



The Control of warfarin drug post-prosthetic cardiac valve replacement

Salah A. Alkhadr

Muthanna University- College of Medicine

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Abstract:

Depending on producing the scientific research on the clinical work in the hospitals, And the Academic work that based on guideline American collage of chest Physicians (ACCP) and the national heart the British society of hematology, And (ACC/AHA) 2015 for giving warfarin drug oral anticoagulation control prevention risk of bleeding and thromboembolism to keep on life's people, After post implantation of prosthetic valve, Requires optimal consideration for anticoagulation, the current guideline recommends warfarin on all cardiac valve replacement, So most people in Iraq have taken a daily dosage from that (1mg–5mg) orally, Moreover take care this drug interaction with food and another drugs and it has another uses prevent ischemic stroke in atrial fibrillation (AF), Or venous thromboembolism (VTE), Deep vein thrombosis (DVT) after myocardial infarction (MI), This study included 52 patients' in different ages and analysis, Concentration of the research is on the patients who make these operations cardiac replacement valve 36 cases randomized (men 19 and 17 women), So some people received warfarine under control without any risk, But the others have some complication So adding antiplatelet (Aspirin or dipyridamole, Limited time aspirin) with warfarin reduced the thrombosis and total mortality (death), INR (BT, PT, PTT) has a very important role in checking patients prophylactic in the safe International Normalised ratio (INR) < 1.5 and in preparing operation Can be achieved by stopping anticoagulants 4 days before and starting again on the same day after the procedure. The after operations ratio of INR changes into 2-3 after giving warfarin to the patient from physician good ratio , Finally in the state of risk thromboembolism the INR Will be 2-3.5 maximum. After all these procedures the patient should take a drug to live a long time.

Aim:

Our first goal in the research is to keep patients a life and reach to the Optimal therapeutic rang seriously after

operation to prevent risk bleeding and thrombosis and decreased incidence of deaths.

Introduction:

Warfain is the oral anticoagulant of choice, For it is reliably effective and has the lowest incidence of adverse effects[1,2]. The group coumarin

anticoagulants, Which include **warfarin** [WAR-far-in], Vitamin K antagonists, Warfarin inhibits the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X), Peak effects delayed for (72 to 96

hours) readily absorbed from the gastrointestinal tract (100% bioavailability with little individual patient variation) [1,2]. Dose (1mg-10mg orally), Metabolism in the liver, Major complication of treatment bleeding, Consist in researcher uses in Prosthetic valves require consideration for anticoagulation postoperatively to prevent thrombotic events[3,4]. The traditional method of anticoagulation is warfarin which requires frequent blood test to check bleeding time (BT) prothrombin time (PT), Partial thromboplastin (PTT) and International Normalsed ratio (INR).[7] American College of Cardiology and American Heart Association (ACC/AHA) have a guideline to show the adequate anticoagulation level for each position depending on the valve type, Mechanical (The most widely used mechanical valves are made from paralytic carbon,

Which has been used for over 30 years), Or biologic (Tissue valves are made with tissues from porcine (pig) heart valves or bovine (cow). [10,4] However, anticoagulation is not without a risk. As mentioned earlier, Frequent blood testing is required and being off the target level exposes patients to risk of thrombosis and bleeding. Also, Patients who are on anticoagulation have restrictions on activities to prevent bleeding events which limits lifestyle to the young patients. Warfarin carries a risk during childbearing never be used during pregnancy, Because it is teratogenic and can cause abortion as well as birth defects. [1,2,3,4] Which necessitates conversion to alternative anticoagulation method. Will discuss the current guideline and show evolving new evidence which may change the way of anticoagulation with prosthetic valves.

