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RESEARCH ARTICLE

THE CHALLENGES OF CHRONIC ANTICOAGULATION IN PATIENTS WITH PROSTHETIC HEART VALVES

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ABSTRACT

The vitamin K antagonists (VKA) had been the sole option to reduce or prevent the mechanical prosthetic valve thrombosis and thromboembolic phenomena for last several decades. Their chronic usage can lead to both bleeding as well as thrombotic complications. As the therapeutic window for the drug levels is very narrow, VKA therapy needs close monitoring and periodic blood testing (PT-INR). Patients have to follow bothersome diet restrictions. Patient-education and co-operation are paramount for maintaining the INR in the prescribed safe range. The recommendation for bridging therapy when the patients with mechanical valves are subjected to any procedure or surgery is not standardized and such instructions are often confusing to patients, family members and ill-trained health professionals. The management of special populations such as the pregnant and the elderly continue to be very challenging. Anticoagulation is generally avoided in those with bioprosthetic valves unless there is atrial fibrillation. An early clinical trial with rivaroxaban in patients with bioprosthetic valves and atrial fibrillation (RIVER trial) proved it to be non-inferior to warfarin. The role of newer oral anticoagulants in patients with prosthetic valves is the current focus of research. With large number undergoing transcutaneous aortic valve implantation (TAVI) which is a bioprosthetic device, deciding what constitutes the optimal anticoagulant for them has become an emerging clinical challenge.

Keywords: Prosthetic valves, Warfarin, DOACs, oral anticoagulants

INTRODUCTION

Over last several decades the vitamin K antagonists (VKA) remained as the only option to reduce or prevent the prosthetic valve thrombosis and thromboembolic phenomena. Their usage on chronic basis has the potential for bleeding complications as well as sub-therapeutic levels leading to valve thrombosis and stuck valves. VKA therapy needs close monitoring, repeated blood testing and is associated with some bothersome food restrictions posing challenges to the patient as well as the physicians caring for them[1].The aim of this review is to have a relook at the status of anticoagulation practices and the likely challenges when used for the patients on mechanical prosthetic valves, in the light of emergence of newer molecules in the recent past.

SCIENCE BEHIND ANTICOAGULATION:

There are two major groups of oral anticoagulants in current clinical practice as follows:

1. Warfarin, Acenocoumarol (nicoumalone) and phenprocoumon: They act by Inhibition of synthesis of Vitamin K dependent factors or by modification of their properties in liver.

2. Direct thrombin inhibitors, direct factor X a inhibitors and factor-XI a inhibitors: They act by prevention of formation of fibrin clot.

Table-1 shows the important and popular oral anticoagulant drugs every physician needs to know about.

GROUP	MOLECULE	AVAILABILITY	Special Precautions
Vitamin K Dependent Antagonists (VKA)	WARFARIN	Widely available with strengths of 1,2,2.5,3,4,5,6,7.5 and 10 mg	Leafy green vegetables, Fruits like avocado and kiwi, cabbage can affect the PT test value
	ACENOCOUMAROL (Acitrom-Abbott)	Available as 1, 2, 4 mg tablets	This is found to have greater INR stability, superior efficacy and safety compared to warfarin Diet restrictions like warfarin
Direct thrombin Inhibitors	DABIGATRAN	Available as 150 mg tablet (some countries have 110 mg as well)	Idarucimab is a specific antidote for Dabigatran
Direct factor X a inhibitors	RIVAROXABAN,	Available as 2.5,5,10,15 and 20 mg	Andexanet alfa is the recently introduced antidote for all direct factor X a inhibitors; FDA approved this agent
	APIXABAN	2.5 and 5 mg tablets	
	EDOXABAN	30 and 60 g tablets	
Direct Factor XI inhibitors	ASUNDEXIAN	Still under phase 2 and 3 trials	
	ABELACIMAB		

VITAMIN K ANTAGONISTS: The coumarin derivatives-warfarin, phenprocoumon and acenocoumarol are the common preparations under this category. They act by inhibition of vitamin K epoxide reductase, thus preventing the gamma-carboxylation of factors II, VII, IX, X, protein C and S which are all dependent on vitamin K. The therapeutic range is narrow and hence, appropriate levels have to be ascertained and titrated by periodic PT and INR tests.

