

# Oral Anticoagulation after Mechanical Heart Valve Replacement: Low Intensity Regimen can Make the Difference

Michele Torella<sup>1\*</sup>, Daniele Torella<sup>2</sup>, Gianantonio Nappi<sup>1</sup>, Paolo Chiodini<sup>3</sup>, Marco Torella<sup>4</sup> and Luca Salvatore De Santo<sup>5</sup>

<sup>1</sup>Department of Cardio-Thoracic Sciences, Second University of Naples, Naples, Italy

<sup>2</sup>Molecular and Cellular Cardiology, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy

<sup>3</sup>Department of Medicine and Public Health, Second University of Naples, Naples, Italy

<sup>4</sup>Department of Gynaecology, Obstetric and Reproductive Science, Second University of Naples, Naples, Italy

<sup>5</sup>Department of Medical and Surgical Sciences, Chair of Cardiac Surgery, University of Foggia, Foggia, Italy - Casa di Cura Montevegine, Avellino, Italy

## Abstract

Despite continuous improvement in the field, the ideal prosthetic heart valve remains to be developed. Patients with mechanical prosthetic heart valves are at risk of thrombosis and systemic embolism. The incidence rate of these serious complications is significantly reduced by lifelong Oral Anticoagulant Therapy (OAC) vitamin K antagonist (VKA) therapy. Despite its undeniable benefits, VKA therapy with warfarin is affected by a number of known limitations, including bleeding complications, dietary and drug interactions, and need for international normalized ratio (INR) monitoring and dose adjustments. In particular, the optimal intensity of anticoagulant therapy remains a delicate equilibrium and continues to be an ongoing matter of debate. A significant number of trials has been published on this topic. In this review article we review the pathogenesis of OAC related complications, the evidences supporting current recommendations along with the results of major prospective randomised trials on low intensity OAC regimens and self-management. Safe and effective chronic OAC therapy after mechanical valve replacement requires a thorough examination of patients' features, optimal surgical techniques, state of the art definition of target INR levels and close surveillance. Based on our and other work, we argue that low-dose anticoagulation is safe and feasible in selected mechanical valve recipients and also it may be of benefit during pregnancy. Concurrently, evidence from most recent reports highlights that even higher risk patients' subsets may profit from low intensity protocols. These data postulate that low intensity regimen of OAC coupled with close INR monitoring can make a significant difference for low to intermediate risk patients with aortic mechanical valve replacement.

**Keywords:** Mechanical heart valve; Thromboembolism; Bleeding; Anticoagulation; Low dose; Anticoagulation

## 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 aetiologies in those industrialised [1,2]. Valvular heart replacement is a milestone in the management of patients with complex severe valvular heart disease. However, significant improvements, the quest for the ideal valvular prosthesis is still ongoing. Indeed, current tissue valves are still prone to structural deterioration, while modern mechanical valves display an inherent thrombogenic potential. Despite in nearly every study performed, mechanical valves seem to improve survival, definitive quantitative data are still lacking. In this context, the choice between the inconvenience and morbidity of oral anticoagulation therapy vs the spectre of reoperation is still the patient dilemma.

The prevention of mechanical prostheses thrombosis and thromboembolism relies not only on effective antithrombotic therapy but also on the understanding of the complex interplay between surgical procedure, amount of time from surgery, individual type and site of valvular device, number of implanted prostheses, and the patient's own risk factors [3].

In this review article we review the pathogenesis of chronic oral anticoagulation therapy related complications, the evidences supporting current recommendations along with the results of major prospective randomised trials on low intensity anticoagulation and self-management. Authors experience in this field is finally forwarded and discussed.

