

# PRACTICE GUIDELINES FOR ANTICOAGULATION MANAGEMENT

3<sup>RD</sup> EDITION



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with contributions from the Division of Cardiology,  
the Thrombosis Research Group, Department of  
Dentistry and Department of Neurology**

These guidelines are based on the 2012 ACCP guidelines for antithrombotic therapy and incorporate the usual practice at the Jewish General Hospital.



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*A French version is available upon request. Une version française est disponible sur demande.*



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## Introduction

These guidelines were developed to serve as a tool for physicians and other healthcare professionals to help with the management of anticoagulation. They should in no way be used to replace clinical judgment. We are not responsible for any adverse medical outcomes as such responsibility lies with the treating physician. The Hematology or Thrombosis consult services can always be consulted for specific patients with more complex needs. Pharmacy can be consulted as well for help with dosing and monitoring of anticoagulant medications.

## Abbreviations

ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
aPTT	activated Partial Thromboplastin Time
CHF	Congestive Heart Failure
CrCl	Creatinine Clearance
DVT	Deep Vein Thrombosis
FFP	Fresh Frozen Plasma
HIT	Heparin-Induced Thrombocytopenia
INR	International Normalized Ratio
LMWH	Low Molecular Weight Heparin
MI	Myocardial Infarction
PE	Pulmonary Embolism
pRBC	packed red blood cells
TIA	Transient Ischemic Attack
UFH	Unfractionated Heparin
VTE	Venous Thromboembolism

# 1. Overview of Anticoagulant Medications

## A. Unfractionated heparin

- ▶ Inhibits thrombin by accelerating the activity of antithrombin.
- ▶ Dose of heparin
  - ▶ Treatment: 80 units/kg IV bolus (if desired) then 18 units/kg/hr IV infusion. Check aPTT 6 hours after bolus and adjust infusion to maintain aPTT within the therapeutic range established by the local laboratory.
    - It is recommended to use an algorithm-based dosing protocol
    - Consult Thrombosis if weight > 120 kg
  - ▶ Prophylaxis: 5000 units sc q12hr (or q8hr if obese i.e. weight >120 kg).
- ▶ There are no dose adjustments required for renal failure

## B. Low Molecular Weight Heparin

Enoxaparin (Lovenox®)

Dalteparin (Fragmin®)

Tinzaparin (Innohep®)

- ▶ Directly inhibits factor Xa activity
- ▶ Dose of enoxaparin
  - ▶ Treatment: 1.5 mg/kg sc qday **or** 1 mg/kg sc BID (the latter regimen is preferred in ACS and obesity)
    - Renal failure (CrCl 15-30 mL/min): 1 mg/kg sc qday
  - ▶ Prophylaxis: 40 mg sc qday (except post-op hip/knee surgeries: 30 mg sc BID)
    - Renal failure (CrCl 15-30 mL/min): 30 mg sc qday

- ▶ Dose of dalteparin
  - ▶ Treatment: 200 units/kg sc qday
    - Renal failure (CrCl 15-30 mL/min) :  
Consider Anti-Xa levels for dose adjustments
  - ▶ Prophylaxis: 5000 units sc qday
- ▶ Dose of tinzaparin
  - ▶ Treatment: 175 units/kg sc qday
  - ▶ Prophylaxis: 3500 units/kg sc qday
- ▶ Consult Thrombosis if weight > 120 kg for all forms of LMWH
- ▶ Monitoring
  - ▶ Routine monitoring is not required for LMWHs
  - ▶ Anti Xa levels, which must be approved by Thrombosis or Hematology, may be useful in the following situations:
    - Renal failure
    - Extreme weights
    - Pregnancy
    - Recurrent thromboses on therapeutic doses

## C. Warfarin (Coumadin®)

- ▶ Inhibits the proper synthesis of the vitamin K-dependent clotting factors.
- ▶ Initiate warfarin at 5-10 mg po qday. Consider lower doses in the elderly, patients with impaired nutrition, liver failure, congestive heart failure, or with a high risk of bleeding.
- ▶ No dose adjustment is required in renal failure.
- ▶ An initial INR should be done on Day 3. **In the absence of any bleeding**, the warfarin dose should be adjusted based on the table below. An INR should then be done every 3-4 days, until the INR is therapeutic and stable.

