INR before changing dose (e.g., patient adherence, medication interactions, dietary changes) • 10% warfarin dose adjustment changes INR approximately 0.7-0.8	Bleeding Patients treated with usual doses of warfarin have a 2%-4% risk per year of bleeding episodes requiring transfusion, and a 0.2% risk per year of fatal hemorrhage. Skin necrosis: rare but serious complication typically occurs on the 3rd to 8th day of therapy; four times as common in women as in men. Purple toe syndrome (or other manifestations of peripheral emboli) may rarely complicate warfarin therapy, usually 3-10 weeks after initiation of therapy.	Contraindications: Absolute: • Pregnancy (teratogenic) • Active hemorrhage Risk of bleeding is highest in 1 month of therapy. GU bleeding in a patient on warfarin must be evaluated. A baseline INR value is helpful to rule out underlying coagulopathy. Note: do not cut pills • For unstable or variable INR, consider daily low dose of vitamin K (100-200 mcg daily)
INDIRECT THROMBIN INHIBITORS (PARENTERAL)			
ENOXAPARIN Lovenox® Nonformulary Concentration: 100 mg/mL 150 mg/mL **$$**	DVT treatment (acute): Inpatient treatment (with or without pulmonary embolism): 1 mg/kg/dose subQ every 12 hours or 1.5 mg/kg subQ once daily Outpatient treatment (without pulmonary embolism): 1 mg/kg/dose subQ every 12 hours** **Note: Start warfarin on 1st treatment day and continue enoxaparin until INR is between 2-3 (usually 5-7 days). DVT treatment (acute) in pregnant patients: 1 mg/kg/dose subQ every 12 hours throughout pregnancy DVT prophylaxis after knee or hip replacement surgery: 30 mg subQ every 12 hours, start within 12-24 hours after surgery • Duration of treatment: 10 days or until risk of DVT has diminished or the patient has therapeutic INR on warfarin DVT prophylaxis for acute illness: 40 mg subQ once daily (usually 6-11 days) DVT prophylaxis for abdominal surgery: 40 mg subQ once daily starting 2 hours prior to surgery (usually 7-10 days) Unstable angina and non-Q-wave MI: 1mg/kg subQ every 12 hours with ASA (100-325 mg once daily) for 2-8 days Acute STEMI (<75 yo): 30 mg IV bolus plus 1 mg/kg subQ followed by 1 mg/kg subQ every 12 hrs (with 75-325 mg ASA once daily) [Note: 1st two doses not to exceed 100 mg] Acute STEMI (≥75 yo): 0.75 mg/kg subQ every 12 hours (no bolus) with 75-325 mg ASA once daily [Note: 1st two doses not to exceed 75 mg] Geriatric: dose alteration may be required due to increased incidence of bleeding Renal Impairment: CrCl < 30 mL/min • DVT prophylaxis during acute illness, after abdominal or hip/knee replacement surgery: 30 mg subQ once daily • DVT treatment (during warfarin initiation) or acute STEMI (≥75 yo): 1 mg/kg subQ once daily • Acute STEMI (<75 yo): 30 mg IV bolus plus 1 mg/kg subQ then 1 mg/kg subQ once daily Do not administer IM; administer by subQ injection	Bleeding Heparin-induced thrombocytopenia (HIT) is a rare complication of heparin exposure due to an HIT antibody which activates platelets and can cause life-threatening arterial and venous thrombosis. HIT should be suspected in patients who: • Develop necrosis at the injection site • Have a systemic Reaction (fever, chills, dyspnea, etc.) to a bolus administration of heparin • Develop a greater than 50% decrease in platelet count from baseline labs while on heparin • Experience a new thrombotic event within 5 to 14 days of initiating heparin therapy, even if the heparin has been discontinued HIT can occur in patients getting ≥ 1 dose of unfractionated heparin (including heparin IV flushes) within the past 100 days	Contraindications: Absolute: • Active major bleeding, including intracerebral hemorrhage within past 2 weeks, subarachnoid hemorrhage until definitively treated • Thrombocytopenia, with positive antiplatelet test in presence of enoxaparin • Hypersensitivity to heparin or pork products Other contraindications: • Recent thrombolytic therapy • History Heparin-induced thrombocytopenia (HIT) Reversal of enoxaparin: No agent is effective for complete reversal in the event of supratherapeutic anticoagulation (inc. FFP, vitamin K, protamine) If life threatening bleeding, consider protamine:(Do not exceed 50 mg in 10 minutes) • First dose: 1 mg for each 1 mg enoxaparin; give by slow IV over 10 minutes • Second dose: 0.5 mg protamine for each 1 mg enoxaparin; give by slow IV infusion over 10 minutes

*See prescribing information for complete description of adverse effects and drug interactions.