## A Brief Pathogenetic Overview

Exposure of both surgically damaged peri-valvular tissue and artificial surfaces to the circulating blood causes haemostatic activation within the end of the procedure. Prosthetic valves generate abnormal flow conditions, namely: trans-protesic turbulence and stagnation. High-velocity, turbulent flow causes endocardial damage through significant increases in regional shear stress. Stagnation is linked to recirculation areas on the outflow side of the device, which enhances trapping of platelets and coagulation factors. In order to overcome such derangements, a regurgitant jet, the so-called washing jet, is provided in all devices. Individual device thrombogenicity is also dependant on the size, design and materials [4]. As far as size is concerned, consistent evidence exists that the higher the surface of the device in contact with blood, the higher the risk of thrombus formation [3]. On the other side, the smaller the prostheses, the lower the effective orifice area with a proportioned net increase in turbulence [3]. Historically, three types of mechanical substitutes have been subsequently developed: caged-ball, monoleaflet, and bileaflet. Newer generation bileaflet devices are those

**\*Corresponding author:** Michele Torella, Second University of Naples, Department of Cardiothoracic sciences, Naples, Italy, Tel: +390817062521; E-mail: [michele.torella@unina2.it](mailto:michele.torella@unina2.it)

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providing less trans-protetic turbulence and stagnation, with symmetric and central blood flow. Most recent prostheses have also enhanced inlet and hinge design in order to create streamlined blood flow [5]. Finally, from the original alloy and silicone rubber structure, through the wide spread adoption of graphite-coated pyrolytic carbon surfaces and up to the newest pure pyrolytic carbon technology, several improvements have been introduced in the choice of materials for the sake of reduced thrombogenicity [5]. Despite that, the early post-operative period is plagued by a higher risk for thromboembolism, which is actually up to seven times greater in the first six months than months and years after [3,4]. Perioperative hemodynamic instability and arrhythmias, incomplete endothelial proliferation and inconsistencies of oral anticoagulation management account for this temporal pattern. When compared to aortic position, rates of thromboembolism associated with mitral prostheses are nearly doubled, mainly due to relatively larger size of the devices, higher stagnation and, usually, a more complicated patients' profile [3]. Combination of two or more devices further enhances the thromboembolic risk [4]. Several patients' features modulate the risk of thromboembolism. Dilated heart chambers' size, atrial fibrillation, low left ventricular ejection fraction, endothelial damage from rheumatic disease, previous thromboembolism or thrombotic problems, advanced age and hypercoagulable states each separately and, even worse, synergistically, provide a detrimental milieu for thrombus formation [3,4].

### Chronic Oral Anticoagulation with Vitamin K-antagonists: The Dark Side of a Life-Saving Therapy

Lifelong oral anticoagulation therapy is the standard of care after mechanical prosthesis implantation [3]. Indeed, warfarin reduces the incidence of major embolic complication by nearly 75% when compared to isolated antiplatelet therapy or no anticoagulation at all. However, achieving the desired anticoagulation is difficult because of its narrow therapeutic window. Moreover, vitamin K-antagonist drugs' effectiveness is dose dependent, but the dose-response relationship displays wide inter-individuals discrepancies and even significant variations in the individual patient over the time. There is growing evidence that an individual's warfarin maintenance is associated with clinical factors (mainly diet changes, patient compliance, co-medication, aging, hepatic and renal function, and inter-current disease) and genetic variations [6]. In this respect, polymorphisms in cytochrome P450 2C9 (CYP2C9) gene is known to affect warfarin pharmacokinetics while vitamin K epoxide reductase subunit 1 (VKORC1) gene to influence pharmacodynamics [6]. Up to date, randomized trials incorporating pharmacogenetic dosing of warfarin have been too small to draw solid conclusions about the value of genotyping. Three large ongoing trials should fill this gap in knowledge in the upcoming future [6]. As a matter of fact, dose requirements vary more than tenfold, ranging from <10 to >100 mg per week. The anticoagulant effect therefore needs to be carefully monitored, especially during the initiation of therapy. This is done by measuring the Prothrombin Time (PT) International Normalized Ratio (INR), which is a measure of three of the four vitamin K-dependent coagulation factors: II, VII and X. The most common adverse effect of warfarin is bleeding and the risk is highly related to the intensity of oral anticoagulation therapy. Warfarin-related haemorrhage is actually the single most common drug-related cause of hospitalization for adverse events among older adults in the USA (nearly 21,010 hospitalizations from 2007 to 2009) [7]. After mechanical valve replacement, thromboembolism and anticoagulant-related bleeding still continue to account for 75% of all complications [4]. Theoretically, there is overwhelming evidence that safe and

effective oral anticoagulation should be characterised by an optimal intensity and very low variability. Nevertheless, the optimal intensity of anticoagulant therapy, defined as the level at which the incidence of both thromboembolism and bleeding complication is lowest continues to be an ongoing matter of debate with a suboptimal implementation into clinical practice. On the other side, published data underscore that even in the best hands, less than 70% of the intensity measurements are within the target range while anticoagulation variability clearly proved to be an independent predictor of survival [8].