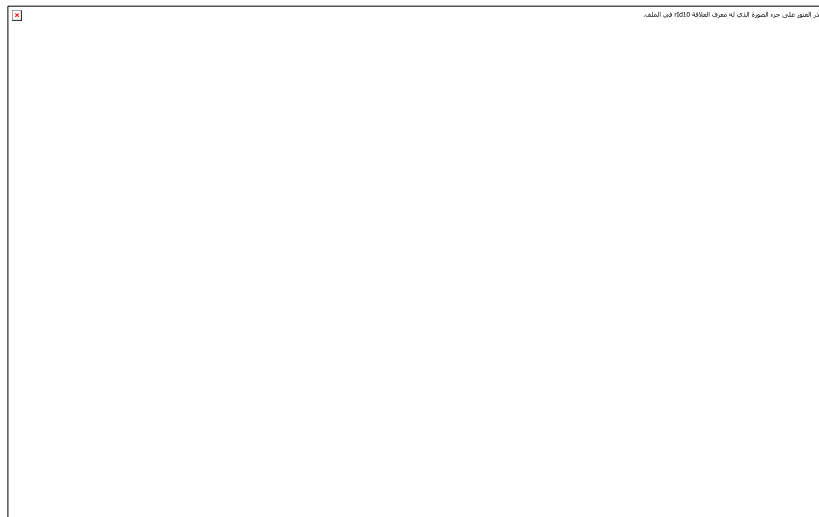


Fig (1): [1,2] [16,17,18]



Method and material:

52 patients who take warfarin have been composed in different reasons but the concentration of the research is on the patients who make these operations cardiac replacement valve 36 cases (men 19 and 15 women) with aortic valve replacement (AVR group), Cases with mitral valve replacement (MVR group) and cases with double valve replacement (DVR group) and they have been followed by direct work, Using patient files, Getting information, Recheck themselves in the hospital, Taking dosage drug, And the lifestyle and food of the patients for one year, Most patients take warfarin (5-10 mg) at the beginning and then we depend on INR degree in Iraq after checking their state most patients take (1-5mg) warfarin those who make operations in different times cardiac replacement valve and the patient have been divided in to four groups in randomized shape 1) taking drug from physician warfarin (2mg +Aspirin 81-100mg) low dosage enteric coated Antiplatelet 2) (3 mg warfarin + dipyridamole 75 mg Antiplatelet) 3) 4mg alone warfarin 4) 5mg alone warfarin, in order to avoid blood bleeding, Thrombosis and follow guideline American heart Association

(AHA/ACC),Text Book) to keep the patient's life without problems. In one daily dosage with recheck INR-PT weekly in the first month and after that every two week we notice in the first three month gradually to the year the state was peacefully and no risk, 30% Without thrombosis the (INR 2-3) without risk, The second group the patient will be peacefully for one year and the thrombosis 20% Without risk or bleeding, The third and fourth there was a bleeding because the increasing (INR to 7) in the long time, So the INR must be reduced 2.5-3 the normal standard, Subsequently included in the analysis, Oral anticoagulation alone, Or the addition of antiplatelet drugs, Has been used to minimize this risk. As a means of improving the efficacy of antithrombotic therapy after cardiac valve implantation, Anticoagulation has been augmented with an antiplatelet agent. Our first target are similar to the guidelines to use antiplatelet therapy for patients receiving mechanical valves and bioprosthetic valves with high risk factors such as atrial fibrillation, Venous thromboembolism, Left ventricular dysfunction, And hypercoagulable state. Risk of bleeding

was the lowest with low dose aspirin, similar.
Dipyridamole and the benefits were



Table 2: Dosage adjustments for patients on warfarin maintenance therapy (Target INR 2.0 – 3.0 or 2.5 or 3.5, No significant bleeding) : British Columbia (BC Guidelines.ca)