ACENOCOUMAROL: Acenocoumarol is mono-coumarin derivative of the racemic mixture of R (+) and S (-) enantiomers. It is rapidly absorbed from gastrointestinal tract, reaches peak concentration in 2-3 hours and has a half-life of 10.9 (±1.5) hours. Elimination is by renal route (60%) and via stools (29%). The duration of action is about 2 days. It is only a little dependent on CYP2C9 enzyme system. It is given once daily at a fixed time of the day. It is usually started at 4 mg daily and titrated to therapeutic range over a few days. When early anticoagulation is needed it is advisable to overlap the initial 2 to 3 days with heparin after starting of the first dose. Long term maintenance is done looking at the PT/ INR once in a month for most patients. It is effective and reasonably safe at all ages. It has the advantage of more stable anticoagulation effect compared to warfarin. Severe hepatic or renal dysfunctions are contra-indications for its use.

WARFARIN: It is structurally different from Acenocoumarol providing anticoagulant action that is less stable than the laterIt is absorbed rapidly and completely from gastrointestinal tract, reaching its peak concentration in about 4 hours. Almost all of it is protein bound. It has a long half-life of 30 to 80 hours and duration of action is as long as 5 days. About 90% is eliminated renally. Dependence on CYP2C9 enzyme system is unique to its metabolism. It has longer shelf life than acenocoumarol[2]. In SPORTIF study, Acenocoumarol provided stable therapeutic range in higher percentage of patients compared to warfarin. Incidence of supra-therapeutic values was significantly higher in the warfarin group[3].

PROTHROMBIN TIME TEST [PT] & INTERNATIONAL NORMALIZED RATIO [INR]

PT, along with INR is the main parameter to monitor the level of anticoagulation while on VKAs. It denotes the time take for the blood to generate thrombin. It reflects the integrity of extrinsic and common pathways of coagulation that involve the factors II, V, VII and X. Blood samples are collected in sodium citrate tubes and the sample is not shaken after collection. Samples stored for less than 24 hours at room temperature or at more than 4 degrees Celsius have to be used. In laboratory testing it is measured in seconds of time required for the plasma of the patient to clot on adding thromboplastin (a mixture of tissue factor, calcium, and phospholipid). Most laboratories mention 10 to 13 seconds as normal range for PT. Any intentional inhibition by use of VKAs or a deficiency of the vitamin K dependent factors during pathological conditions can prolong it. For monitoring of level of anticoagulation during long term therapy with VKAs, the International Normalized Ratio (INR) has been designed by World Health Organization (WHO) to have uniform therapeutic decisions. These variations in different labs are due to use of different preparations of thromboplastin reagents. INR is the ratio of the patients PT divided by the control sample value, obtained by using the reference reagent supplied by WHO[4].

It is a good practice to decide the patient's target international normalized ratio (INR) and acceptable range in the initial visits after surgery, depending on the type and location of the mechanical valve and presence of atrial fibrillation, any hyper-coagulable states, previous thrombotic event or LV dysfunction. Table-2 below indicates the recommended target INR values for different valves at different positions.[5]

Table-2: showing recommended INR targets in patients with prosthetic valves

Type of Valve	Valve Position	Factors	INR target	Duration
Mechanical Heart valve	Aortic	Bi-leaflet, Sinus rhythm, No LAE	2.5 (2.0-3.0)	Indefinite/long term
		Prosthetic valve thrombus	3.5(3.0-4.0)	
	Mitral	Bi-leaflet/tilting disc	3.0 (2.5-3.5)	
		Caged –ball/caged-disc	3.0 (2.5-3.5)	
		Prosthetic valve thrombus	4.0 (3.5 -4.5)	
	Any	*Risk factors+ / recent systemic embolism	3.0 to 3.5 (3.0 to 4.0	
Bioprosthetic valves	Mitral	-	2.5 (2.0-3.0)	Mitral position-3 months Risk factors-long term
		Systemic embolism/LAE/Risk factors	2.5 (2.0-3.0)	

- *Risk factors: Atrial fibrillation, AWMI, LAE, Hypercoagulable states, Low LVEF*
- *Abbreviations LAE-Left atrial enlargement; SR-Sinus rhythm; Af-atrial fibrillation:*

Any patient with mechanical valve replacement is placed on life-long oral anticoagulation using a vitamin K dependent antagonist (VKA) as per guidelines[6]. VKA therapy with a target of 2.5 is a class-1 recommendation for mechanical aortic valves if no high risk factors like atrial fibrillation, prior thromboembolism, LV dysfunction, or hypercoagulable states. The target INR is 3 if these risk factors are present or the valve used is Starr-Edwards or disc valve other than Medtronic Hall without risk factors. For mitral position irrespective of type of valve, the target INR is 3. AHA also advocates use of aspirin at 75 mg daily in addition as a class 1 recommendation. The later recommendation is modified subsequently as an individualized decision based on bleeding risk[7].