### Evidence and Lack of Evidence of Current Recommendations on Anticoagulation

The common prescription policy for patients with mechanical valve replacement declares a therapeutic range from INR 2.5 to 4.5. This large range includes a zone of higher risk for bleedings, beginning from INR 3.5. After mechanical Aortic Valve Replacement (AVR), the goal of oral anticoagulant therapy is usually to achieve an International Normalized Ratio (INR) of 2.5 to 3.5 for the first 3 months after surgery and 2.0 to 3.0 beyond that time [3,4]. Low-dose aspirin (75 to 100 mg per day) is also indicated in addition to Warfarin [3,4,9,10]. At that level of anticoagulation, the risk of significant haemorrhage appears to be 1% to 2% per year [4]. Thrombosis and thromboembolism risks are greater with any mechanical valves in the mitral than the aortic position, and, therefore, higher INR levels (2.5 to 3.5) are generally recommended for mechanical mitral valve prostheses [9,10]. These recommendations must be read with the knowledge that several biases in published investigations actually prevent any firm conclusion. The most common are: study cohort including patients implanted with different generation devices, non-randomised series without controls, lack of stratification for additional risk factors associated with the type and location of prosthetic valves, concomitant antiplatelet therapy. More importantly, the safety and efficacy of a given INR range is often derived from an intention-to-treat analysis rather than based on the intensity of anticoagulation actually achieved. Notably though adding antiplatelet therapy decreases the risk of systemic embolism or death, it concurrently results in a definite increase of the risk of major bleeding [11].

### Feasibility and Safety of Low-dose Anticoagulation: Evidence from Randomised Trials

The aim of the AREVA trial was to compare moderate oral anticoagulation (International Normalized Ratio [INR] of 2.0 to 3.0) with the usual regimen (INR of 3.0 to 4.5) after a single-valve replacement with a mechanical prosthesis, either Omniscarbon or St Jude. Patients included were between 18 and 75 years old, in sinus rhythm, and with a left atrial diameter < or = 50 mm. From 1991 to 1994, 380 patients were randomized for INR: 188 for INR 2.0 to 3.0 and 192 for INR 3.0 to 4.5. In this highly selected patient population, moderate anticoagulation provided protection against thromboembolic risk similar to that offered by a more intense regimen while significantly decreasing the risk of any haemorrhage by 38% [12].

In the GELIA study, 2,848 patients after aortic, mitral valve replacement, or combined valve replacement with a St. Jude Medical (SJM) device were enrolled between 1993 and 1999. Main exclusion criteria were contraindications to oral anticoagulation, coagulation abnormalities, pre-existing anticoagulant therapy, replacement with any valve prostheses other than a SJM valve. On the third postoperative month, patients were randomly assigned to three intensities of oral anticoagulation: stratum A, International Normalized Ratio (INR)

3.0 to 4.5; stratum B, INR 2.5 to 4.0; and stratum C, INR 2.0 to 3.5. The three distinct levels of oral anticoagulation proved essentially equivalent in terms of moderate-to-severe thromboembolic and bleeding complications [13].

Meschengieser and associates performed a prospective randomized trial comparing oral anticoagulation (INR 2.5 to 3.5) in combination with aspirin versus oral anticoagulation alone (INR 3.5 to 4.5). 503 patients were randomized either after surgery or at different variable intervals. Previous gastrointestinal bleeding and previous history of embolic episodes or suspected haemorrhagic tendency were main exclusion criteria. At a median follow-up of 23 months, the two treatments offered similar antithrombotic protection but major bleeding episodes were insignificantly reduced from 2.33 to 1.13% per patient-year favoring patients with low-intensity anticoagulation. Nevertheless, the addition of aspirin to only one treatment group prevented any firm conclusion on the effects of anticoagulation intensities [14].