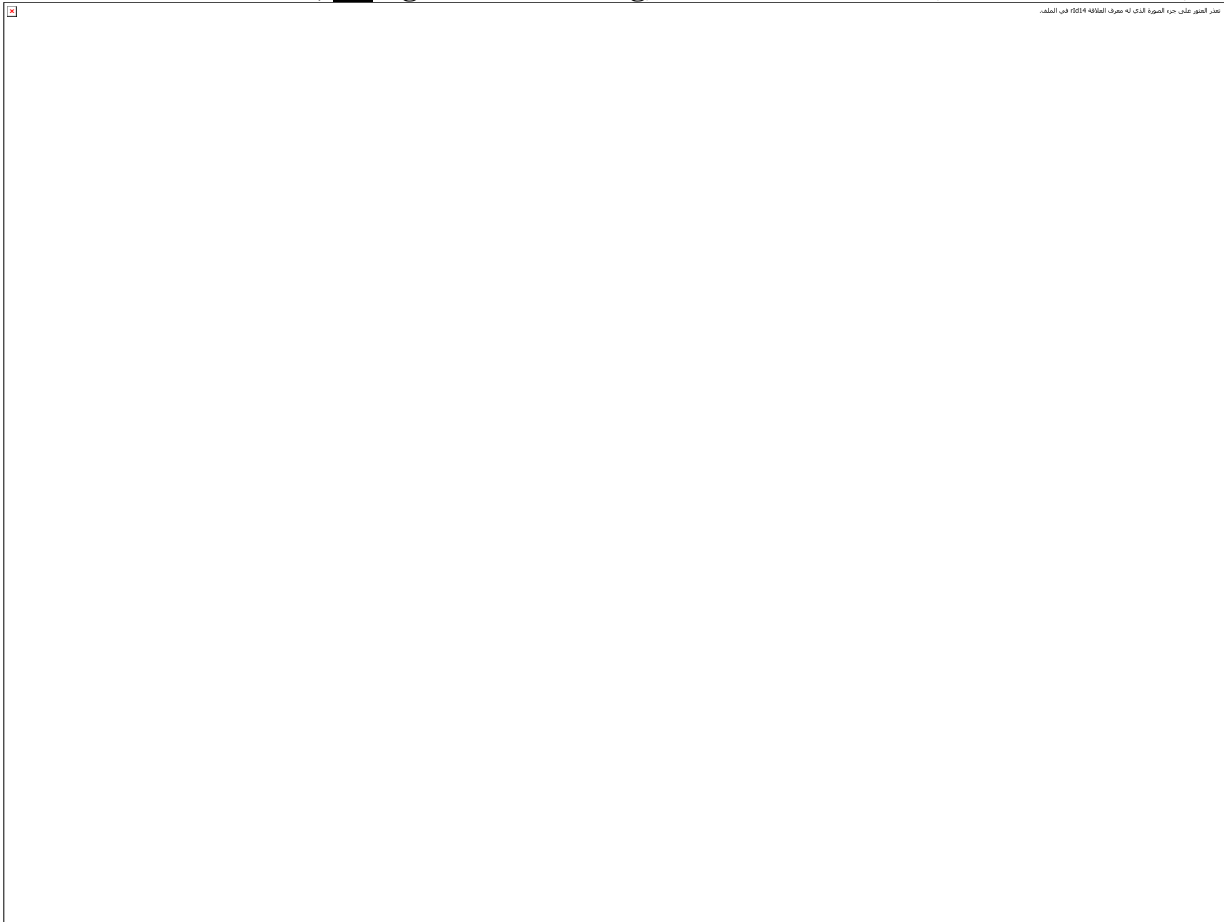
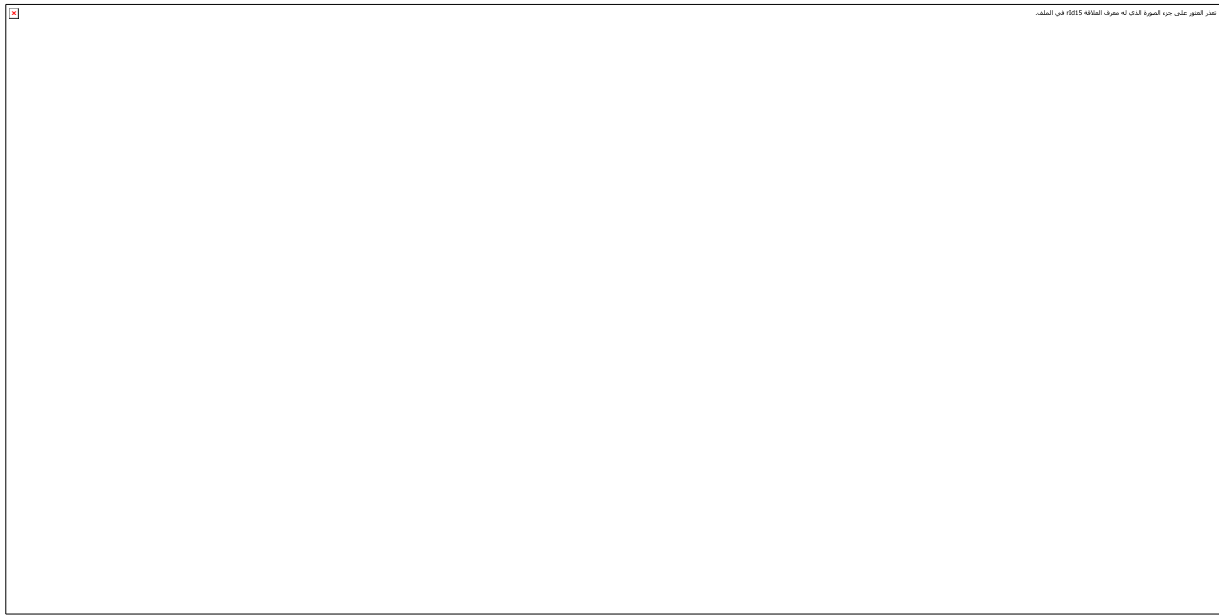