In a study of medical database of 900 patients, Huang J et al observed that among Asian patients the incidence of thromboembolic events in patients with prior Mitral Valve Replacement (MVR) with INR range of 2.0 to 2.5 was not higher than a group with INR 2.5 to 3.0 and among patients who had Aortic valve replacement (AVR), the events in INR group 1.5 to 2 were no higher than those in INR range 2.0 to 2.5. They suggested that Asians are likely need slightly less intense anti-coagulation compared to the European and American populations[8].

Every patient and his family members have to be educated about the implications of maintaining the INR in a recommended range and about the dietary recommendations that have to be followed. Many hospitals run *heart valve clinics* where PT test and INR, ECG and ECHO tests are done on each patient with mechanical valve and clinical status is reviewed periodically. Patients at considerable distance are monitored over telephonic contact. Unlike mechanical valves, the Bioprosthetic valves have less life-time risk for thromboembolic risk. Anticoagulation is generally avoided in them unless there is atrial fibrillation. Many believe in putting them on long-term low dose aspirin therapy instead. The first 90-180 days of Bioprosthetic valve surgery (that is when the endothelisation is still incomplete), a short-term anti-coagulation may protect from thrombo-embolic effects (Class II B).

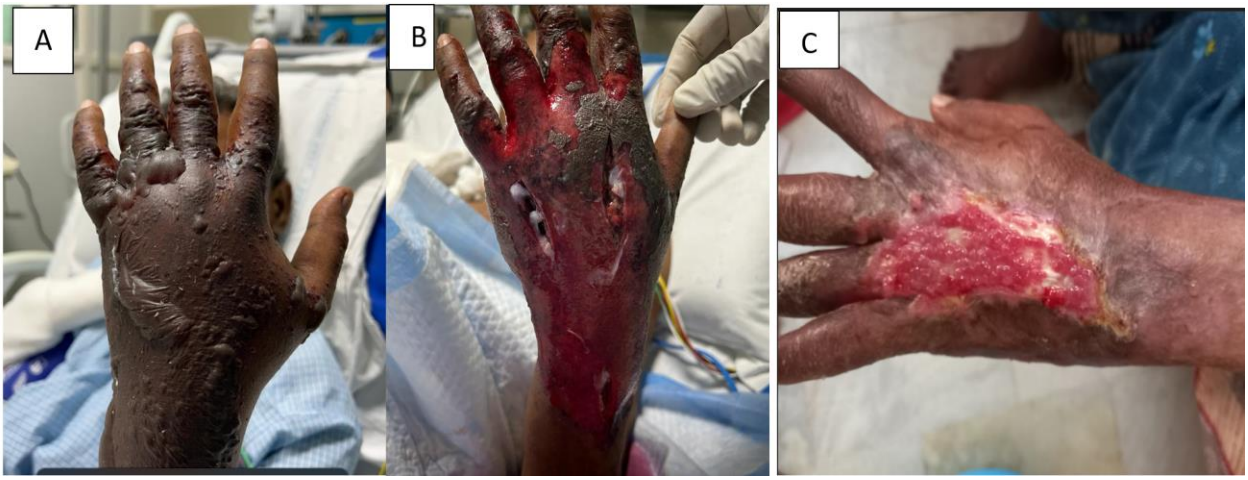
COMPLICATIONS OF VKAs:

Anticoagulant -related bleeding and thromboembolism account for about 75% of all complications after mechanical prosthetic valves. These complications are most frequent in the first 6 months of valve implantation[9]. In ISCOAT study, Palareti et al reported 7.6 per 100 patient years of bleeding complications among 2745 Italian subjects who were on warfarin in 64% and the rest on acenocoumarol at a mean follow up of 267 days. Twenty-three patients had major bleeds of which 5 had fatal outcome. Bleeding risk was higher in the elderly[10].