INR	Dose Adjustment
<2.0	Increase weekly dose by 10-20%, consider bridging
2.0-3.0	None
3.1-4.0	Decrease dose by 10-20%
4.1-6.0	Omit one dose then restart with a lower dose (10-20%)
6.1-10.0	Omit two doses and remeasure INR in 48 hours
>10.0	Hold Warfarin and Administer 2.5mg Vitamin K, Remeasure INR in 48 hours

- ▶ The INR should be checked within 1-2 weeks of any change in dose.
- ▶ Any INR that falls below the therapeutic range should be checked within 1-2 weeks whether or not the dose is adjusted.
- ▶ INRs should be checked every 8 weeks (6 weeks for mechanical valves) and only if INR values are stable.
- ▶ For **very** stable patients i.e. within the therapeutic range for the previous 6 months, INRs may be checked every 12 weeks (does not apply to patients with mechanical valves)

## **D. Rivaroxaban (Xarelto®)**

- ▶ Inhibits Factor Xa
- ▶ Indicated for the prevention of VTE in patients who have undergone elective total hip replacement or total knee replacement surgery, for the prevention of stroke and systemic embolism in patients with atrial fibrillation, and for the treatment of DVT without symptomatic pulmonary embolism.
- ▶ Dose:
  - ▶ For orthopaedic prophylaxis: 10 mg po qday (14 days for knee replacement/ 35 days for hip replacement)
  - ▶ For Atrial Fibrillation: 20 mg po qday or 15 mg po qday if CrCl 30-49 mL/min
  - ▶ For treatment of DVT: 15 mg po BID for 3 weeks, followed by 20 mg po qday or followed by 15 mg po qday if CrCl 30-49 mL/min
  - ▶ Contraindicated in severe renal failure (CrCl < 30 mL/min)
- ▶ No anticoagulation monitoring required

## **E. Dabigatran (Pradax®)**

- ▶ Direct thrombin inhibitor
- ▶ Indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation and for the prevention of VTE in patients who have undergone elective total hip replacement or total knee replacement surgery.
- ▶ Dose in atrial fibrillation:
  - ▶ 150 mg po BID or
  - ▶ 110 mg po BID if age > 75 or in patients with increased risk of bleeding

- ▶ Dose in hip/knee replacement surgery
  - ▶ 220 mg po qday or
  - ▶ 150 mg po qday if age > 75
- ▶ Contraindicated in severe renal failure (CrCl < 30 mL/min), caution for patients with moderate renal impairment (CrCl 30-50 mL/min)
- ▶ Monitoring
  - ▶ Normally, no anticoagulation monitoring required
  - ▶ **PTT: INSENSITIVE:** If abnormal then there is significant drug present. However, a normal PTT does not necessarily mean there is no effect of dabigatran.
  - ▶ **Thrombin Time (TT): TOO SENSITIVE** but a normal TT assures that there is no remaining anticoagulant effect of dabigatran. An abnormal thrombin time from dabigatran does not imply that hemostasis is impaired.

## F. Fondaparinux (Arixtra®)

- ▶ Inhibits Factor Xa
- ▶ Dose for VTE prophylaxis
  - ▶ 2.5 mg sc qday
- ▶ Dose for VTE treatment and for suspected HIT
  - ▶ 5 mg sc qday if weight < 50 kg
  - ▶ 7.5 mg sc qday if weight 50-100 kg
  - ▶ 10 mg sc qday if weight > 100 kg
- ▶ Dose for Unstable Angina/NSTEMI
  - ▶ 2.5 mg sc qday

- ▶ Dose for STEMI (in patients who are managed with thrombolytics or who initially are to receive no form of reperfusion therapy)
  - ▶ 2.5 mg IV x 1, then 2.5 mg sc qday
- ▶ Not recommended in severe renal failure (CrCl < 30 mL/min)
- ▶ No monitoring required

## **G. Argatroban**

- ▶ Direct thrombin inhibitor
- ▶ Indicated in patients with heparin-induced thrombocytopenia who require anticoagulation.
- ▶ Dose and monitoring
  - ▶ Initial: 2 mcg/kg/min continuous IV infusion (0.5 mcg/kg/min if moderate hepatic impairment).
  - ▶ Send aPTT 2 hours after initiation of therapy
  - ▶ Adjust dose to reach target aPTT of 1.5 to 3X baseline
  - ▶ Infusion rate should not exceed 10 mcg/kg/min
  - ▶ Argatroban prolongs the INR, thus complicating the monitoring of warfarin.
- ▶ No dose adjustments required in renal failure

## 2. Reversal Agents

### A. Protamine

- ▶ Dose for heparin reversal (**max. dose 50 mg**):
  - ▶ Unfractionated heparin:
    - 1 mg IV per 100 units (if administered within previous 30 minutes)
    - 0.5 mg IV per 100 units (if 30-60 minutes have elapsed since heparin administration)
    - 0.25 mg IV per 100 units (if more than 2 hours have elapsed since heparin administration)
  - ▶ Enoxaparin: 1 mg IV per 1 mg (only 50% effective)
  - ▶ Dalteparin: 1 mg IV per 100 units (only 75% effective)
  - ▶ Tinzaparin: 1 mg IV per 100 units (only 80% effective)
- ▶ Protamine should be administered over at least 10 minutes to avoid severe hypotension and patients must be monitored for anaphylactoid reactions.