Table: 3 Target INR is 3.0 in American Heart Association (AHA)/American College of Cardiology (ACC) guidelines and in the Ninth American College of Chest Physicians (ACCP) consensus and 3.0 or 3.5 in European Society of Cardiology (ESC)/European Association of Cardiothoracic Surgery (EACTS) guidelines, Which makes little difference in practice (Current recommendations for anti-thrombotic therapy following surgical prosthetic valve replacement) :European heart journal-www.cardiostim.com



Abbreviations :

- AF : Aterial fibrillation.
- DVT : Deep vein thrombosis.
- VTE : venous thromboembolism.
- INR : international normalized ratio.
- RCT : randomized controlled trial.
- TE : thromboembolic events.

**Table 4 : Regimen for Subsequent Maintenance Dosing Using Warfarin
Target range of INR 2 – 3* (weekly)**

Initiation of therapy:

Warfarin is usually started at a dose of 5–10 mg. The dose is then titrated to

achieve the desired target INR. Because of its delayed onset of action, Patients

with established thrombosis or those at high risk for thrombosis are given

concomitant treatment with a rapidly acting parenteral anticoagulant, Such as heparin, LMWH(low molecular Wight

INR – PT:

The INR (international normalised ratio) is a good indicator of effectiveness and risk of bleeding during warfarin therapy and is best kept at about 2.5, With a target range of 2.0-3.0, For most clinical indications, Although higher levels may be better for certain patients. The lower limit of

Side Effects:

Like all anticoagulants, The major side effect of warfarin is bleeding. A rare complication is skin necrosis. Warfarin crosses the placenta and can

Risk Bleeding and treatment:

At least half of the bleeding complications with warfarin occur when the INR exceeds the therapeutic range. Bleeding complications may be mild, Such as epistaxis or hematuria, Or more severe, such as retroperitoneal or gastrointestinal bleeding. Life-threatening intracranial bleeding can also occur. To minimize the risk of bleeding, The INR should be maintained in the therapeutic range. In asymptomatic patients whose INR is between 3.5 and 4.5, Warfarin should be withheld until the INR returns to the therapeutic range. If the INR is >4.5, A therapeutic INR can be achieved more rapidly by administration of low doses of sublingual vitamin K. A vitamin K dose of 1 mg is usually adequate for patients with an INR between 4.9 And

heparin .Harrisons' Internal medicine 2008 p.112-6. [5]

this target range recognizes a threshold level for effectiveness, While the upper limit is set to minimise bleeding. Australasian Society of Thrombosis and Haemostasis Consensus guidelines for warfarin therapy. [5,12,13]

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cause fetal abnormalities. Consequently, warfarin should not be used during pregnancy. Harrisons' Internal medicine(2008 p.112-6). [4]

9, Whereas 2–3 mg can be used for those with an INR>9. Higher doses of vitamin K can be administered if more rapid reversal of the INR is required or if the INR is excessively high. Patients with serious bleeding need more aggressive treatment. These patients should be given 10 mg of vitamin K by slow IV infusion. Additional vitamin K should be given until the INR is in the normal range. Treatment with vitamin K should be supplemented with fresh-frozen plasma as a source of the vitamin K–dependent clotting proteins. For life-threatening bleeds, Or if patients cannot tolerate the volume load, Recombinant factor VIIa or prothrombin complex concentrates can be used. Harrisons' Internal medicine (2008 p.112-6) .[4,3,7,8,11]

