

CHAPTER 19

Oral Anticoagulants

- Introduction
 - Types
 - Mechanism of Action
 - Pharmacokinetics
- Monitoring of Oral Anticoagulant Therapy
 - Laboratory Monitoring
 - Preparations and Dosages
 - Management of Patients with High INR Value
 - Treatment of Overdose and Severe Hemorrhage
 - Adverse Reactions
 - Contraindications
 - Drug Interaction
- Indications
 - Primary Prevention of Coronary Artery Disease
 - Stable Angina
 - Acute Coronary Syndromes
 - Rationale
 - Unstable Angina and NSTEMI
 - Myocardial Infarction

- The PT ratio observed with the local thromboplastin is converted into an INR, which is the patient's PT divided by plasma control PT (median normal range PT) times a value (C) that represents the international sensitivity index (ISI).

$$\text{INR} = \left[\frac{\text{Patient PT}}{\text{Mean Normal PT}} \right] \text{ISI}$$

- Two levels of anticoagulation intensity are recommended:
 4. Less intense therapy with INR of 2.0-3.0.
 5. More intense regimen with INR of 2.5-3.5.

Preparations and Dosages

1. Warfarin sodium (Marevan)- available in 1, 3 and 5 mg tablets:

The initial dose is 10 mg/day for 2 days.

The maintenance dose is 1-10 mg/day according to the INR.

- Anticoagulant effect appears after about 3 to 5 days. Therapeutic INR values are usually achieved by day five of treatment.
- INR measurements are made initially, after 2 days and then weekly until it persists within the therapeutics range for one month then every 2-4 weeks. The early INR changes with a 10 mg loading dose of Warfarin are caused by a more rapid reduction in F. VII levels (half-life 4-6 hours) and do not reflect a true antithrombotic state, which is more accurately reflected by reduced levels of factor II (half-life 4-6 hours) and factor x (half life 60 hours).

In view of increased sensitivity of elderly patients to Warfarin, it is suggested that a 5 mg (or lower) initial dose is preferable to 10 mg.

- Recent guidelines recommend:
 - Daily checking of INR until the therapeutic range has been reached and sustained for 2 consecutive days, then 2 or 3 times weekly for 1 to 2 weeks, then less often according to the stability of the results.
 - Once the INR becomes stable, the frequency of testing can be reduced to intervals as long as 4 weeks.
 - Treatment can be started with the average maintenance dose of about 5 mg daily of warfarin which usually results in an INR of ≥ 2.0 after 4 or 5 days.

2. Phenindione (Dindevan)- available in 50 mg tablets.

The initial dose is 150 mg/day for two days then the maintenance dose is 25-100 mg/day.

Management of Patients with High INR Values

- There is a close relationship between the INR and risk of bleeding.
- The risk of bleeding increases when the INR exceeds 4.

- In patients with excessively prolonged INR values, vitamin K₁, 1 mg to 2.5 mg orally, rapidly lowers the INR within 24 hours.
- For more rapid reversal of INR to allow urgent surgery or dental extraction vitamin K₁ can be given orally in a dose of 2 to 5 mg.

Treatment of Overdose and Severe Hemorrhage

- Excessive anticoagulation without bleeding or with only minor bleeding can be treated by dose reduction or temporary discontinuation. The risk of bleeding is decreased by lowering the INR from 3 to 4.5 down to 2.0 to 3.0 which can be achieved by reducing Warfarin by only 1 mg/day.
- Vitamin K₁: 15-25 mg IM or IV if bleeding becomes significant. This will render the patient refractory to oral anticoagulants for about 2 weeks. It should not be given to patients with artificial prosthetic cardiac valves.
- Fresh blood transfusion, fresh frozen plasma or factor IX concentrates are given to patients unresponsive to vitamin K.

Adverse Reactions

1. Hemorrhage: the most common sites are the GIT and brain. Risk of bleeding is related to the intensity of anticoagulation.
 - Conditions associated with increased risk of bleeding:
 - a. Concomitant use of high doses of aspirin or NSAIDs.
 - b. Age over 65 years. Elderly patients have increased sensitivity to the anticoagulant effect of Warfarin. Patients ≥ 75 years need less than one-half the daily dose of Warfarin compared to subjects < 35 years for an equivalent amount of anticoagulation.
 - c. History of stroke or cerebrovascular disease.
 - d. GIT bleeding.
 - e. Renal insufficiency.
 - f. Uncontrolled hypertension.

Cranial hemorrhages, predominantly subdural hematomas, are the most common fatal form of hemorrhage.

2. Skin necrosis: more frequent in women with decreased or absent protein C. It can be fatal if severe.
3. Intrahepatic cholestasis.
4. Hypersensitivity reactions, more common with indanediones.
5. Coumarins may cause alopecia, dermatitis, fetal hemorrhages, and abortion.