MEDICATION	DOSING	ADVERSE EFFECTS / INTERACTIONS*	COMMENTS
DIRECT THROMBIN INHIBITORS AND DIRECT FACTOR Xa INHIBITORS ARE NEW ORAL ANTICOAGULANTS WHICH ARE NONFORMULARY AND NOT RECOMMENDED FOR USE IN CCHCS **Formulary warfarin is the preferred oral anticoagulant in nearly all patients.** **Patients who come to CCHCS on one of these direct acting agents should be converted to warfarin.** **Use of these agents may be considered only with a documented valid reason why warfarin cannot be used, such as:** • **Warfarin allergy** • **Specialist intervention required for IV access to monitor INR** • **Rarely on a case by case basis for other indications**			
Direct Thrombin Inhibitor			
DABIGATRAN PRADAXA® Nonformulary Strengths: 75 mg 150 mg **$$**	150 mg twice daily Renal Impairment: 75 mg twice daily • CrCl 30 to 50 mL/min and concurrent use of dronedarone (Multaq) or systemic ketoconazole: • CrCl 15 to 30 mL/min Severe renal impairment: avoid use • CrCl < 30 mL/min and concurrent use of a P-glycoprotein inhibitor: No data for patients on dialysis To change patient from dabigatran to warfarin: Based on CrCl start warfarin 3 days (> 50ml/min), 2 days (31-50 ml/min) or 1 day (15-30 ml/min) before discontinuation of dabigatran To change to dabigatran from warfarin: d/c warfarin and start dabigatran when INR < 2.0	Bleeding Dyspepsia Avoid concurrent use with P-glycoprotein inducers (e.g., rifampin). Evaluate P-glycoprotein inhibitors individually. Increased bleeding risk with certain medications (e.g., clopidogrel, nonsteroidal anti-inflammatory drugs)	Do not chew, break, or open capsules. Capsules must be dispensed in original container and not repackaged due to sensitivity to moisture. Indications: reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, management of VTE Half-Life: 12-17 hours Monitoring: none recommended Antidote: none available Contraindications: • Active pathological bleeding • Prosthetic heart valves (mechanical/ bioprosthetic) • Pregnancy or breastfeeding • CrCl < 15 mL/min
Direct Factor Xa Inhibitors			
APIXABAN ELIQUIS® Nonformulary Strengths: 5 mg 2.5 mg **$$**	5 mg twice daily for stroke prevention in A fib Treatment and secondary prevention of VTE: 10 mg twice daily for 10 days, then 5 mg twice daily 2.5 mg twice daily for VTE prophylaxis in surgical pts (35 days hip replacement, 12 days knee replacement) Consider 2.5 mg twice daily if patient has at least 2 of the following: • age ≥80 years • body weight of ≤ 132 lb (60 kg) • serum creatinine level of ≥ 1.5 mg/dL Dose reduction (2.5 mg twice daily) recommended if patient is on a strong dual inhibitor of CYP3A4 and P-glycoprotein (e.g., ketoconazole, itraconazole [Sporanox], ritonavir [Norvir], clarithromycin [Biaxin]). Avoid use of these medications if baseline dose is 2.5 mg twice daily Convert from apixaban to warfarin: D/C apixaban and begin warfarin plus parenteral anticoagulant at time of next apixaban dose. D/C parenteral anticoagulant when INR is therapeutic Convert to apixaban: D/C warfarin, start apixaban when INR <2.0	Bleeding Increased bleeding risk with certain medications (e.g., clopidogrel [Plavix], nonsteroidal anti-inflammatory drugs) Avoid concurrent use with strong dual inducers of CYP3A4 and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin)	Indications: reduce risk of stroke in patients with nonvalvular atrial fibrillation and prevention of VTE, management of VTE. Half-Life: 12 hours Monitoring: none recommended Antidote: none available Contraindications: • Active pathological bleeding • Prosthetic heart valves • Severe hepatic impairment • Pregnancy or breastfeeding No data on usage with renal or hepatic impairment
RIVAROXIBAN XARELTO® Nonformulary Strengths: 10 mg 15 mg 20 mg **$$**	Post surgical DVT prophylaxis: 10 mg once daily Duration: 12 days (knee replacement), 35 days (hip replacement) DVT prophylaxis following recurrent DVT or PE (after acute treatment): 20 mg once daily with food Treatment of acute DVT (not recommended in place of unfractionated heparin): 15 mg twice daily with food for 21 days then 20 mg once daily with food for a total of 6 months Prevent stroke in patients with nonvalvular atrial fibrillation: 20 mg once daily Renal Impairment: DVT prophylaxis: CrCl < 30 mL/min: avoid use Prevent stroke in patients with nonvalvular atrial fibrillation: CrCl 15-50 mL/min: 15 mg once daily Convert from rivaroxaban to warfarin: D/C rivaroxaban and begin warfarin plus parenteral anticoagulant at time of next rivaroxaban dose. D/C parenteral anticoagulant when INR is therapeutic. Convert from warfarin to rivaroxaban: D/C warfarin and start rivaroxaban when INR < 3.0	Bleeding Avoid with combined P-glycoprotein inhibitor and CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, ritonavir, conivaptan [Vaprisol])	Indications: FDA approved for the prevention of DVT and PE in patients undergoing knee or hip replacement surgery, treatment of DVT and PE and stroke prevention in nonvalvular atrial fibrillation. Half-Life: 5-9 hours Monitoring: none recommended Antidote: none available Contraindications: • Active pathological bleeding • Pregnancy or breastfeeding • Prosthetic heart valves • CrCl < 15 mL/min • Moderate-severe hepatic impairment