Most recently, Puskas and coworkers have reported the interim results of the Prospective Randomized On-X Anticoagulation Clinical Trial (PROACT). The On-X valve is a recently developed prosthetic device with highly efficient design and state of the art materials that imply very low thrombogenicity. From September 2006 to December 2009, a total of 375 aortic valve replacement patients with elevated risk factors for thromboembolism, on the third postoperative month, were randomized, at 33 US centres, to receive lower dose warfarin (INR: 1.5-2.0) or continue standard warfarin (INR: 2.0-3.0). The INR was adjusted by home monitoring; all patients received also low dose aspirin. The incidence of stroke, transient ischemic attack, total neurologic events, and all-cause mortality were similar between the two groups. Importantly, lower dose warfarin resulted in significantly lower major and minor bleeding rates [15].

### Anticoagulation Self-Management: Evidence from Randomised Trials

INR self-monitoring and adjustment has been proposed to improve the quality of anticoagulation. Advantages of this strategy over conventional management include improved patient compliance and convenience, along with improved quality of life and greater frequency of monitoring. Higher initial costs and the need for patient training and education prevented widespread implementation of such programs. The Early Self-Controlled Anticoagulation Trial (ESCAT I) showed that INR-self management effectively reduces the INR oscillations even though this more intense control did not result in a reduced rate of bleeding complications [16]. ESCAT II study aimed to evaluate the effects of low-range INR self-management on oral anticoagulant-related complications in patients with mechanical heart valve prostheses compared with conventional-range INR self-management. This trial provided evidence that the INR target range could be reduced to 1.8 to 2.8 in patients with aortic valve replacement and to 2.5 to 3.5 in patients with mitral valve or double valve replacement. The reduced anticoagulation level resulted in fewer severe bleeding complications without increasing thromboembolic event rates. Notably the percentage of clinically relevant bleeding events (1.5%) was approximately threefold to fourfold higher than the percentage of clinically relevant thromboembolic events, even in patients with low-dose INR self-management. This observation underscored the need for a further reduction in the intensity of anticoagulation [17]. The most recent ESCAT III trial investigated the efficacy and safety of very low-dose INR self-management compared

with low-dose INR self-management. Enrolled patients performed low-dose International Normalized Ratio (INR) self-management with a target INR range of 1.8 to 2.8 for aortic valve replacement recipients and 2.5 to 3.5 for mitral or double valve replacement recipients for the first six postoperative months. Thereafter, LOW group patients continued to achieve the aforementioned INR target range, whereas the INR target value was set at 2.0 (range, 1.6 to 2.1) for the remaining patients with aortic valve replacement and 2.3 (range, 2.0 to 2.5) for the remaining patients with mitral valve or double valve replacement. Very-low range INR self-management resulted in a gratifying low incidence of thromboembolic events (<0.6%) and a slightly higher rate of bleeding complications (1%) further adding to the safety and efficacy of this therapeutic approach [18].

### Authors' Experience

In the last 15 years we have been mainly involved into clinical research aiming at establishing the most effective and safe anticoagulation regimen for patients with mechanical valve prosthesis. In particular, we performed two prospective studies on low-dose anticoagulation after mechanical heart valve replacement.