Contraindications

1. Active bowel or stomach ulcer with overt bleeding.
2. Abnormal vitamin K absorption or metabolism e.g. liver disease.
3. Pregnancy.
4. Intensive salicylate therapy.

Drug Interaction with Oral Anticoagulants

A. *Increased anticoagulant activity:*

1. Reduction of vitamin K production by gut flora, e.g. with oral antibiotic therapy. Moxalactam inhibits vitamin K epoxide reductase.
2. Reduced vitamin K absorption, e.g. prolonged use of liquid paraffin.
3. Increased level of free drug due to competition for plasma proteins by phenylbutazone, thyroxine, aspirin, clofibrate, sulphonamides,
4. Inhibition of enzymes that metabolize Warfarin: Amiodarone, disulfiram and cimetidine decrease the metabolism of warfarin. Lipid-soluble B-blockers impair warfarin metabolism.
5. Quinidine, thyroxine, anabolic steroids and phenformin potentiate oral anticoagulants by affecting other coagulation factors, e.g. fibrinolysis. Clofibrate lowers plasma TG which carry vitamin K.
6. Interference with platelet function e.g. aspirin, phenylbutazone,

B. *Reduction of anticoagulant activity:*

1. Binding of drug in the intestine by cholestyramine or aluminum hydroxide interferes with absorption.
2. Increased hepatic metabolism of anticoagulant due to enzyme induction by barbiturates, rifampicin, antirheumatics, griseofulvin,
3. Increased in blood clotting factors due to estrogens (including oral contraceptives) and vitamin K.

* *Anticoagulants during pregnancy:*

Heparin is used during the first trimester (Coumarin anticoagulants are teratogenic). In the last 3 months of pregnancy, heparin should be given instead of oral anticoagulants to avoid fetal and neonatal bleeding which may be fatal (*oral anticoagulants cross the placenta*).

INDICATIONS OF ORAL ANTICOAGULANTS IN CORONARY DISEASES

1. Primary prevention.
2. Stable angina.

3. Acute coronary syndromes.
 - a. Unstable angina and NSTEMI.
4. Systemic embolization.
5. Patients at increased risk of thrombo embolism.
 - LV thrombus.
 - Low LV ejection fraction (below 30%) with or without HF.
 - Atrial fibrillation.
 - LV aneurysm.
6. Deep venous thrombosis.

Primary Prevention of Coronary Artery Disease

- Anticoagulation with warfarin sodium to an INR of 1.5 and 75 mg aspirin per day each reduced the incidence of CAD by about 20% in men at increased risk of CAD. Warfarin achieved this benefit through a reduction in fatal episodes.
- Combined treatment with warfarin and aspirin reduced all major CAD events, fatal and non fatal, by 34%.
- Compared with placebo warfarin reduced all ischemic heart disease by 24%. It also increased hemorrhagic and fatal stroke.
- Despite its effectiveness, low intensity warfarin is not preferred over aspirin for primary prophylaxis in high risk patients because warfarin requires INR monitoring and is associated with greater potential for bleeding.

Stable Angina

- Intensive anticoagulation with warfarin in patients with stable angina was associated with much lower mortality than with moderate intensity anticoagulation.
- Warfarin can replace aspirin, when aspirin is contraindicated or not tolerated for secondary prevention of ischemic events.

Acute Coronary Syndromes

Rationale of Oral Anticoagulants in ACS

1. Angioscopic studies revealed residual thrombus and soft (vulnerable) plaques in the majority of patients for several months after MI, with coexisting evidence of thrombin generation.
2. In MI (and other ACSs) there is a systemic proinflammatory state with elevation in plasma inflammatory markers. Inflammatory cytokines (TNF and IL-1) facilitate thrombin generation by stimulating the release of tissue factor (TF) from monocytes and vascular endothelial cells. TF is the chief procoagulant stimulating the extrinsic pathway of blood clotting by binding F VIIa

(from plasma). This systemic proinflammatory state is therefore associated with systemic procoagulant state that persists for several months.

3. Inflammatory cytokines impair fibrinolysis through provoking the release of thrombin-activatable fibrinolysis inhibitor and PAI-1.

Unstable Angina and NSTEMI

- Two randomized trials have evaluated the role of long-term oral warfarin therapy in patients with unstable angina; both suggested but did not prove benefit from warfarin therapy of appropriate intensity.
- Long-term treatment with moderate-intensity warfarin (INR 2.0 - 2.5) plus aspirin but not low-intensity warfarin (INR 1.5) plus aspirin reduces the rate of recurrent ischemic events in patients with unstable angina. Similar to the findings in patients with MI.
- Clear reductions in total mortality, MI, and stroke occurred among patients at high intensity (INR 2.8 to 4.8) oral anticoagulation but with a significant increase in major bleeding.

