GUIDELINES FOR THE THERAPEUTIC USE OF ORAL ANTICOAGULANTS

**Target INR**: The International Normalised Ratio (INR) is the recommended method for reporting Prothrombin Time results for the control of oral anticoagulation (British Committee for Standards in Haematology, 1990). Dosages are calculated according to deviation of the INR from a single target taken as the midpoint of the designated range eg. target INR of 2.5 for a range of 2.0 – 3.0. Dose adjustment is dependant on deviation of the INR from the target and also individual patient characteristics such as the reason for anticoagulation, stability of the INR’s over time, previous bleeding and thrombotic events.

**Indications of for oral anticoagulation and target INRs**

- **Pulmonary embolus**: 2.5
- **Proximal deep vein thrombosis**: 2.5
- **Calf vein thrombosis**: 2.5
- **Recurrence of venous embolism when no longer on Warfarin therapy**: 2.5
- **Recurrence of venous embolism whilst on Warfarin therapy**: 3.5
- **Symptomatic inherited thrombophilia**: 2.5
- **Antiphospholipid Syndrome**: 3.5
- **Non-rheumatic atrial fibrillation**: 2.5
- **Atrial fibrillation due to rheumatic or congenital heart disease, thyrotoxicosis**: 2.5
- **Cardioversion**: 2.5
- **Mural thrombosis**: 2.5
- **Cardiomyopathy**: 2.5
- **Mechanical prosthetic heart valve**: 3.5
- **Bioprosthetic valve**: not indicated
- **Ischemic stroke without atrial fibrillation**: not indicated
- **Retinal vessel occlusion**: not indicated
- **Peripheral arterial thrombosis and grafts**: not indicated
- **Coronary artery thrombosis**: not indicated
- **Coronary artery graft thrombosis**: not indicated
- **Coronary angioplasty and stents**: not indicated

**Venous thromboembolism in non-pregnant patients**

- **First event of PE or proximal vein thrombosis**: INR 2.5 for 6 months
- **Calf vein thrombosis in non-surgical patients with no persistent risk factors (eg cancer, thrombophilia)**: INR 2.5 for 3 months
- **Post-operative calf vein thrombosis without persistent risk factors**: INR 2.5 for 6 weeks
  - Continued treatment should be considered if risk factors are persistent
  - A recurrence after stopping Warfarin requires a further episode of treatment (target INR of 2.5)
  - A recurrence on treatment requires intensification of treatment, INR 3.5 or alternative anticoagulation treatment (evaluation for carcinoma, the Antiphospholipid Syndrome, Sticky Platelet Syndrome)
**Inherited Thrombophilia**

No episode of thromboembolism

**antithrombotic prophylaxis for high risk periods**

After an episode of thromboembolism

acute events should be treated with initial heparinisation and oral anticoagulant, INR 2.5. The duration of the therapy will vary with the genetic defect, whether more than one defect is present, whether previous events were precipitated and whether other family members with the defect are thrombosis prone.

**Antiphospholipid Syndrome**

Arterial thrombosis should be treated immediately with heparin initially and then Warfarin INR 3.5, life long.

**Atrial Fibrillation**

Non-rheumatic atrial fibrillation

INR 2.5 with at least one risk factor for thromboembolism

Low risk patients, aspirin only

Rheumatic heart disease

INR 2.5

Congenital heart disease and thyrotoxicosis

INR 2.5 to prevent stroke

Cardioversion

INR 2.5 for 3 weeks before and 4 weeks after cardioversion

**Heart Valve Disease without Atrial Fibrillation**

Mitril valve prolapse, mitral annular calcification and aortic valve disease in the absence of atrial fibrillation or previous thromboembolic events, not indicated

Rheumatic mitral valve disease without atrial fibrillation, INR 2.5

**Mural Thrombosis**

INR 2.5 for 3 months following initial heparin therapy

**Cardiomyopathy**

INR 2.5, prolonged therapy recommended

**Heart Valve Prostheses**

Mechanical prosthetic valves

INR 3.5, life long

Bioprosthetic valves

Long term Warfarin not required in the absence of atrial fibrillation (consider antiplatelet therapy)

In mitral position, INR 2.5 for 3 months

In mitral position with fibrillation, INR 2.5, life long

**Ischemic Stroke**

Consider aspirin as secondary prophylaxis

**Retinal Vein Thrombosis**

Not indicated unless complicated by the Antiphospholipid Syndrome.
Peripheral arterial thrombosis and grafts
Consider aspirin as secondary prophylaxis

Coronary artery thrombosis
Consider aspirin as secondary prophylaxis

Coronary artery graft thrombosis
Consider aspirin as secondary prophylaxis

Coronary angioplasty and stents
Consider heparin as first line therapy

Alternatives
- Vena cava filters can be used to prevent pulmonary embolism in patients in whom anticoagulation is contraindicated or in whom it has failed. The use of Warfarin must be determined by individual risk/benefit analysis.
- Low dose Warfarin has been evaluated in gynaecological and orthopaedic surgery. Absolute recommendations, duration and intensity of low dose regimens cannot be given at present.