The LOWERING-IT study was a prospective, open-label, single-centre randomized controlled trial that compared the thromboembolic and bleeding events between two different anticoagulation intensity levels in low-risk patients undergoing a single aortic mechanical replacement. The two anticoagulation intensity levels were the low anticoagulation intensity, with a range INR of 1.5 to 2.5 (LOW-INR group), and the currently recommended intensity, with the standard range INR of 2.0 to 3.0 (CONVENTIONAL-INR group). Patients in the age range 20 to 60 years were eligible for the study if they presented with the following features: valve prosthesis dimension  $\geq 21$  mm, with normal ejection fraction, with a left atrium diameter < 47 mm (the latter 2 were defined preoperatively by echocardiogram), in normal sinus rhythm, and "warfarin-naïve" (ie, they had never been on warfarin before). 396 patients (197 in the LOW-INR group and 199 in the CONVENTIONAL-INR group) were consecutively enrolled on the study from January 2001 to January 2005. Anticoagulation levels were achieved with warfarin, and no aspirin was added. Median follow-up was 5.6 years. The primary outcome was assessment of non-inferiority of the low over the standard anticoagulation regimen on thromboembolic events. Secondary end point was the superiority of the reduced INR target strategy on bleeding events. The mean of INR was  $1.94 \pm 0.21$  and  $2.61 \pm 0.25$  in the LOW-INR and CONVENTIONAL-INR groups, respectively ( $P < 0.001$ ). One versus three thromboembolic events occurred in the LOW-INR and CONVENTIONAL-INR, respectively, meeting the noninferiority criterion ( $P = 0.62$ ). Total haemorrhagic events occurred in 6 patients in the LOW-INR group and in 16 patients in the CONVENTIONAL-INR group ( $P = 0.04$ ). The major findings from this trial were: a) in a highly selected subset of low-risk patients with primary single mechanical AVR, a low anticoagulation intensity with an INR of 1.5 to 2.5 is safe and feasible; b) this low-intensity anticoagulation strategy is associated with a significant reduction of the average hemorrhagic events when compared to conventional therapy (INR of 2.0 to 3.0), without any increase of thromboembolic complication. Interestingly, this trial included different types of bileaflet prostheses highlighting the low-thrombogenicity of these devices. It is also useful to stress that in perspective, the long-term maintenance at the suggested low INR range would clearly require adjustment in these "low-risk" patients as their characteristics might change over time. Since the proportion of patients who are at low risk of thromboembolic events is considerable in relation to the total number of recipients

of mechanical heart valves, the data of the LOWERING-IT trial are important also because they begin to fill a void in the context of the other studies available so far [19] (Figure 1).

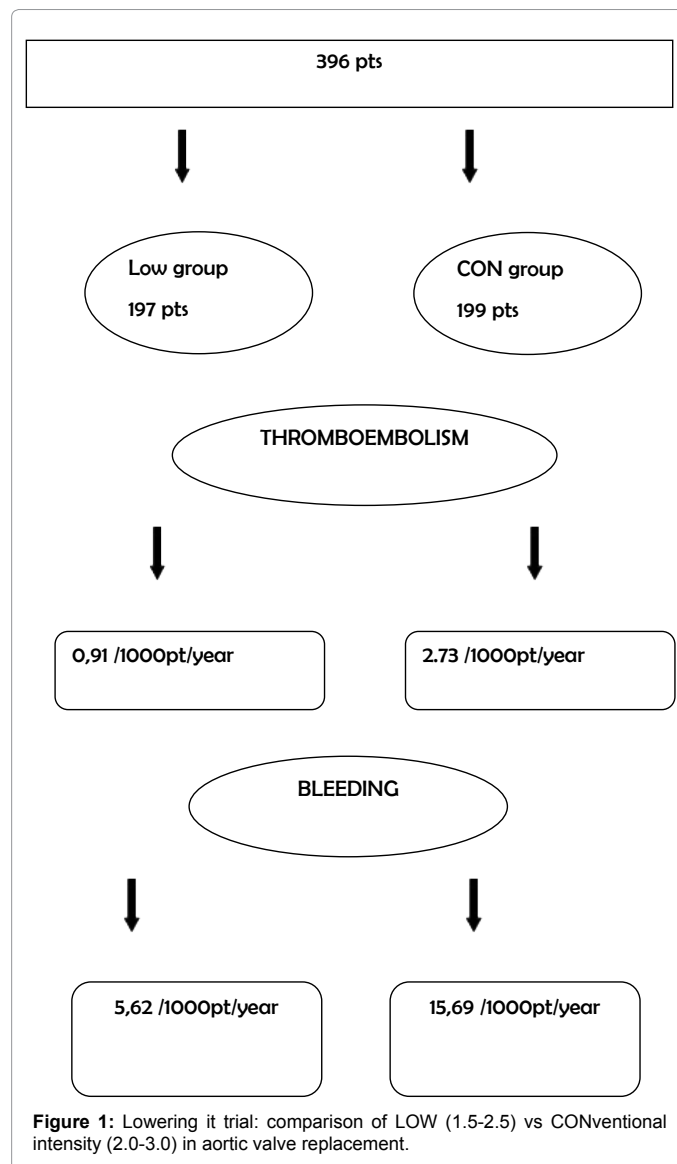
A significant issue for oral anticoagulation therapy in patients with a mechanical valve is pregnancy. Indeed, pregnancy with a mechanical valve has a high maternal complication rate. Indeed, it is associated with alterations in hemostasis and coagulability that significantly increase the risk of thromboembolic events [20]. Maternal mortality in such patients varies between 1% and 4% [20]. Coumarin derivatives are relatively safe for the mother with a significantly lower incidence of valve thrombosis than Unfractionated (UFH) and Low-Molecular-Weight Heparin (LMWH), but carry the risk of embryopathy, which is probably dose-dependent [21]. Indeed, as reported in several studies, warfarin daily dose < 5 mg allows good foetal outcomes. In a clinical situation implying tremendous ethical issues and several medico-legal drawbacks, such a counselling has to face both the limited follow-up data and the lack of consensus documents. Such discrepancies together with the limited experience of most of cardiac surgery centres have led to patient under treatment. Thus, there is a clear need for a multidisciplinary counselling in this peculiar setting. Strict patient selection, advanced expertise of anticoagulation drugs and protocols along with close long-term follow-up capabilities are prerequisites for pregnancy management and ensuring good late maternal outcomes.