Possible Mechanism of Benefit

- Changes in coronary artery lesion morphology, reducing the risk of progression or reocclusion of the culprit coronary lesion.
- Repeat angiography in patients with ACS showed that after 10 weeks of warfarin (INR 2.5) the culprit lesion was less likely to progress and more likely to regress. New lesions or reocclusion are less likely.
- Low-intensity (INR<2.0) in the presence of aspirin does not confer any benefit over aspirin alone but still increases major bleeding.

Table (19-1): Randomized Trials in MI Comparing ASA with ASA-Warfarin Combination

Study	Pts No	Follow-up Period	ACS	Outcome	ASA %*	Warfarin + ASA %
ASPECT II	993	26 Mo	ACS	D, MI, Stroke	9.0	5.0
WARIS II	3630	48 Mo	MI	D, MI, Stroke	20	16.7
APRICOT 2	308	3 Mo	MI	Angio-reocclusion	30	18

* Percentage of events (outcome)

Myocardial Infarction

- Long-term intense anticoagulation (INR >2.0) after acute MI has been proved to improve survival and reduce reinfarction rates.

- Warfarin or combination of low fixed doses of warfarin and aspirin with low intense anticoagulation (INR <2.0) has not been shown to be more effective than aspirin alone in decreasing mortality and infarction.
- High intensity (INR 2.8 to 4.8) and moderate intensity (INR 2 to 3) anticoagulation was associated with a reduction of death, MI and stroke. Moreover, there was increased risk of bleeding.
- Coumarin therapy was associated with significant reduction in reocclusion on repeat angina after AMI.

THROMBOLYTIC THERAPY
ANTICOAGULANTS : WARFARIN

Rationale after MI

- Residual thrombus + vulnerable plaque several months after MI (angioscopy)
- Persistent thrombin generation
- Persistent inflammation – release of TF

Possible Mechanism of Benefit

- Limits the ongoing thrombotic risk after AMI. There is progression of culprit lesion and persistent systemic procoagulant state with elevation in markers of thrombin generation.
- Healing of the vulnerable yellow (angioscopy) culprit lesion occurs over six months after the infarction. At angioscopy, the atherosclerotic plaque lost its yellow color and became whiter after six months and the incidence of intracoronary thrombus fell progressively from 93% immediately after reperfusion to 5% on 6 months.

LV Thrombus

- Oral anticoagulants reduce the risk of embolization.
- Anticoagulation did not appear to affect the likelihood of resolution of the thrombus.
- Anticoagulation should continue for at least six months.

LV Aneurysm

- Warfarin therapy is recommended for at least three to six months after diagnosis of a post infarction LV aneurysm, specially if intracardiac thrombus is present.

Atrial Fibrillation

- Patients with AMI who develop AF should be started on intravenous heparin.
- If AF persists or cardioversion is not performed, therapy with warfarin should be initiated.

Severe LV Dysfunction

- There are limited data on the value of prophylactic anticoagulation in patients with severe LV dysfunction after acute MI.
- Every 5% point decrease in LV EF is associated with an 18% increase in the risk of stroke.
- Anticoagulation appears to have a protective effect.

Recommendation for Anticoagulation after AMI (ACC/AHA 2001, 2004)

Warfarin should be given to aspirin-allergic post STEMI patients with indications for anticoagulation as follows:

Without stent implanted or without PCI

- Warfarin (INR 2.5-3.5) is a useful alternative to Clopidogrel in aspirin allergic patients after STEMI who do not have stent implanted.
- Chronic warfarin therapy with a goal INR 2.5 (range 2.0 to 3.0) should be added to aspirin in the following settings.
 - Patients unable to take aspirin.
 - Paroxysmal or persistent atrial fibrillation.
 - LV thrombus. Warfarin should be prescribed for at least 3 months (ACC/AHA 2004).
 - Extensive wall motion abnormalities (i.e. a large akinetic segment of LV).
 - LV systolic dysfunction (EF<30%).
 - When no thrombolytic therapy has been given, long term warfarin is recommended in patients at high risk of thrombo embolism.

In post-STEMI patients less than 75 years of age without specific indications for anticoagulation who can have their level of anticoagulation monitored reliably, warfarin alone (INR 2.5 to 3.5) or warfarin (INR 2.0 to 3.0) in combination with aspirin (75 to 162 mg) can be useful for secondary prevention (ACC/AHA 2004).

An alternative policy is routine anticoagulation with an attended INR over 2.0 to all patients following AMI or with unstable angina.

- One limitation of all of the warfarin trials is that patients were not treated with clopidogrel which is now recommended in patients with a non-ST elevation MI and in those with an ST elevation MI undergoing PCI.
- There are no data assessing a possible benefit of warfarin in patients taking aspirin and clopidogrel.

Oral anticoagulation after Coronary Stenting

- Oral anticoagulation is not recommended after stent implantation unless indications such as LV dysfunction, AF, or mechanical heart valves are also present.