INTRODUCTION

The burden of valvular heart disease is growing worldwide due to the high incidence of rheumatic heart disease in developing countries and the increase in degenerative etiologies in those industrial once. Valvular heart replacement is a milestone in the management of patients with However, significant improvements, the quest for the ideal valvular prosthesis is still ongoing.(1)

Advancement in valve repair and replacement surgeries has improved the symptoms, quality of life and life expectancy of the cardiac patients.

However, postoperatively all patients with valve replacement are required to take oral anticoagulation either temporarily or for life according to the type of the valve prosthesis to avoid the risk of valve thrombosis.(2)

Oral anticoagulant (OA) therapy provides the best thromboprophylaxis for patients with heart valve prosthesis. Since oral anticoagulants (OAs) increases the risk of bleeding, the therapy requires a careful attention to the balance between the risks of these two outcomes.(3)

In order to optimize the therapeutic effect without risking dangerous side effects such as bleeding, close monitoring of the degree of anticoagulation is required by blood testing through measuring the International Normalized Ratio (INR).(4)

The risk of severe bleeding is small but definite with the standard anticoagulation therapy in patient with prosthetic valve replacement. Any benefit needs to outweigh this risk when warfarin is considered as a therapeutic measure. Risk of bleeding is augmented if the INR is out of range (due to accidental or deliberate overdose or due to interactions).[5,6]

Several trials were started targeting lower INR in patients with mechanical prosthetic heart valves in order to lower the risk of bleeding without increasing the risk of thrombosis.

Thus, this study was conducted aiming to test the hypothesis that patients with mechanical prosthetic heart valves could be maintained on low INR profile (1.8-2.5) regarding their anticoagulation therapy.

ANTITHROMBOTIC THERAPY

Patients with prosthetic valves are at risk of thromboembolic complications, including systemic embolization, most commonly cerebral, and prosthetic thrombosis causing valve obstruction and/or regurgitation. The risk of thromboembolic events is higher with mechanical than with bioprosthetic valves, higher with mitral than with aortic prosthetic valves, and higher in the early (<3 months) versus late postoperative phase. [6,7]

Antithrombotic agents: are the drugs that reduce thrombus formation. They can be used therapeutically for primary prevention, secondary prevention, or treatment of an acute thrombosis.

They are divided into the following major groups [8]:

1. **Antiplatelet drugs.**
2. **Anticoagulant drugs.**
3. **Thrombolytic drugs"fibrinolytic drugs".**
4. **Non medical: EDTA, citrate.**

Patients with mechanical prostheses require lifelong anticoagulation with warfarin.

Mechanism of Action of Coumarin Anticoagulant Drugs:[9]

Warfarin, a coumarin derivative, produces an anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its epoxide (vitamin K epoxide). Vitamin K is a cofactor for the carboxylation of glutamate residues to γ-carboxyglutamates (Gla) on the N-terminal regions of vitamin K–dependent proteins. These proteins, which include the coagulation factors II, VII, IX, and X, require γ-carboxylation by vitamin K for biological activity. By inhibiting the vitamin K conversion cycle, warfarin induces hepatic production of partially decarboxylated proteins with reduced coagulant activity.

Carboxylation promotes binding of the vitamin K–dependent coagulation factors to phospholipid surfaces, thereby accelerating blood coagulation. γ-Carboxylation requires the reduced form of vitamin K (vitamin KH_2). Coumarins block the formation of vitamin $KH_2$by inhibiting the enzyme vitamin K epoxide reductase, thereby limiting the γ-carboxylation of the vitamin K–dependent coagulant proteins. In addition, the vitamin K antagonists inhibit carboxylation of the regulatory anticoagulant proteins C and S. The anticoagulant effect of coumarins can be overcome by low doses of vitamin K_1 (phytonadione) because vitamin K_1bypasses vitamin K epoxide reductase.

Patients treated with large doses of vitamin K_1 (usually >5 mg) can become resistant to warfarin for up to a week because vitamin K_1 accumulating in the liver is available to bypass vitamin K epoxide reductase.