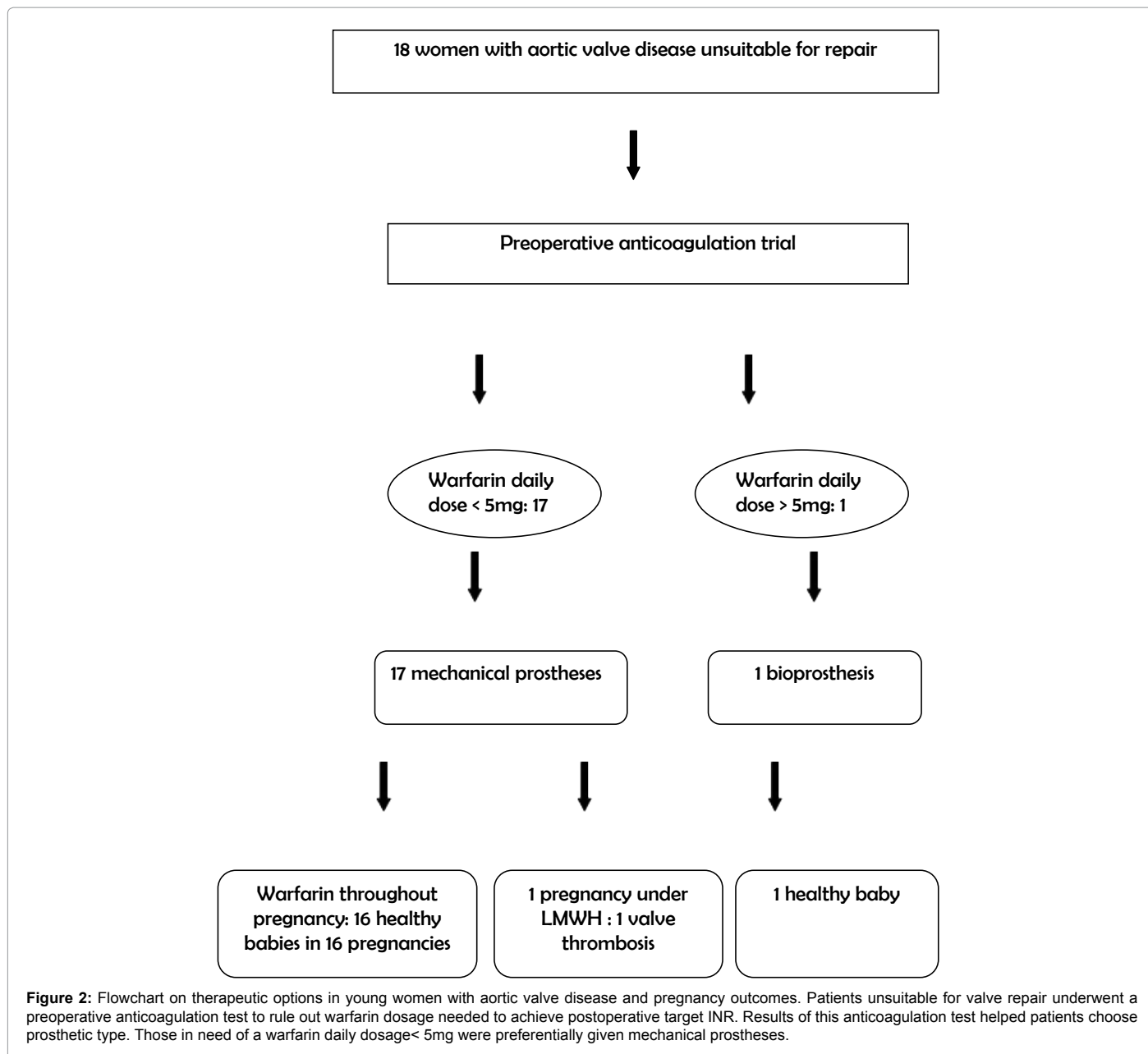
Experience at our Department dates back to more than twenty years ago and the multistage counselling initially devoted to patients who had already undergone a valve replacement and wanted to have pregnancies has been lately extended to women referred for surgical treatment [22]. Patients with aortic disease not suitable for a valve repair procedure underwent an informative counselling on the choice of valve substitute and inherent drawbacks, and namely: reduced durability of biological prostheses and need for oral anticoagulation for mechanical devices. Information was given about the risks of maternal and perinatal morbidity and mortality, and the risks and benefits of each anticoagulant treatment option. Such a counselling included also the advice that, theoretically, the safest option was to avoid pregnancy after surgery. In order to help in this decision process, patients underwent a preoperative three months trial of anticoagulation to evaluate the dose of warfarin needed to achieve the target International Normalized Ratio (INR). As described in the LOWERING-IT trial, a target INR 1.5 to 2.5 was prescribed. Selected young women achieving this target INR with a warfarin daily dose lower than 5 mg were preferentially offered a third generation mechanical device. When pregnant, such women were kept on the same low-dose sodium warfarin anticoagulation throughout all pregnancy with a weekly INR estimation and joint cardiologic and obstetric monthly evaluations. Cesarean delivery was scheduled before the end of the 37th gestational week. Warfarin therapy was discontinued only 2 days before section and restarted 1 day after surgery. As recently reported, no maternal nor foetal complications were detected in sixteen pregnancies managed by this anticoagulation protocol [23] (Figure 2).