## B. Vitamin K/Octaplex/Fresh Frozen Plasma

- ▶ The following table summarizes the management of anticoagulated patients on warfarin with either elevated INRs, bleeding, or in need for urgent reversal for surgical/medical procedures:

Bleeding	INR	Action
No	< 4.5	<ul style="list-style-type: none"> <li>■ Decrease warfarin dose by 10-20%</li> </ul>
No	4.5-10	<ul style="list-style-type: none"> <li>■ Hold warfarin until INR therapeutic</li> <li>■ Restart at lower dose</li> </ul>
No	> 10	<ul style="list-style-type: none"> <li>■ Hold warfarin until INR therapeutic</li> <li>■ Vitamin K 2.5 mg <b>PO</b> x 1</li> <li>■ Restart at lower dose</li> </ul>
No	> 2 and urgent procedure needed	<ul style="list-style-type: none"> <li>■ Hold Warfarin</li> <li>■ Octaplex candidate*:                             <ul style="list-style-type: none"> <li>– Vitamin K 10 mg IV over 30 min</li> <li>– Octaplex as per Blood Bank protocol</li> <li>– INR corrects within 1 hour</li> </ul> </li> <li>■ Not Octaplex candidate**:                             <ul style="list-style-type: none"> <li>– Vitamin K 5-10 mg IV over 30 min</li> <li>– FFP 15 mL/kg</li> <li>– INR corrects within 8 hours</li> </ul> </li> </ul>
Yes	> 2	

\* Octaplex candidate: patient on warfarin or vitamin K deficient requiring urgent normalization of their INR for active bleeding or urgent surgery (< 6 hours)

\*\* Contraindication to Octaplex: history of HIT, allergy to product, high risk of thrombosis (recent MI, PE, DVT, CVA)

### **Dosing of Octaplex:**

- ▶ 1000 U if INR < 3.0
- ▶ 2000 U if INR 3.0-5.0
- ▶ 3000 U if INR >5.0

### **Vitamin K particularities:**

- ▶ High doses of vitamin K may lower INR more than is necessary and may lead to warfarin resistance for up to one week.
- ▶ Oral vitamin K is the treatment of choice due to its predictable efficacy and to its safety and convenience
- ▶ IV vitamin K may be associated with anaphylaxis. It should be reserved for more urgent situations to reverse anticoagulation.
- ▶ Response to SC vitamin K may be unpredictable and sometimes delayed

### **Dabigatran/Rivaroxaban**

- ▶ No available reversing agent
- ▶ Supportive care with pRBCs and FFP while drug wears off (depending on half life and creatinine clearance)
- ▶ Dialysis suggested for dabigatran but efficacy unproven
- ▶ HEMATOLOGY OR THROMBOSIS CONSULT SUGGESTED

## 3.

## Conversion from One Anticoagulant to Another

### A. Unfractionated Heparin to Low Molecular Weight Heparin

- ▶ Initiate LMWH 1-2 hours after the discontinuation of intravenous unfractionated heparin
- ▶ VTE prophylaxis may be initiated 2 hours after discontinuation of IV heparin

### B. Low Molecular Weight Heparin to Unfractionated Heparin

- ▶ Initiate unfractionated heparin without bolus 6-12 hours after the last dose of LMWH

### C. Dabigatran

	CrCl	FROM Dabigatran/ Rivaroxaban	TO Dabigatran/ Rivaroxaban
Unfractionated heparin	30-50 mL/min	24 hours after last dose	start immediately after discontinuing IV heparin
	>50 mL/min	12 hours after last dose	start immediately after discontinuing IV heparin
Low Molecular Weight Heparin	30-50 mL/min	12-24 hours after last dose	start 6 hours after last dose
	>50 mL/min	6-12 hours after last dose	start 6 hours after last dose
Warfarin	30-50 mL/min	4 days before discontinuing. Check INR 4 days after warfarin initiation	Start 4 days after discontinuing warfarin or when INR <2.0
	>50 mL/min	2 days before discontinuing. Check INR 4 days after warfarin initiation	Start 4 days after discontinuing warfarin or when INR <2.0.

## 4. Atrial Fibrillation

### A. Indications for indefinite anticoagulation therapy

- ▶ Paroxysmal, persistent, or permanent atrial fibrillation or atrial flutter
- ▶ Patients should initially be stratified for stroke risk and bleeding risk to determine appropriate therapy and management.