PROBLEMS OF EXCESS ANTICOAGULATION:

Patients on warfarin for prolonged periods can at times present with super-therapeutic values and present with minor or major bleeding episodes. Major or life-threatening bleeding can occur gastro-intestinal or intracranial can occur in about 2-10% of the users in the first one year of the warfarin treatment. At times the bleeding can occur in unexpected sites with significant morbidity in the patient (Figure-1). This is more likely when anti-platelet drugs are used concurrently in situations like recurrent embolism or co-existent atherosclerotic disease. Higher dose, elderly, racial predisposition (Black and brown populations are at higher risk), recent surgery, liver dysfunction and coagulopathy can enhance the risk for bleeding. Currently it is not a routine recommendation to use aspirin along with warfarin in patients of mechanical heart valves. It is a class IIb indication to use them in patients with co-existent coronary or peripheral atherosclerotic disease. The first step in management of a bleeding situation while on VKAs is to stop the next dose and all subsequent doses till evaluation is done. Water-soluble vitamin –K1 injection in a start dose of 5 to 10 mg is generally recommended and a single dose is effective in most cases. In life threatening situation the options may include activated charcoal within 2 hours of last oral dose, packed cell transfusion and hemodialysis[11].

Figure-1: This patient developed bleeding into compartments of forearm and hand needing surgical debridement to save the hand. A. Initial picture of the affected hand B. Day 3 of surgery; C. Day 10 of surgery.



GENOTYPING TO INDIVISUALISE WARFARIN DOSING

Warfarin is eliminated by conversion to its inactive metabolites by cytochrome P450 (CYP) enzymes in liver; CYP2C9 is the main enzyme of this system. Warfarin metabolism is variable and is dependent on genetic factors. This results in very narrow therapeutic range as well as inter-and intra-patient variability. Patients of *2 or *3 variants of CYP2C9 incases the risk of life-threatening bleeding by 2 or more times. The variants also effect the time need to reach a stable dosing. Pharmacogenomic testing of CYP2C9 or VKORC1 alleles is suggested to help in deciding a patient's response to a particular dose. Such a test needs to be only once at the commencement and it does not replace the need to monitor PT-INR testing. Several studies were favorable in recommending this test but a few other studies were not supportive. Authorities differ in their views about the need for such attesting in routine practice[12].

SUB-OPTIMAL ANTICOAGULATION

All recently implanted mechanical valves have an intrinsic tendency for thrombogenicity. With effective anti-coagulation the risk as about 2.2 per 100 patient-years and it can be further reduced by adding antiplatelet therapy[13]. Singh et al in a follow -up of 235 survivors 4.8% per patient year had thrombo-embolic events. These events were higher in those with mitral prosthesis[14].In another Indian study, in 165 post-operative cases at 1 year follow-up, thromboembolic complications occurred in 3.6% and in all of them INR was less than 1.6[15].

Frequent use of echocardiograms in follow-up visits and symptomatic patients has helped in early diagnosis and prompt fixation of the problem with better salvage of patients. Despite the standard care prescription of anticoagulants and wider use of echocardiography, prosthetic valve thromboembolism is not uncommon. Sub-optimal anticoagulation is a common problem in developing countries, especially in patients with low-education and with poor resources to procure the medication. Singh et al found that 15% of their patients showed poor compliance to anti-coagulation; among them 43% had thromboembolic complications[16].

In the author's own practice, a significant number are found to have sub-therapeutic levels of anticoagulation, despite being asymptomatic. Our unpublished data revealed that drug interruptions by patients are due to non-availability at nearest pharmacy, poor financial status of the patient, negligence to purchase the next stock in time, disruption for menorrhagia, dental procedures, confusion about doses and ill-advice by local medical practitioners. In non-emergent cases appropriate titration and patient education has to be done at all levels of care. If patient presents with partial or near total stuck valve thrombolytic therapy helps in most cases. A few unfortunate patients need surgical debridement with or without a redo valve-replacement[17].