Guidelines
- Perform baseline PT/PTT/FBC and liver functions
- Start with 5mg daily for three days and request an INR. Reduce this dosage if there is a high risk present: elderly, congestive cardiac failure, liver disease or drugs that potentiate Warfarin.
- Oral anticoagulation can be commenced on day 1 in conjunction with heparin in most patients with deep venous thrombosis.
- As the initial period of treatment with Warfarin may be associated with a procoagulant state due to rapid reduction in Protein C levels, it is recommended that patients receive heparin therapy for at least 4 days and it should not be discontinued until the INR has been in the therapeutic range for 2 consecutive days.

Management in the pre-operative period
- Stop anticoagulant or perform surgery with the INR <2.0.
- If there is a risk of dangerous bleeding, then stop anticoagulation at least 3 days before surgery or reverse anticoagulation with low dose Vitamin K (check pre-operatively).
- The short term risk of thromboembolism in patients with mechanical heart valves when not anticoagulated is small, manage in the same way.
- In rare circumstances where it is necessary to continue therapy e.g. life threatening thromboembolism in patients with adenocarcinoma, reduce the INR to <2.5 and start heparin.
- Restart the warfarin as soon as the patient goes on oral intake.

Management of bleeding and excessive anticoagulation
3.0 <INR<6.0 (target INR 2.5) and 4.0<INR<6.0 (target INR 3.5)
reduce Warfarin dose or stop
restart Warfarin when INR <5.0

6.0<INR<8.0, no bleeding or minor bleeding
stop Warfarin
restart when INR <5.0

INR >8.0, no bleeding or minor bleeding
stop Warfarin
restart Warfarin when INR<5.0
if other risk factors for bleeding give 0.5 – 2.5 mg of vitamin K (oral)
Major bleeding
- stop Warfarin
- give prothrombin complex concentrate 50 units/kg or FFP 15ml/kg
- give 5mg of vitamin K (oral or intravenous)

Contraindications
- Pregnancy: embryopathy during 6 – 12 weeks of gestation. Treat with heparin for the first trimester and for 2 – 3 weeks before delivery
- Haemorrhagic stroke

Dietary guidelines
- It is important to eat a diet with a consistent amount of Vitamin K to maximize the effect of the medication
- It is important to be consistent with Vitamin K intake rather than to avoid it. The amount of high Vitamin K food eaten on a daily basis should not be changed

Low Vitamin K foods
- artichoke, asparagus, beets, red cabbage, carrots, cauliflower, celery, cilantro, com, peeled cucumber, eggplant, green beans, green pepper, mushrooms, onion, parsnip, radish, potato, summer squash, tomato, turnip

Medium Vitamin K foods
- broccoli, Brussels sprouts, endive, green cabbage, chayote, garbanzo beans, lettuce, lentils, liver, mustard greens, parsley, spinach, soy beans, tounayo, turnip greens, tziton, watercress

High Vitamin K foods
- algae, canola oil, green tea, kale, natto, seaweed, swiss chard, soy bean oil, tea from tonka beans, wheat grass powder

Foods very low in Vitamin K
- starches and breads, fruits, dairy products, meat, fish, poultry, nuts, tofu, fats and sugar

Dietary supplements which potentiate Warfarin:
- Garlic, ginger, ginko, quinine, willow bark, fenugreek, horse chestnut, red clover, sweet clover, sweet woodruff

Dietary supplements which may inhibit Warfarin:
- ginseng, devil’s claw, dong quai, green tea, papain, dan shen

Drug interactions
- If the drug change lasts <5 days either no change, minor dose reduction or omit one complete dose of Warfarin if it is a known potentiating drug.
- If the drug change lasts >5 days, check INR after the start of the new drug and adjust the Warfarin dose on the basis of that result

Drugs that enhance the anticoagulant effect of Warfarin:
- alcohol (acute ingestion)
- allopurinol
- amiodarone
- anabolic steroids
- certain antibiotics (broad spectrum agents may cause suppression of the intestinal flora)
- antiplatelet drugs (aspirin, clopidogrel, dipyridamole, ticlopidine increase the risk of bleeding)
- high dose aspirin and other NSAIDS (celecoxib, diclofenac, ibuprofen, indometacin, ketorolac, mefenamic acid, meloxicam, piroxicam, phenylbutazone and other pyrazolones, rofecoxib, sulindac and salicylates including methyl salicylate ointment and topical NSAIDS)
- chloramphenicol
- cimetidine
- danazol
- dextropropoxyphene
- disulfiram
Drugs that diminish the anticoagulant effect of Warfarin:

- alcohol (chronic ingestion)
- antiepileptics (carbamazepine, phenobarbital, phenytoin – both reduced and enhanced effects reported with phenytoin)
- azathioprine
- mercaptopurine
- colestDVamine (decreases absorption – administer 3 – 6 hours after Warfarin)
- griseofulvin
- nevirapine
- oral contraceptives
- rifampicin
- sucralfate (reduces absorption)
- vitamin C
- vitamin K (dietary)

References:
3. Kaiser Permanente. SCPMG Regional Health Education. HealthEdLink, MH-0720-E1 (on line 4/00)

"Constructive criticism, as far as the content or format is concerned, is welcome and may be sent to mvvuurenj@ampath.co.za"