### B. Stratification of patients

- ▶ Stroke risk using the CHADS<sub>2</sub> score:

C = Congestive Heart Failure – 1 point

H = Hypertension – 1 point

A = Age > 75 years – 1 point

D = Diabetes mellitus – 1 point

S = Prior stroke or TIA – 2 points

CHADS <sub>2</sub> Score	Adjusted stroke rate without anticoagulation, %/yr (95% CI)
0	1.9 (1.2 – 3.0)
1	2.8 (2.0 – 3.8)
2	4.0 (3.1 – 5.1)
3	5.9 (4.6 – 7.3)
4	8.5 (6.3 – 11.1)
5	12.5 (8.2 – 17.5)
6	18.2 (10.5 – 27.4)

► Stroke risk using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score:

C = CHF or LVEF ≤ 40 % – 1 point

H = Hypertension – 1 point

A = Age ≥ 75 years – 2 points

D = Diabetes mellitus – 1 point

S = Prior stroke or TIA or thromboembolism – 2 points

V = Vascular disease (prior MI, peripheral artery disease, or aortic plaque) – 1 point

A = Age 65-74 years – 1 point

Sc = Sex category (female) – 1 point

CHA <sub>2</sub> DS <sub>2</sub> -VASc Score	Adjusted stroke rate, %/yr
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

► Major bleeding risk using the HAS-BLED score:

- H = Hypertension – 1 point
- A = Abnormal renal or hepatic function – 1 point each
- S = Stroke – 1 point
- B = Bleeding – 1 point
- L = Labile INRs – 1 point
- E = Elderly (Age > 65 years) – 1 point
- D = Drug or alcohol – 1 point each

HAS-BLED score	Major Bleeds (%/yr)
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50

- Calculate CHADS<sub>2</sub> score
  - CHADS<sub>2</sub> ≥ 2 → Oral anticoagulant
  - CHADS<sub>2</sub> = 0 or 1 → calculate CHA<sub>2</sub>DS<sub>2</sub>-VASc
- CHA<sub>2</sub>DS<sub>2</sub>-VASc is recommended if CHADS<sub>2</sub> ≤ 1
  - CHA<sub>2</sub>DS<sub>2</sub>-VASc = 0 → no antithrombotic therapy
  - CHA<sub>2</sub>DS<sub>2</sub>-VASc = 1 → Oral anticoagulant or ASA, oral anticoagulant preferred
  - CHA<sub>2</sub>DS<sub>2</sub>-VASc ≥ 2 → Oral anticoagulant.
- Vigilance is required in patients with high risk of major bleeds (HAS-BLED ≥ 3). Closer monitoring and follow-up is warranted in this population.
- Aspirin (≥ 80 mg) is effective but not as effective as warfarin.

## C. Choice of oral anticoagulant

- ▶ Currently, the oral vitamin K antagonist, warfarin (Coumadin®), is the most widely used. For dosing information on warfarin, see page 5.
- ▶ An alternative vitamin K antagonist is nicoumalone (Sintrom®), for patients allergic to warfarin.
- ▶ Need to **maintain an INR of 2.0-3.0** with vitamin K antagonists to prevent embolic stroke.
- ▶ Patients with chronic atrial fibrillation of unknown duration, in the absence of an acute embolic event, do not require heparin therapy during the initiation of warfarin therapy.
- ▶ Dabigatran (Pradax®), an oral direct thrombin inhibitor, and rivaroxaban (Xarelto®), an oral factor Xa inhibitor, are new alternatives to vitamin K antagonists.
- ▶ Both dabigatran and rivaroxaban are as efficacious as warfarin in preventing stroke, with lower risk of intracranial bleeding. However, they are excreted primarily by the kidney, lack an antidote, and are not readily monitored with standard laboratory tests.
- ▶ It is the practice of the JGH Anticoagulation Clinic that patients over of 75 years old with creatinine clearances less than 50 mL/min not use dabigatran. For those patients over the age of 75 whose CrCl > 50, dabigatran, if prescribed, should be used at a dose of 110 mg po BID.

## **D. Atrial Fibrillation following open heart surgery**

- ▶ Warfarin is recommended for 3 months following open heart surgery, provided the patient reverts to normal sinus rhythm.

## **E. Cardioversion of Atrial Fibrillation**

- ▶ For AF < 48 hours, anticoagulation is not required prior to cardioversion
- ▶ For AF >48 hours (or of unknown duration), warfarin is recommended for 3 weeks before and at least 4 weeks after successful cardioversion. The duration of warfarin therapy, regardless of cardioversion outcome, will be decided by the treating cardiologist.