*See prescribing information for complete description of adverse effects and drug interactions.

CCHCS Care Guide: Anticoagulation

MEDICATION	DOSING	ADVERSE EFFECTS / INTERACTIONS*	COMMENTS
DIRECT THROMBIN INHIBITORS AND DIRECT FACTOR Xa INHIBITORS ARE NEW ORAL ANTICOAGULANTS WHICH ARE NONFORMULARY AND NOT RECOMMENDED FOR USE IN CCHCS **Formulary warfarin is the preferred oral anticoagulant in nearly all patients.** **Patients who come to CCHCS on one of these direct acting agents should be converted to warfarin.** **Use of these agents may be considered only with a documented valid reason why warfarin cannot be used, such as:** • **Warfarin allergy** • **Specialist intervention required for IV access to monitor INR** • **Rarely on a case by case basis for other indications**			
Direct Factor Xa Inhibitors			
EDOXABAN SAVAYSA® Nonformulary Tablet Strengths: 15 mg 30 mg 60 mg **$$**	Treatment of nonvalvular A-fib (dosing based on CrCl) CrCl > 95 mL/min: Use not recommended CrCl > 50-95 mL/min: 60 mg orally once daily CrCl 15-50 mL/min: 30 mg orally once daily CrCl < 15 mL/min: Use not recommended Treatment of DVT and PE: 60 mg orally once daily following 5-10 days of initial therapy with parenteral anticoagulant Dose reduction to 30 mg once daily recommended if: • CrCl 15-50 mL/min; or • body weight ≤ 60 kg; or • concomitant use of P-gp inhibitors (e.g., verapamil, quinidine, azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole) CrCl < 15 mL/min: Use not recommended Moderate or severe hepatic impairment: use not recommended Switching from edoxaban to warfarin: D/C edoxaban and administer parenteral anticoagulant and warfarin at same time of next scheduled edoxaban dose. D/C parenteral anticoagulant when INR ≥ 2.0 Switching from warfarin to edoxaban: D/C warfarin and start edoxaban when INR ≤ 2.5	Bleeding Anemia Increased bleeding risk with anticoagulants, antiplatelets, and thrombolytics. Avoid long term concomitant treatment with other anticoagulants. Avoid concurrent use with rifampin.	**Warning**: Not recommended for use in nonvalvular A-fib patients with CrCl > 95 mL/min due to reduced efficacy Indications: reduction in risk of stroke and systemic embolism in nonvalvular A-fib; treatment of DVT and PE Half-life: 10-14 hours Monitoring: none recommended Antidote: none available Contraindications: • Active pathological bleeding • Mechanical heart valves • Moderate to severe mitral stenosis