Warfarin also interferes with the carboxylation of Gla proteins synthesized in bone.[10]

Although these effects contribute to fetal bone abnormalities when mothers are treated with warfarin during pregnancy, there is no evidence that warfarin directly affects bone metabolism when administered to children or adults. [11,12]

Complications of Warfarin:

1. The only common side effect of warfarin is hemorrhage (bleeding). The risk of severe bleeding is small but definite (a median annual rate of 0.9 to 2.7% has been reported) and any benefit needs to outweigh this risk when warfarin is considered as a therapeutic measure. Risk of bleeding is augmented if the INR is out of range (due to accidental or deliberate overdose or due to interactions), and may cause hemoptysis, excessive bruising, bleeding from nose or gums, or blood in urine or stool.[13]

2. **Warfarin necrosis;** when warfarin is newly started, it may promote clot formation temporarily. This is because the level of protein C and protein S are also dependent on vitamin K activity. Warfarin causes decline in protein C levels in first 36 hours. In addition, reduced levels of protein S lead to a reduction in activity of protein C (for which it is the co-factor) and therefore reduced degradation of factor Va and factor VIIIa. A rare but serious complication resulting from treatment with warfarin is warfarin necrosis, which occurs more frequently shortly after commencing treatment in patients with a deficiency of protein C. Protein C is an innate anticoagulant that, like the procoagulant factors that warfarin inhibits requires vitamin K-dependent carboxylation for its activity. Since warfarin initially decreases protein C levels faster than the coagulation factors, it can paradoxically increase the blood's tendency to coagulate when treatment is first begun (many patients when starting on warfarin are given heparin in parallel to combat this), leading to massive thrombosis with skin necrosis and gangrene of limbs. [14]

3. **Osteoporosis;** initial reports demonstrated that, warfarin could reduce bone mineral density. Warfarin use for more than one year was linked with a 60% increased risk of osteoporosis related fracture in men; there was no association in women. The mechanism was thought to

be a combination of reduced intake of vitamin K, which is necessary for bone health, and inhibition by warfarin of vitamin K-mediated carboxylation of certain bone proteins, rendering them nonfunctional [14].

4. Another rare complication that may occur early during warfarin treatment (usually within 3 to 8 weeks of commencement) is **purple toe syndrome**. This condition is thought to result from small deposits of cholesterol breaking loose and flowing into the blood vessels in the skin of the feet, which causes a bluish purple color and may be painful. It is typically thought to affect the big toe, but it affects other parts of the feet as well, including the bottom of the foot (plantar surface). The occurrence of purple toe syndrome may require discontinuation of warfarin.[15]

Drug interactions: Warfarin interacts with many commonly used drugs, and the metabolism of warfarin varies greatly between patients. Some foods have also been reported to interact with warfarin. Apart from the metabolic interactions, highly protein bound drugs can displace warfarin from serum albumin and cause an increase in the INR. This makes finding the correct dosage difficult, and accentuates the need of monitoring; when initiating a medication that is known to interact with warfarin (e.g. simvastatin), INR checks are increased or dosages adjusted until a new ideal dosage is found.

Many commonly used antibiotics, such as metronidazole or the macrolides, will greatly increase the effect of warfarin by reducing the metabolism of warfarin in the body. Other broad spectrum antibiotics can reduce the amount of the normal bacterial flora in the bowel, which make significant quantities of vitamin K, thus potentiating the effect of warfarin. In addition, food that contains large quantities of vitamin K will reduce the warfarin effect. Thyroid activity also appears to influence warfarin dosing requirements; hypothyroidism makes people less responsive to warfarin treatment, while hyperthyroidism boosts the anticoagulant effect. Several mechanisms have been proposed for this effect, including changes in the rate of breakdown of clotting factors and changes in the metabolism of warfarin.[16]

Excessive use of alcohol is also known to affect the metabolism of warfarin and can elevate the INR. Patients are often cautioned against the excessive use of alcohol while taking warfarin.

Warfarin also interacts with many herbs and spices such as ginger and garlic. All may increase bleeding and bruising in people taking warfarin; similar effects have been reported with fish oils.