## 5. Venous Thrombosis (DVT/PE)

### A. Standard Treatment

- ▶ In the absence of any contraindications, warfarin is the treatment of choice for DVT/PE. The target INR is 2.0 – 3.0.
- ▶ Therapeutic heparin therapy (either UFH or LMWH) should be initiated concomitantly with warfarin. A minimum of 5 days of heparin therapy is required and it can be discontinued once the INR >2.0 for two consecutive days.
- ▶ For a 1<sup>st</sup> unprovoked (**without an obvious risk factor**) DVT/PE - warfarin should be continued for **at least 3 months** maintaining the INR between 2.0-3.0, and possibly continued indefinitely depending on the risk of thrombosis vs. bleeding and patient preference.
- ▶ For a 2<sup>nd</sup> unprovoked DVT/PE - warfarin should be continued, possibly indefinitely. Continued use of warfarin should be evaluated in Thrombosis Clinic annually, taking into account any new patient-related factors that could alter the risk-benefit balance of long term use of warfarin.
- ▶ For a provoked (secondary) DVT/PE i.e. a DVT/PE due to a temporary risk factor (e.g. surgery, pregnancy, plaster cast, etc) - warfarin should be continued for **3 months** (INR maintained between 2.0 and 3.0) following the withdrawal of the temporary risk factor.
- ▶ Should the INR fall below 2.0 during the first three months of therapy after a DVT, therapeutic LMWH should be instituted and warfarin adjusted until the INR is >2.0 for two consecutive days.
- ▶ An alternative treatment to warfarin, for DVTs without symptomatic PE and approved by Health Canada, is rivaroxaban alone, without heparin, at a dose of 15 mg po BID for 3 weeks followed by 20 mg po qday. Total treatment time is usually for 3 months but can be extended for up to one year. It is not recommended to be used for greater than one year.

## **B. Duration and type of heparin**

- ▶ A minimum of five days of heparin therapy is required for the treatment of a DVT/PE to allow for warfarin to begin its anticoagulant effect.
- ▶ LMWH is preferable to intravenous UFH due to its favourable pharmacokinetic profile.
- ▶ IV heparin should be used only in situations where bleeding is a concern and a quick reversal of heparin is desired or in the presence of severe renal failure (i.e. CrCl < 15 mL/min).

## **C. Inferior Vena Cava (IVC) Filters**

- ▶ IVC filters should be placed in only two situations
  - ▶ When anticoagulation is absolutely contraindicated
  - ▶ When a PE is likely to result in a fatality due to compromised respiratory function
- ▶ A Thrombosis/ Hematology /Pulmonary consult should be obtained prior to the placement of an IVC filter.
- ▶ Anticoagulation should be resumed as soon as medically feasible in all patients with acute VTE and IVC filters.

## **D. Thrombophilia Testing**

- ▶ There is no indication to perform thrombophilia screening testing during the acute thrombotic event.
- ▶ It is recommended that thrombophilia testing be performed only by the Thrombosis Clinic.

- ▶ Thrombophilia testing is usually done in all patients with unprovoked and pregnancy-associated DVTs for the following reasons:
  1. Secondary prophylaxis decisions in high risk situations
  2. Primary prophylaxis in 1<sup>st</sup> degree relatives
  3. The presence of a thrombophilia will, on occasion although not usually, affect the duration of therapy with warfarin
- ▶ In patients < 55 years of age, the following thrombophilias should be tested for:
  - ▶ Antithrombin, Protein C and Protein S deficiency
  - ▶ Factor V Leiden and Prothrombin G20210A
  - ▶ Lupus Anticoagulant and Anticardiolipin antibodies
  - ▶ Homocysteine and Factor VIII levels
- ▶ In patients > 55 years of age, the following thrombophilias should be tested for:
  - ▶ Factor V Leiden and Prothrombin G20210A
  - ▶ Lupus Anticoagulant and Anticardiolipin antibodies
  - ▶ Homocysteine and Factor VIII levels

## **E. Treatment of VTE in Pregnancy**

- ▶ Pregnant women diagnosed with a VTE should be treated with full dose LMWH (e.g. dalteparin 200 units/kg/qday or enoxaparin 1.5 mg/kg/qday) for the remainder of their pregnancy. Patients should complete at least 6 months of anticoagulation including treatment throughout pregnancy and 6 weeks post-partum.
- ▶ Warfarin is contraindicated during the first trimester of pregnancy because of the risk of teratogenicity.
- ▶ Primary prophylaxis (with prophylaxis doses of Low Molecular Weight Heparin) is reserved for thrombophilic women during the six weeks post-partum.

- ▶ Secondary prophylaxis (with prophylaxis doses of Low Molecular Weight Heparin) during pregnancy is indicated in women who have a previous history of an unprovoked VTE, a VTE associated with estrogen use, pregnancy, and/or obesity or a VTE associated with a thrombophilia. Anticoagulation post partum can be either warfarin or LMWH, as neither are excreted in breast milk and both are safe for the newborn.

## F. Cancer associated VTE

- ▶ It is recommended that anticoagulation for the first six months after a VTE be dalteparin (200 units/kg/qday for the first month then 150 units/kg/qday for the following 5 months) or enoxaparin (1.5 mg/kg/qday for the first month then 1.125 mg/kg/qday for the following 5 months). Thereafter, anticoagulation can either be LMWH or warfarin depending on patient preference and co-morbid conditions (e.g. ongoing chemotherapy.)
- ▶ Anticoagulation treatment should be continued indefinitely as long as the malignancy is active or chemotherapy is ongoing.