*See prescribing information for complete description of adverse effects and drug interactions.

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UNFRACTIONATED HEPARIN (UFH) Hep-Lock HepFlush-10 Nonformulary **$**	Thromboprophylaxis: Generally 5,000 IU subQ every 8-12 hours Therapeutic: Not covered in this Care Guide	**Bleeding** Risk of HIT 0.1%-1.0%	Rapid Onset of action Contraindications: severe thrombocytopenia, uncontrolled active bleeding, porcine protein hypersensitivity
VITAMIN K Strengths: Mephyton 5 mg (scored) 100 mcg tablet AquaMephyton Injectable 1 mg/0.5ml 10 mg/ml Nonformulary **$**	Supratherapeutic INR (anticoagulant induced) Outpatient setting: 2.5-5 mg orally single dose then re-evaluate before repeat administration Hospital setting (patient NPO): IV vitamin K should be given over 30 minutes in a mixture of D5W 50 mL under monitored conditions Avoid subQ or IM injections due to unpredictable absorption, which can lead to erratic correction of INR and resistance to warfarin	Most people do not experience any side effects taking small doses of vitamin K Serious allergic reactions to vitamin K are rare (patient should report any rash, itching, dizziness or breathing problem)	Severe hypersensitivity reactions, including anaphylactoid reactions and deaths have been reported following parenteral administration. The majority of these reported events occurred following intravenous administration.

Adapted from: Venous Thromboembolism Prophylaxis (Guideline)" - American College of Chest Physicians Guidelines-Anticoagulation. Feb 1, 2012.
UpToDate – "Correcting excess anticoagulation after warfarin" - Karen A Valentine, MD, PhD, Russell D Hull, MBBS, MSc UpToDate. 11/10/2014

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FACTORS AFFECTING WARFARIN, INR, OR BLEEDING RISK

Endogenous Factors that may DECREASE INR	Endogenous Factors that may INCREASE INR	
Edema	Blood dyscrasias	Hepatic disorders (infectious hepatitis, jaundice)
Hereditary factors	Cancer	Hyperthyroidism
Hyperlipidemia	Collagen vascular disease	Poor nutritional state
Hypothyroidism	Congestive heart failure	Steatorrhea
Nephrotic syndrome	Diarrhea	Vitamin K deficiency
	Elevated temperature	Hereditary factors: CYP2CP and/or VKORC1 genotype

FACTORS WHICH MAY INCREASE RISK OF BLEEDING ON ANTICOAGULANTS	
Altered vitamin K synthesis in GI tract (antibiotics)	INR > 3.0
Increased age	Pretreatment INR > 1.2
Female sex	Presence of bleeding lesion or injury (GI, PUD, etc.)
DM	Bleeding disorder (coagulation, platelets)
Malignancy	Instability of INR control
Hypertension	Poor drug or clinic adherence
Acute or chronic alcohol use	Concomitant use aspirin, NSAID, clopidrogel, antibiotics, amiodarone, statins, floxacins
Liver disease	
Severe chronic kidney disease / elevated creatinine	

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MEDICATION INTERACTIONS WITH WARFARIN*:

MEDICATION	EFFECT ON INR	ANTICIPATED ONSET	SUGGESTED MANAGEMENT: MONITOR INR CLOSELY WHEN STARTING, STOPPING OR ADJUSTING THESE MEDICATIONS
Antiinfectives			
Ciprofloxacin (CIPRO®)	↑ INR (Moderate)	2-5 days	Increase in INR in most patients, but sometimes no effect; consider reducing warfarin dose by 10-15%
Clarithromycin (BIAXIN®)	↑ INR (Moderate)	3-7 days	Consider reducing warfarin dose by 15-25%
Erythromycin	↑ INR (Moderate)	3-5 days	Consider reducing warfarin dose by 10-15%
Fluconazole (DIFLUCAN®)	↑ INR (Moderate)	2-3 days	Effect more pronounced with impaired renal function; consider 25-30% warfarin dose reduction, with eventual reductions up to 80%
Isoniazid	↑ INR (Moderate)	3-5 days	Consider reducing dose of warfarin by 10-15% initially, monitor INR at least weekly
Itraconazole (SPORANOX®)	↑ INR (Moderate)	2-5 days	Consider reducing warfarin dose by 25-30%
Levofloxacin (LEVAQUIN®)	↑ INR (Moderate)	3-5 days	INR will also be affected by severity of illness; variable effect on INR, consider reducing warfarin dose by 0-15%
Metronidazole (FLAGYL®)	↑ INR (Major)	3-5 days	Avoid use if possible. If used concurrently, consider reducing warfarin dose by 25-40%
Rifampin (RIFADIN®)	↓ INR (Moderate to severe)	1-3 weeks	Avoid use if possible. If used concurrently, consider increasing warfarin dose 25-50% initially (at least weekly INRs). Patients may require 2-3 times their regular weekly warfarin dose when rifampin added.
Sulfamethoxazole Trimethoprim (BACTRIM®)	↑ INR (Severe)	2-5 days	Avoid use if possible. If used concurrently, consider reducing warfarin dose by 25-40%
Tetracyclines	↑ INR (Moderate)	2-5 days	Monitor INR when therapy with any tetracycline is started or stopped
Anticonvulsants			
Carbamazepine (TEGRETOL®)	↓ INR (Moderate to severe)	10-35 days	Increase in warfarin dose of 50-100% may be required initially; decrease warfarin dose by 50% when stopping carbamazepine.
Phenobarbital	↓ INR (Moderate)	Delayed	Warfarin dose increase of 30-60% may be required after barbiturate initiation.
Phenytoin (DILANTIN®)	Initially, ↑ bleeding risk; ↓ INR with long term use (Moderate)	Initial:1-3 d Subsequent: 2-4 wk	No dose adjustment when phenytoin is initiated, but INR should be monitored at least weekly during initiation; some patients may require warfarin dose increase of up to 50% several weeks after phenytoin initiated; warfarin also affects phenytoin concentrations.
Analgesics and Antipyretics			
Acetaminophen (>2 g/d)	↑ INR (Moderate)	2-5 days	Minimize use of APAP [e.g., <2 g/d for short courses (<1 week)]
Aspirin	↑ bleeding risk	1-3 days	No effect on INR at doses <6 g/d. Use lowest effective dose; use enteric-coated tabs; monitor for bleeding
NSAIDs (Ibuprofen, Naproxen)	↑ bleeding risk	2-5 days	No effect on INR. Monitor for bleeding (especially GI); minimize or avoid concurrent use with warfarin; take with food
Cardiovascular Agents			
Amiodarone (CORDARONE®)	↑ INR (Moderate to severe)	3-7 days	If loading doses of amiodarone are used, interaction will occur sooner; consider reducing warfarin dose by 10-25% one week after starting amiodarone, in anticipation of eventual dose reductions up to 60%
Gemfibrozil (LOPID®)	↑ INR (Moderate)	5-7 days	Consider reducing warfarin dose by 10-30%
Simvastatin (ZOCOR®)	↑ INR (Mild to moderate)	3-7 days	Interaction may range from negligible to clinically significant; consider using atorvastatin or pravastatin
Gastrointestinal Agents			
Omeprazole (PRILOSEC®)	↑ INR (Mild to moderate)	3-5 days	Interaction of doubtful clinical significance; minimal effect on INR; no empiric warfarin dose adjustment required
Thyroid Agents			
Levothyroxine (LEVOXYL®)	↑ INR (Moderate)	1-2 weeks	Monitor INR closely (every 1-2 weeks) when starting or adjusting levothyroxine; adjust warfarin gradually according to INR results

Adapted from Bungard et al. Drug interactions involving warfarin: practice tool and practical management tips. CPJ/RPC 2011;144:21-34.