Between 2003 and 2004, the UK Committee on Safety of Medicines received several reports of increased INR and risk of hemorrhage in people taking warfarin and cranberry juice. Data establishing a causal relationship is still lacking, and a 2006 review found no cases of this interaction reported to the FDA; nevertheless, several authors have recommended that both doctors and patients be made aware of its possibility. The mechanism behind the interaction is still unclear.[16]

Laboratory Tests for Coagulation Profile

Prothrombin time & INR:

The **prothrombin time** is used as a measure of activity for warfarin when used therapeutically.

The **INR**: there was a large degree of variation between the various prothrombin time assays, a discrepancy mainly due to problems with the purity of the thromboplastin (tissue factor) concentrate. The INR became widely accepted worldwide, especially after endorsement by the World Health Organization.[18]

The **prothrombin time (PT)** and its derived measure of **international normalized ratio (INR**) are measures of the *extrinsic pathway* of coagulation. This test is also called "ProTime INR" and "PT/INR". They are used to determine the clotting tendency of blood, in the measure of warfarin dosage, liver damage, and vitamin K status. PT measures factors I (fibrinogen), II (prothrombin), V, VII, and X. It is used in conjunction with the activated partial thromboplastin time (aPTT) which measures the *intrinsic pathway*[19].

Normal range:

The reference range for prothrombin time is usually around 12-13 seconds, and the INR in absence of anticoagulation therapy is 0.8-1.2. The target range for INR in anticoagulant use (e.g. warfarin) is 2 to 3. In some cases, if more intense anticoagulation is thought to be required, the target range may be as high as 3-4 depending on the indication for anticoagulation.[19]

2017 AHA/ACC focused Update of 2014 AHA ACC Guidelines for anticoagulation

Class I

1. Anticoagulation with a VKA and international normalized ratio (INR) monitoring is recommended in patients with a mechanical prosthetic valve. [20]

2. Anticoagulation with a VKA to achieve an INR of 2.5 is recommended in patients with a mechanical AVR and no risk factors for thromboembolism. [20,21,22]

3. Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage). [20,21,22]

4. Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical MVR. [20,22-25].

5. Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis. [26,27-29].

Class IIa

1. Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve. [20,22-25].

2. Anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and for as long as 6 months after surgical bioprosthetic MVR or AVR in patients at low risk of bleeding. [27-29]

Class IIb

1. A lower target INR of 1.5 to 2.0 may be reasonable in patients with mechanical On-X AVR and no thromboembolic risk factors. [30]

2. Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding. [31-33]

3. Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily.

Class III: Harm

1. Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses. [34,35,36]

Pathogenesis of Mitral valve disease

The leading cause of mitral valve disease is rheumatic fever, causing post-rheumatic deformities. Other etiologies include congenital and degenerative mitral valve stenosis and regurge, severe mitral annular and/or leaflet calcification and cases related to previous implanted prosthesis or commisurotomy.(37)

Rheumatic valvular disease causes diffuse thickening of the valve leaflets by fibrous, or fibrocalcific distortion, with fusion of one or more valve commisures, and fusion and shortening of the subvalvular apparatus. This combined with increasingly rigid cusps results in narrowing of the valve.(37)

The area of the normal mitral valve orifice is 4-6 cm2. In patients with mitral stenosis, when the valve area approaches 2 cm2 or less, a diastolic transvalvular gradient is present between the left atrium and ventricle. With progressive mitral stenosis, transvalvular pressure gradient increases. Mitral transvalvular flow depends on cardiac output and heart rate. Shortening of diastolic phase in increased heart rate causes symptoms by reducing forward cardiac output. Mitral stenosis develops gradually, and may be asymptomatic for years.(37)

Mitral valve regurgitation results from inadequate mitral leaflet coaptation during systole. This allows the systolic regurgitation of blood from the high-pressure LV to the normally low-pressure LA. The regurgitating volume depends on both the size of the regurgitant orifice and the pressure gradient between the left ventricle and the left atrium. In primary mitral regurgitation, inadequate mitral leaflet coaptation results from an abnormality in any of the functional components of the mitral apparatus. Secondary or functional mitral regurgitation results from left ventricle disease and remodeling.

The regurgitant volume causes left ventricular enlargement and contractile dysfunction. Left ventricle dilation may cause enlargement of the mitral annulus and the regurgitant orifice, increasing the mitral regurgitation.[37]