RESULT:

Improved design has greatly reduced the thrombogenicity of mechanical prosthetic heart valves, But the need for effective, Lifelong warfarin therapy remains because systemic embolism is still the main source of late mortality and morbidity. The risk is determined by the type of valve and its position (higher for mitral than aortic valves, Greatest when both are replaced). Tissue valves, by contrast, Are almost free of thromboembolic complications, Except during the first three months. The American College of Chest Physicians recommends an INR of 2.0-3.0 For recent-model bileaflet or tilting disc valves, And 2.5-3.5 for older and more thrombogenic valves that have a caged ball or disc; Patients with a newly placed bioprosthetic (tissue) valve require three months of warfarin and an INR of 2.0-3.0. However, In the research, Because the evidence is incomplete, It remains prudent to retain a target range of 2.5-3.5 For most

("low-risk") prosthetic valves while aiming higher (3.0-4.5) for older and more thrombogenic models, Provided there is no contraindication. This research is consistent with recent recommendations from the British Society for Hematology. Antiplatelet drugs alone are ineffective, But combining dipyridamole (75mg/day) improve 20% or aspirin (81-100 mg/day) with warfarin reduces the risk of systemic embolism 30%. So the Reduction in thromboembolism in the warfarin plus dipyridamole group (20% -10 patient], Or as compared with warfarin plus aspirin (30% patient-10), Or warfarin alone (74% patient- 16). Combination is perhaps best avoided, Except in patients considered to be at unusually high risk of systemic thromboembolism (more than one mechanical valve, Previous embolism, Associated AF atrial fibrillation). So we depend on guideline .[7,16,12]

Current Guideline:

The latest guideline from ACC/AHA in 2008 on anticoagulation for prosthesis is as follows. [7]

2.1. Class I

heart valves and those patients with biological valves who have risk factors. (1)After aortic valve replacement (AVR) with mechanical prostheses, warfarin is indicated to achieve an INR of 2.0 to 3.0. If the patient has risk factors, warfarin is indicated to achieve an INR of 2.5 to 3.5.(2)After mitral valve replacement (MVR) with mechanical valve, is indicated warfarin to achieve an INR of 2.5 to 3.5.(3)After AVR or MVR with a bioprosthesis and

no risk factors, aspirin is indicated at 75 to 100 mg per day. With risk factors, warfarin is indicated to achieve an INR of 2.0 to 3.0.(4)For those patients who are unable to take warfarin, aspirin is indicated with a dose of 75 to 325 mg per day. The addition of aspirin 75 to 100 mg once daily to therapeutic warfarin is recommended for all patients with mechanical.

2.2. Class IIa

(1) During the first 3 months after AVR with a mechanical prosthesis, it is reasonable to give warfarin to achieve an INR of 2.5 to 3.5.(2)During the first 3 months after bioprosthesis, it is

reasonable to give warfarin to achieve INR of 2.0 to 3.0.

2.3. Class IIb

(1) In high-risk patients with prosthetic heart valves in whom aspirin cannot be used, it may be reasonable to give clopidogrel (75 mg per day) or

Drug interaction:

with warfarin therapy are a common and significant cause of morbidity and mortality and should be considered whenever starting or stopping a drug (particularly antibiotics). With expert advice it may be possible to predict a dose effect. In general, dose adjustments should only be made after checking the INR at 48-72 hours after initiating an interacting medication, The INR should continue to be monitored every 48-72 hours for the course of interacting medication therapy or until INR is again confirmed stable.

warfarin to achieve an INR of 3.5 to 4.5.

low-dose aspirin (81 to 100 mg daily) and a target INR of 1.8 to 2.5. In this study the rate of reliable anticoagulation was only 33% to 36%.[6]

In assessing potential drug interactions, consider all concomitant therapy including herbal/ complementary and over-the-counter medications.

□ Dramatic changes in diet can affect the INR due to varying vitamin K levels within different foods (e.g. green leafy vegetables are high in vitamin K).