CHALLENGES OF BRIDGING:

When a patient has to undergo major surgery or an interventional procedure, he is advised to interrupt VKA and go for bridging with heparin or low-molecular heparins[18]. This strategy is often a bit confusing to the patients and is a clinical dilemma for the cardiac surgeons and physicians. It is a complex decision as the physician has to consider the type and location of the mechanical valve, type and complexity of the procedure or surgery to be taken up, thrombo-embolic risk and minimum period of desired interruption of oral anti-coagulants. For simple superficial procedures like dental implants there no need for interruption of anti-coagulation[10]. The US guidelines do not recommend bridging for short duration of interruption if the patients are on aortic mechanical valves in absence of risk for thromboembolism (class I). For other scenarios the benefit –risk balancing is recommended on case-to-case basis (class IA)[6]. Low Molecular weight Heparins (LMW) was not specially tested for use as bridging. Intravenous rather than sub-cutaneous regular unfractionated heparins are preferred agents for more predicable outcomes, ease of rapid dose change and neutralization by protamine if needed. LMWs if used it is better to monitor anti-Xa activity. Fondaparinux is also not recommended for bridging.

PREGANCY IN PATIENTS WITH MECHANICAL PROSTHETIC VALVES [MPV]

The World Health Organization (WHO) categorized the pregnant women with MPVs as III (of scale ranging I-IV) reflecting significant risk for maternal mortality[19]. The higher risk for maternal and fetal mortality and morbidity are due to the need to maintain anticoagulation even during pregnancy due to presence of a MPV and the associated potential for thrombosis and hemorrhagic complications. The fetus is prone to still birth, miscarriage, fetal hemorrhage or warfarin-embryopathy[20]. Warfarin embryopathy is a recognized problem on use of warfarin in first trimester of pregnancy especially if a dose of more than 5 mg per day is used. It is reported in about 2% of cases[21]. It is primarily characterized by nasal hypoplasia and skeletal malformations. The features like bradydactyly and stippled epiphyses are common features. In a meta-analysis of 41 live births with this syndrome among 976 women on this medication, 29 had classical nasal hypoplasia and epiphyseal stippling. Four had neurological manifestations-hydrocephalus with learning difficulties and 4 had left lip/palate and another 4 had isolated anomalies of one organ. The fetal wastage was as much as 33.6% in this analysis.

What constitutes the best way to manage anticoagulation during pregnancy of women

on mechanical prosthetic valves is fully settled. Currently one of the 3 strategies is followed 1. VKAs continued throughout pregnancy, 2. Heparins throughout pregnancy and 3. Switch to heparins in first trimester and in last few days before delivery. The first strategy has fewest maternal complications at the expense of fewer live-births. Strategy 3 has higher maternal complications and foetopathy is not eliminated significantly. Data using LMWs is limited but appears to improve live-births. Safety of unfractionated heparins throughout of during first trimester alone is also unproven. Individualized strategy taking patient into confidence is the best strategy[22]. The British Society of Hematology recently published guidelines on management of anticoagulation in pregnant women having mechanical valves. The key points are given in the table-3 [23].

Table-3: Key points from the British Society of Hematology on anticoagulation of the pregnant women with mechanical valves

Key points
• Pre-pregnancy counselling mainly focusing on fetal and maternal risk involved • Individualized anticoagulation strategy and Prophylactic aspirin for the high-risk cases • Pregnancy is hypercoagulable state. Needs to be managed with strict compliance to advice. • Contact-information with local expert advice center has to be made available • Pregnancy management should be in centers with experience and expertise • Post-partum anticoagulation and contraception plan has to be made before discharge

DIRECT ACTING ANTICOAGULANTS (DOACS)

Introduction of the DOACs is a big step forward in the anti-coagulant therapy for they are proven as effective as warfarin with lesser incidence of bleeding side-effects, particularly intracranial hemorrhage and fatal bleeding.

DABIGATRAN: It is the first approved direct oral non-vitamin K dependent anticoagulant following the evidence of its better efficacy and safety over warfarin in RELY trial. It inhibits the cleavage of fibrinogen to fibrin by thrombin and is renally metabolized. In a short time, it became a big hit for prevention of stroke in risk patients with non-valvar atrial fibrillation. The relief from the need for periodical monitoring by a blood test and availability of a specific antidote made this molecule to stand out as a unique agent [24].