## G. Thrombosis in the setting of a lupus anticoagulant

- ▶ All venous and arterial thrombotic events in the setting of a lupus anticoagulant or an anticardiolipin antibody should be treated with lifelong warfarin therapy, maintaining an INR of 2.0-3.0.

## H. Recurrent fetal loss

- ▶ Women with recurrent fetal loss, defined as at least **three** 1<sup>st</sup> trimester losses, **two** 2<sup>nd</sup> trimester losses or **one** 3<sup>rd</sup> trimester loss in the setting of a positive lupus anticoagulant or anticardiolipin antibody should be treated throughout the pregnancy with prophylactic LMWH dose (either dalteparin 5000 units sc qday or enoxaparin 40 mg sc qday) and ASA 80 mg po qday for all subsequent pregnancies.

- ▶ The role of anticoagulant therapy in women with recurrent fetal loss and other thrombophilias is controversial and such women should be enrolled in currently available clinical trials.

## I. VTE prophylaxis

- ▶ All patients admitted to hospital for a surgical intervention or for acute medical illness should receive VTE prophylaxis unless they are deemed to be low risk or if anticoagulation is contraindicated.
- ▶ Refer to the JGH VTE prophylaxis protocol for the complete prophylaxis guidelines.
- ▶ Risk assessment scores for VTE include the Padua score (for medical patients) or the Caprini score (for surgical patients).

Padua risk assessment score for medical patients (score of < 4 is considered low risk)	
Risk Factor	Points
Active cancer	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (> 1 mo) trauma and/or surgery	2
Elderly age (>70 y)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI >30)	1
Ongoing hormonal treatment	1

## Caprini risk assessment score for surgical patients (score of < 3 is considered low risk)

1 Point	2 Points	3 Points	5 Points
Age 41-60 y	Age 61-74 y	Age >75 y	Stroke (<1 mo)
Minor surgery	Arthroscopic surgery	History of VTE	Elective arthroplasty
BMI >25 kg/m <sup>2</sup>	Major open surgery (> 45 min)	Family history of VTE	Hip, pelvis, or leg fracture
Swollen legs	Laparoscopic surgery (>45 min)	Factor V Leiden	Acute spinal cord injury (< 1mo)
Varicose veins	Malignancy	Prothrombin 20210A	
Pregnancy or postpartum	Confined to bed (>72 h)	Lupus anticoagulant	
History of unexplained or recurrent spontaneous abortion	Immobilizing plaster cast	Anticardiolipin antibodies	
Oral contraceptives or hormone replacement	Central venous access	Elevated serum homocysteine	
Sepsis (<1 mo)		Heparin-induced thrombocytopenia	
Serious lung disease, including pneumonia (<1 mo)		Other congenital or acquired thrombophilia	
Abnormal pulmonary function			
Congestive heart failure (< 1 mo)			
History of inflammatory bowel disease			
Medical patient at bed rest			

- ▶ In most patients, the recommended agent is enoxaparin 40 mg sc qday. In the case of severe renal failure (CrCl 15- 30 mL/min), enoxaparin 30 mg sc qday may be used. For CrCl < 15 mL/min, heparin 5000 units sc BID may be used.
- ▶ Some patient populations use different forms of anticoagulation as VTE prophylaxis:
  - ▶ Hip fracture pre-op: heparin 3500 units sc q8h
  - ▶ Hip fracture post-op: enoxaparin 30mg sc BID x 35 days
  - ▶ Total hip or knee arthroplasty: rivaroxaban 10mg po qday or enoxaparin 30mg sc BID x 35 days (hip) or x 14 days (knee)
- ▶ Although LMWHs have not been shown to be superior to UFH therapy for VTE prophylaxis (except in orthopaedic patients), they are preferable for the following reasons:
  - i) Easier implementation will lead to more universal use
  - ii) Much lower risk of HIT
  - iii) Less need for CBC monitoring
  - iv) Once daily injection in lieu of BID orTID injections

## 6. Heart Valves

### A. Bioprosthetic Heart Valves:

- ▶ Patients who undergo valve replacement with **bioprosthetic** valves in the **mitral position** and without atrial fibrillation or a left atrial thrombus require anticoagulation with warfarin (to keep an INR between 2 and 3) for three months followed by ASA (80 mg) indefinitely
- ▶ Patients who undergo valve replacement with **bioprosthetic** valves in the **aortic position** require anticoagulation with ASA 80 mg/qday for three months