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CCHCS Care Guide: Anticoagulation

WARFARIN (COUMADIN): WHAT YOU SHOULD KNOW

Q: What is warfarin and why do I need it?

Warfarin is a medicine that helps your blood not clot as fast. Sometimes this drug is called a blood thinner. Warfarin is prescribed to prevent serious blood clots from forming in your body, which can cause a stroke or other life-threatening events.

Q: How long do I have to be on warfarin?

It depends on why you take warfarin and what other health problems you have.

Some people take warfarin for only a few months, but many people take it for the rest of their life.

Q: How should I take warfarin?

Always follow your doctor's or nurse's instructions and take the pills exactly as prescribed.

- Go to the pill line every day to get your warfarin pill. Rarely warfarin is given as a "carry med".
- Take your warfarin at about the same time every day, usually in the evening.
- Never take extra pills or skip a day. If you forget your pills one day, write it down and tell a doctor or nurse.
- Never stop taking warfarin unless your doctor tells you to stop. If you have any trouble with taking warfarin or getting refills, send an Urgent CDC 7362 request to the triage nurse.

Q: What tests will I need if I take warfarin?

A simple blood test called "INR" needs to be done regularly when taking warfarin**.** Your doctor will adjust your dose to get to a certain "INR". When you first start warfarin, you may need your blood checked often. Once your dose is adjusted, you only need blood tests about once a month.

Q: What do I need to know about using other medication when I am taking warfarin?

- When warfarin is taken with other medicines, it can change the way other medicines work, and other medicines can change the way warfarin works.
- Tell your doctor or nurse if you are taking other medications, including over-the-counter medicines. Some common medications also raise the risk of bleeding, like aspirin or Motrin®-like medications (Naprosyn®, Advil®, Aleve®). Some "cough and cold medicines" and Pepto-Bismol may have aspirin.

Q: What are the side effects of warfarin?

Side effects with warfarin are uncommon but can include bleeding or bruising. A little bleeding that stops after a few minutes is okay, such as bleeding gums when brushing your teeth or a small nosebleed.

Tell your doctor or nurse right away if you have more serious bleeding, such as:

- Red, dark, coffee or cola–colored urine
- Stools that are black, bloody, or look like tar
- Bad nosebleeds, bleeding gums, or coughing up blood
- Throwing up coffee-colored or bright red vomit
- New bruises that come for no reason
- A cut that will not stop bleeding within 10 minutes
- Stomach, back or side pain that won't go away
- New or bad headache, problems with vision or speech, numbness or weakness, or confusion
- Too much menstrual bleeding

Q: What else should I know?

- Because of the risk of bleeding, don't do sports or other activities that could cause you to get hurt.
- Do not drink alcohol (Pruno), which can cause serious side effects with warfarin.
- **Do not change your diet too much while you are taking warfarin**. Green vegetables like spinach, lettuce, broccoli, cabbage and frozen peas have a lot of vitamin K and change the way warfarin works. Try to keep the amount of vitamin K foods you eat the same every day.
- Know your dose and the color of your pills. The color of warfarin/Coumadin®/Jantoven® pills tells you how strong the pill is. CDCR uses 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg pills.

pink *light purple* *green* *tan* *blue* *orange* *blue-green* *yellow* *white*

Guía de Cuidados CCHCS: Anticoagulación

RESUMEN	AYUDA PARA LA TOMA DE DECISIONES	EDUCACIÓN PARA EL PACIENTE/CONTROL PERSONAL DEL CASO

LA WARFARINA (COUMADIN): LO QUE USTED DEBE SABER

P: ¿Qué es la warfarina y por qué la necesito?

La warfarina es un medicamento que ayuda a que su sangre no coagule tan rápido. En ocasiones, a esta sustancia también se le llama diluyente de la sangre. La warfarina es recetada para prevenir la formación de coágulos graves en el organismo, los cuales podrían causar un infarto u otro evento peligroso para la vida.

P: ¿Durante cuánto tiempo debo tomar la warfarina?