RIVAROXABAN, APIXABAN and EDOXABAN: These agents are FDA approved direct factor Xa inhibitors that act by prevention of cleavage of prothrombin to thrombin by direct binding to factor Xa. These 3 and Dabigatran together are referred as direct oral anticoagulants (DOAC). They are claimed to have lesser bleeding complication, have more ease of dosing and do not warrant very strict monitoring with periodic blood tests. There are no dietary restrictions and minimal drug-drug interactions with DOACs. However, there is no strong evidence for use of non-vitamin K oral anticoagulants (NOACs) for patients on mechanical valves. In RE-ALIGN study, Dabigatran was associated with more valve-thrombosis and bleeding complications than those on warfarin[25]. At the time of this writing the

use of NOACs is a contra-indication for patients on mechanical prosthetic valves (Class III)[6].

RECENT TRIALS ON USE OF DOACS IN VHD

- RIVER TRIAL (2020): In 1005 patients or atrial fibrillation and a Bioprosthetic valve rivaroxaban was studied for primary events and bleeding at 12 months. Rivaroxaban was proven to be non-inferior to warfarin[26].
- INVICTUS TRIAL (2022): In this recent randomized trial of rivaroxaban was compared with VKA in patients with rheumatic valvular heart disease with atrial fibrillation. VKA had lesser cardiovascular events and deaths without higher rate of bleeding[27].

ANTICOAGULATION AFTER TAVI:

ESC 2017 guidelines recommend DAPT for 3 to 6 months after TAVI followed by single anti-platelet drug life-long (Class II a). The US guidelines however suggest VKA (INR target 2.5) for at least 3 months in patients with low bleeding risk. Following TAVI about 50 % are reported to develop atrial fibrillation when anticoagulation becomes mandatory[28]. In GALILEO-RCT trial, 10 mg of rivaroxaban plus 75-100 mg of aspirin was compared with dual antiplatelet regimen in patients of TAVI without atrial fibrillation. The rivaroxaban arm had excess of all cause-mortality, thrombo-embolic events and bleeding. The trial was prematurely terminated[29]. When atrial fibrillation is associated, TAVI patients are recommended VKA by the European guidelines (class I); but NOACs are kept as alternative (class II a) after the first 3 months. It is not very clear if TAVI patients with established indication for anti-coagulation need adjunctive anti-platelet therapy[30].

It is important to realize that the reversal of NOACs action is also very challenging if the bleeding is moderate or severe and the area into which bleeding is occurring is inaccessible or critical. For patients on Dabigatran, Idarucizumab, a specific monoclonal antibody fragment, can be used as a reversal agent. Its dose is 5 grams intravenously. There a number of reports of its efficacy in saving many lives from life-threatening situations. For other NOACs like rivaroxaban, apixaban and edoxaban Andexanet alfa had been recently introduced. If there is no access for it, the other options that may be tried include 4-factor activated prothrombin complex concentrate, factor VIII inhibitor bypassing activator (FEIBA), tranexamic acid, epsilon-aminocaproic acid or desmopressin (DDAVP)[31].

EMERGENCE OF FACTOR-XI INHIBITORS

A few trials with these molecules like *Asundexian* and *Abelacimab* began in 2014 suggesting their potential use for VTE prophylaxis, after stroke or MI and in atrial fibrillation. But only in recent 2 years the results with them were promising in Axiomatic TKR, Pacific Stroke and Azaela-TIMI trials. The bleeding risk was lesser than or comparable to apixaban/ rivaroxaban. AZAELA-TIMI 71 study was stopped early on finding that Abelacimab (a factor-XI inhibitor showed very significant reduction in major and clinically relevant non-major bleeding compared to rivaroxaban in patients with atrial fibrillation. Large scale phase III trials are awaited especially for their use in patients with prosthetic valves[32].

SUMMARY & CONCLUSIONS

The vitamin K antagonists (VKA) had been the sole option to reduce or prevent the mechanical-prosthetic valve thrombosis and thromboembolic phenomena for last several decades. Their chronic usage on led to both bleeding complications as well as valve thrombosis. VKA therapy needs close monitoring and periodic blood testing (PT-INR). Patients have to follow certain bothersome food restrictions. Patient-education and co-operation are para-mount for maintaining the INR in the prescribed therapeutic range which is very narrow. The recommendation for bridging therapy when the patients with mechanical valves are subjected to any procedure or surgery is not standardized and such instructions are often confusing to patients, family members and ill-trained health professionals. The management of special population-the pregnant and the elderly continue to be very challenging. The role of newer oral anticoagulants in patients with prosthetic valves is the current focus of research. With large number undergoing TAVI (a bioprosthetic device), deciding what constitutes the best anticoagulant for them has become an emerging new challenge.

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