### B. Mechanical Heart Valves

- ▶ All patients with mechanical heart valves require lifelong warfarin therapy. The target INR is defined as follows:
  - ▶ **Low risk valves:** St. Jude's, CarboMedics, and Medtronic valves in the aortic position require an INR of 2.0-3.0.
  - ▶ **High risk valves:** All other valves in the aortic position and all valves in the mitral position, require an INR of 2.5-3.5. Other high risk features include the following:
    - 1) Patients who suffer systemic embolism despite adequate anticoagulation with warfarin,
    - 2) Patients with left ventricular dysfunction,
    - 3) Patients with atrial fibrillation,
    - 4) Patients with left atrial enlargement,
    - 5) Patients with caged ball or caged disk valves.
- ▶ Heparin should be added to patients who are subtherapeutic on warfarin in the following situations:
  - a) High risk mechanical valve patients with an INR < 2.0
  - b) Low risk mechanical valve patients with an INR < 1.5

## 7. Bridging Therapy

### A. Peri-operative Management of Anticoagulation

#### ► Indications for bridging therapy:

Patients on warfarin therapy for atrial fibrillation, venous thromboembolism (VTE) or mechanical heart valves who are at **high or moderate** risk of developing thromboembolism.

Risk	AF	VTE	Mechanical heart valve
<b>High</b>	<ul style="list-style-type: none"> <li>■ CHADS<sub>2</sub> = 5 or 6</li> <li>■ CVA or TIA within the past 3 months</li> <li>■ Rheumatic valvular heart disease</li> </ul>	<ul style="list-style-type: none"> <li>■ VTE within the past 3 months</li> <li>■ Severe thrombophilia (ex: deficiency in proteins C, S or antithrombin, antiphospholipid antibodies)</li> </ul>	<ul style="list-style-type: none"> <li>■ Mitral valve prosthesis</li> <li>■ Older aortic valve prosthesis</li> <li>■ CVA or TIA within the past 6 months</li> </ul>
<b>Moderate</b>	<ul style="list-style-type: none"> <li>■ CHADS<sub>2</sub> = 3 or 4</li> </ul>	<ul style="list-style-type: none"> <li>■ VTE within the past 3 to 12 months</li> <li>■ Recurrent VTE</li> <li>■ Active cancer (treated within 6 months or palliative)</li> </ul>	<ul style="list-style-type: none"> <li>■ Bileaflet aortic valve prosthesis and one of the following risk factors:               <ul style="list-style-type: none"> <li>- AF</li> <li>- Prior CVA or TIA</li> <li>- Hypertension</li> <li>- Diabetes</li> <li>- CHF</li> <li>- Age &gt; 75 years</li> </ul> </li> </ul>
<b>Low</b>	<ul style="list-style-type: none"> <li>■ CHADS<sub>2</sub> = 0 to 2, with no prior CVA or TIA</li> </ul>	<ul style="list-style-type: none"> <li>■ VTE &gt; 12 months ago, single episode, no other risk factors</li> </ul>	<ul style="list-style-type: none"> <li>■ Bileaflet aortic valve prosthesis with none of the above risk factors</li> </ul>

► Recommended bridging therapy (not needed in low risk patients):

	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0 Surgery	Day +1	Day +2	Day +3
D/C warfarin									
dalteparin 200 units/kg sc qday or enoxaparin 1.5 mg/kg/qday									
dalteparin 100 units/kg sc qday or enoxaparin 0.75 mg/kg/qday									
warfarin at regular dose No dalteparin									
<p>► Continue warfarin at regular dose</p> <p>► <b>High Risk* Operative Procedure:</b> dalteparin 5000 units sc qday or enoxaparin 40 mg qday (prophylactic or low dose)</p> <p>► <b>Low Risk Operative Procedure:</b> dalteparin 200 units/kg sc qday or enoxaparin 1.5 mg/kg/qday (full dose)</p>									

\* high bleeding risk operative procedures e.g. Major Orthopedic surgery, Genitourinary surgery, Neurosurgery, Vascular Surgery, Endoscopy with possibility of biopsy, Abdominal Hysterectomy

## Note

- ▶ LMWH is NOT to be given within 24 hours of a surgical procedure.
- ▶ For high risk surgeries (e.g. neurosurgery) or surgeries associated with a high incidence of bleeding (e.g. urologic procedures), it is suggested that the pre-surgical dalteparin dose on Day -1 and/or the post-operative doses of dalteparin be omitted.
- ▶ The pre-operative LMWH dose on Day-1 should not be given prior to neuraxial anaesthesia.

## B. Surgical procedures in patients with renal impairment

- ▶ Patients with moderate renal impairment (CrCl 15-30 mL/min) should receive only prophylactic doses of LMWH for bridging.
- ▶ Patients with severe renal impairment (CrCl <15 mL/min) should receive intravenous unfractionated heparin, as described on page 3, for bridging.