Depende de la razón por la cual Ud. esté tomando la warfarina y de qué otros problemas de salud sufra.

Algunas personas toman la warfarina durante unos cuantos meses nada más, pero muchas personas la toman por el resto de sus vidas.

P: ¿Cómo debo tomar la warfarina?

Siga siempre las instrucciones de su médico o su enfermera y tome las pastillas exactamente como fueron recetadas.

- Tiene que ir a la línea de medicamentos todos los días para obtener su pastilla de warfarina. La warfarina casi nunca es recetada como un medicamento que Ud. mantiene en su poder.
- Tome su warfarina a la misma hora todos los días, generalmente en la tarde.
- Nunca tome pastillas extra ni deje pasar un día sin tomar su warfarina. Si se le olvida tomar su pastilla un día, apúntelo y luego informe a su médico o enfermera.
- Nunca deje de tomar su warfarina a menos que su médico se lo haya indicado. Si tiene algún problema para tomar la warfarina o para resurtir su receta, envíe una solicitud 7362 de Emergencia a la enfermera de turno.

P: ¿Qué exámenes médicos necesitaré hacerme si tomo la warfarina?

Cuando esté tomando la warfarina, deberá realizarse periódicamente un examen de sangre sencillo llamado "INR". Su médico ajustará su dosis dependiendo del "INR". Cuando comience a tomar la warfarina, es posible que necesite un análisis de sangre de forma periódica. Una vez que le hayan ajustado la dosis, solo necesitará un análisis de sangre una vez por mes.

P: ¿Qué necesito saber sobre el uso de otros medicamentos cuando estoy tomando la warfarina?

- Cuando se toma la warfarina junto con otros medicamentos podría cambiar la manera en la que otros medicamentos funcionan, y otros medicamentos podrían cambiar la manera en la que funciona la warfarina.
- Informe a su médico o enfermera si Ud. está tomando otros medicamentos, incluyendo aquellos que no son recetados. Algunos medicamentos comunes pueden aumentar el riesgo de hemorragia, como las aspirinas o medicamentos como Motrin®(Naprosyn®, Advil®, Aleve®). Algunos medicamentos para combatir los resfriados y la tos, y el Pepto-Bismol podrían contener aspirina.

P: ¿Cuáles son los efectos secundarios de la warfarina?

Los efectos secundarios producidos por la warfarina son poco comunes, pero pueden incluir hemorragias o hematomas. Sangrar un poco durante algunos minutos se considera dentro de los parámetros normales, por ejemplo, sangrar por las encías después de cepillarse los dientes o pequeñas hemorragias nasales. **Avísele inmediatamente a su médico si presenta sangrados más graves, tales como:**

- Orina roja, oscura o de color café o cola
- Deposiciones negras, sanguinolentas o que parezcan alquitrán
- Hemorragias nasales graves, encías sangrantes o toser sangre
- Vomitar color café o rojo vivo
- Hematomas repentinos sin razón alguna
- Una cortada cuya hemorragia no cesa antes de 10 minutos
- Dolor constante de estómago, espalda, o costado
- Dolor de cabeza repentina o muy fuerte, problemas de visión, aturdimiento o debilidad, o confusión
- Sangrado menstrual excesivo

P: ¿Qué otra cosa debo saber?

- Dado el riesgo de sangrados, no practique deportes o actividades que podrían causarle alguna lesión.
- No beba sustancias alcohólicas (Pruno) que pudiesen causarle efectos adversos con la warfarina.
- **No le haga mayores modificaciones a su dieta mientras esté tomando la warfarina.** Los vegetales verdes como la espinaca, lechuga, brócoli, repollo y los guisantes congelados contienen altas cantidades de vitamina K que podrían modificar el funcionamiento de la warfarina. Procure que la cantidad de alimentos que consuma con vitamina K sea la misma todos los días.
- Es muy importante saber su dosis y el color de sus pastillas. El color de las pastillas de warfarina/coumadin®/ jantoven® le indica qué tan fuerte es su dosis. CDCR utiliza pastillas de 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, y 10 mg.

rosa *púrpura claro* *verde* *marrón claro* *azul* *naranja* *verde azulado* *amarillo* *blanco*