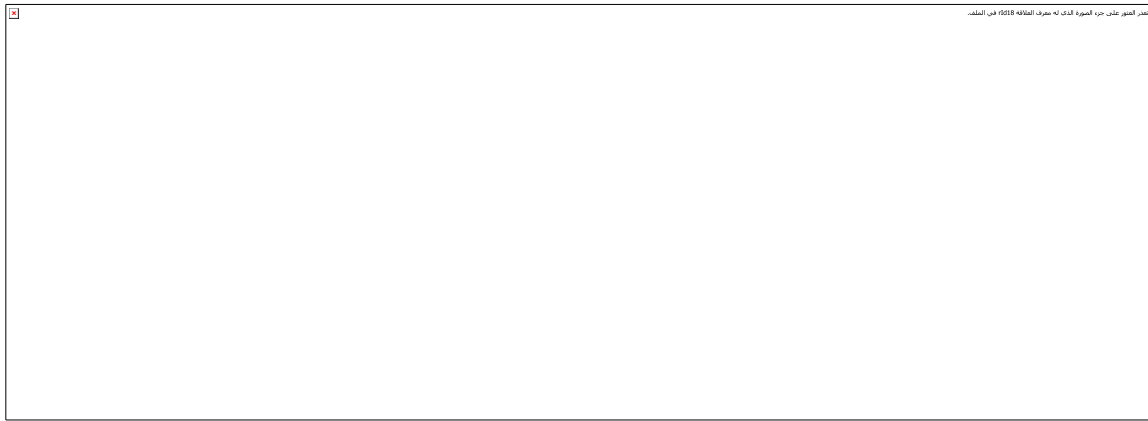
□ Altered health status (e.g. acute illness or worsening chronic renal or hepatic impairment) may alter response to warfarin due to effects on the synthesis of clotting factors or changed metabolism of warfarin.

(Queensland Health Warfarin Working Party 2012) [5,20,21,13].

Table 5 : Food interaction with warfarin

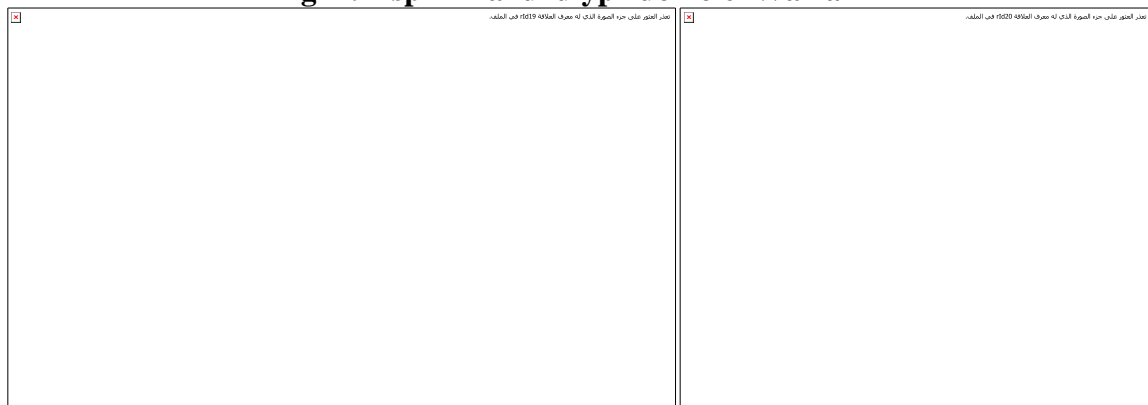
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Table 6 : Medications which can increase the Risk of bleeding



Queensland government Guideline for warfarin management 2012

Fig 2: Aspirin and diypyridomole Warfarin



Typical odds Ratio (Asp: long & Dipy: short) centerline Risk

Discussion:

The research meta-analysis is that the addition of an antiplatelet agent, Either aspirin or dipyridamole, To warfarin in patients with prosthetic heart valves reduces the risk of death and systemic thromboembolic events. The analysis showed that dipyridamole and aspirin reduced the risks of death and thromboembolism similarly. The risk of major bleeding is increased with both dipyridamole and aspirin. Although the point estimate of bleeding risk seemed to favour aspirin over dipyridamole and for trials performed , There was no evidence of research heterogeneity. Lower-dose (100 mg or less) aspirin may have the lowest bleeding risk. These results are consistent with the randomized trial by

compared the effect of a low (INR 2.0 to 3.0) or high (INR 3.0 to 4.3) degree of anticoagulation in combination with dipyridamole (75 mg/day) and aspirin (100 mg/day) in patients with heart valve replacement. The rates of thromboembolic events were similar between the low and high INR groups although there were very few events overall. The risk of bleeding, however was less with the lower target INR (3.8) , They concluded that a lower INR (2.0 to 3.0) used conjointly with platelet inhibitors was effective and safer than a higher target INR. The most recent trial included young patients (mean age of 35 years) with primarily rheumatic heart disease who underwent mechanical valve replacement. The risk of major

bleeding was only 0.4%. In addition the

Conclusion:

Valve implantation requires consideration for anticoagulation postoperatively. A new generation of valves is currently being tested to decrease the bleeding events without increasing the risk of thromboembolism and valve thrombosis. There are cases such as pregnancy or major bleeding

used.

which require augmentation of anticoagulation. The anticoagulation regimen maybe tailored to each individual case considering the risk and the benefit. It is important for physicians to understand the risks and to discuss these risks with the patients.[15]

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الخلاصة:

يعتمد في تقديم البحث العلمي على التطبيق العملي في المستشفيات. وعلى العمل الأكاديمي العلمي وعلى الدليل والمنهج العلمي الأمريكي الكلية الأمريكية لأطباء الصدر (ACCP) والجمعية القلب وعلم الدم الأنكليزية الوطنية وجمعية القلب الأمريكية 2015 عند إعطاء دواء الوارفارين عن طريق الفم مضاد للتجلط وضبط والسيطرة لمنع خطر النزيف والتجلط الدموي للحفاظ على حياة الناس بعد العمليات تغيير صمامات القلب لذلك يتطلب سيطرة مثالية وإجراءات لإدارة مضادات التجلط مع حساب والتوجيه من الدليل والمنهج الأمريكي من التوصيات عند تغيير كل أنواع الصمامات القلب. كذلك أغلبية الناس في العراق يتناولون دواء الوارفارين يوميا جرعة من (1-5 ملغم) عن طريق الفم بالإضافة أخذ الانتباه التداخلات الدوائية والطعام والأدوية الأخرى بالإضافة الى استعمالات أخرى للدواء لمنع السكتات القلبية وارتجاج الأذنين القلب (AF) والتجلط الدموي وأنسداد الأوردة (VTE) وتجلط الأوردة العميقة (DVT)، وأحتشاء عضلة القلب المفاجئ حيث تم البحث بجمع 52 مريض بمختلف الأعمار والتحليلات المختبرية، التركيز في البحث على المرضى اللذين عملوا عمليات تغيير الصمامات عددهم 36 مريض بصورة عشوائية (17 امرأة +19 رجل) لأنه المرضى يأخذون دواء الوارفارين تحت سيطرة التحليل المختبري بدون خطر. ولكن هناك ناس يأخذون الوارفارين بدون سيطرة وضبط مختبري لذلك تحصل تأثيرات وعوارض جانبية بأضافة مادة دواء مضاد لتلاصق الصفيحات الدموية (Antaplatat) Aspirin, diypri domole مع الوارفارين و(الأسبرين يكون بصورة محدودة) للتقليل من خطر الجلطات الدموية والتقليل من الوفيات، INR -PT هذا التحليل الأساس يلعب دورا رئيسي في ضبط والسيطرة والوقاية من النزيف والجلطات الدموية والطبيعي 1.5 < بشكل رئيسي عند تحضير المريض الى العمليات يجب ان يوقف الدواء قبل 4 ايام وبعد العمليات 4 ايام. لذلك بعد العمليات يجب ان يستقر INR من (2-3) بعد إعطائه من قبل الطبيب المسموح به، وختاما في الحالات التي يعاني خطر الجلطات الدموية INR يصبح (2-3,5) كحد أقصى المسموح به بعد كل هذه العمليات وعلى مدى حياة المريض يتناول دواء الوارفارين.