## C. Surgical procedures in patients on dabigatran

(CLCr, mL/min)	Half-life (hours)	Timing of procedure after last dose of dabigatran	Timing of resumption of dabigatran after surgery (depends on procedure)
> 80	13	2 days	The evening on the day <u>after</u> surgery
< 50-80	15	2 days	As above
> 30 to ≤50	18	4 days	As above

## D. Surgical procedures that do not necessarily require interruption of warfarin therapy

### 1) Dental procedures

Dental procedures can be performed as long as the INR<3.0, especially for procedures performed in the Department of Dentistry at the Jewish General Hospital. Very complex procedures may require the perioperative bridging protocol.

### 2) Endoscopies without polypectomy or biopsy

### 3) Cystoscopies without biopsies

### 4) Cataract surgery

## 8. Use of Combined Therapy

The use of combined therapy of warfarin and antiplatelet agents (including low dose aspirin) is discouraged due to the higher risk of bleeding in patients on combined therapy.

### Exceptions include the following:

- 1) For secondary prophylaxis of ischemic heart disease in patients with coronary artery disease who are under the age of 75.
- 2) Antiplatelet agents including aspirin or clopidogrel or both that are used post percutaneous coronary artery intervention (PCI).
- 3) Patients with ***mechanical valves*** who are deemed **high risk** for cerebrovascular events as defined by one of the following factors:
  - a) Systemic embolism despite adequate anticoagulation with warfarin,
  - b) Left ventricular dysfunction,
  - c) Concomitant atrial fibrillation,
  - d) Left atrial enlargement,
  - e) Caged ball or caged disk valves.

- ▶ The main indication for the use of warfarin in coronary artery disease is in patients with acute MI and with any one of the following risk factors:
  - ▶ Large anterior myocardial infarction
  - ▶ Significant heart failure
  - ▶ Intracardiac thrombus on Echocardiography
  - ▶ History of a thromboembolic event.

In these cases, combined therapy of warfarin (INR 2.0-3.0) and low dose aspirin (80 mg/qday) is recommended. The duration of warfarin therapy is three months whereas ASA is continued indefinitely.

- ▶ Other cardiac indications for chronic anticoagulation therapy:
  - ▶ Rheumatic mitral valve disease
  - ▶ Patients with mitral valve prolapse that experience systemic embolism despite ASA therapy
- ▶ **It is not recommended that patients with low ejection fractions from chronic heart failure be anticoagulated with warfarin unless they have one or more of the following factors:**
  1. Atrial fibrillation
  2. Documented left ventricular thrombus on echocardiography
  3. Previous systemic arterial event

- ▶ Warfarin therapy is indicated in patients who suffer a cerebrovascular event from a cardioembolic source as evidenced by one of the following risk factors:
  1. Presence of atrial fibrillation
  2. Presence of a low ejection fraction (<30%)
  3. Presence of cardiac thrombus on echocardiogram
  4. A CVA immediately post MI
  
- ▶ Other uncommon indications for the use of warfarin in the setting of cerebrovascular disease need to be clearly stated by the referring neurologist and can include the following:
  - ▶ Patent foramen ovale
  - ▶ Carotid dissection
  - ▶ Cerebral venous thrombosis
  - ▶ Pedunculated or mobile atheromata at either aortic arch or carotid bifurcation
  - ▶ Symptomatic and very high grade carotid stenosis in patients awaiting endarterectomy
  - ▶ Recurrent TIA/stroke despite trial of all of the antiplatelet agents
  - ▶ Stroke/TIA in the setting of a lupus anticoagulant or anticardiolipin antibody (it is not clear that warfarin is superior to antiplatelet agents)
  - ▶ Central retinal vein occlusion in the setting of a lupus anticoagulant or anticardiolipin antibody

## 11. Heparin-Induced Thrombocytopenia (HIT)

### A. Definition/recognition (The 4Ts):

- a) **THROMBOCYTOPENIA:** The platelet count falls by 50% or more from baseline.
- b) **TIMING:** Occurs between days 4-14 of heparin therapy
- c) **THROMBOSIS:** The presence of a venous or arterial thrombotic event
- d) **ALTERNATIVE DIAGNOSIS:** An alternative explanation for the thrombocytopenia is less likely

### B. Procedure to Follow In Suspected HIT:

- a) Review the definition/recognition section
- b) Stop all heparin sources (iv, sc, catheter flushes, dialysis)
- c) Consult Thrombosis
- d) Draw blood for a HIT antibody assay (1 yellow & 1 blue tube)
- e) Order bilateral ultrasounds of the lower extremities
- f) Start therapy with fondaparinux. Argatroban is a second-line agent, reserved for patients with severe renal failure (CrCl < 30 mL/min) or for patients who may require acute reversal of anticoagulation.
- g) Do not give platelet transfusions unless patient is bleeding significantly
- h) When warfarin therapy is indicated, do not initiate until platelets recover to  $> 150 \times 10^9/L$  or back to baseline.

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