### The Clinical Bottom Line

Safe and effective oral anticoagulation after mechanical valve replacement requires a thorough examination of patients' features, optimal surgical techniques, state of the art definition of target INR levels and close surveillance. Judicious addition of antiplatelet drugs is mandatory. Low-dose anticoagulation is safe and feasible in highly selected mechanical valve recipients. The early postoperative phase, characterised by a higher hazard of anticoagulation-related complications, needs even closer monitoring and management. Definition of effective bridging anticoagulation in this vulnerable

period is still underway. Patients in need for aortic valve replacement with new bileaflet devices are actually those expect to profit the most from low-intensity anticoagulation strategy. Overall, the number of mitral valve replacements in published studies was too low to draw valid conclusions and additional trials are necessary to determine the optimal anticoagulation intensity for these patients. Evidence from most recent reports highlights that even higher risk patients' subsets may profit of low intensity protocols. Anticoagulation self-management ensures a low variability in the level of anticoagulation. This therapeutic approach is possible for all patients, independent of age and education level, with dropout rate as low as 14.6% [18]. Increased stability of anticoagulation intensity significantly reduces the incidence of thromboembolic complications. Bleeding, though significantly reduced, still represent a dreaded complication. The risk of developing bleeding complications is highest within the first half year of valve replacement. This might imply that low intensity anticoagulation should be implemented since the very early postoperative phase. Anyhow, evidence from most recent trials is that factors other than anticoagulation per se are determinant in bleeding pathogenesis. Indeed, vessel anomalies, inadequate medical





treatment of hypertension and genetic polymorphisms that alter warfarin pharmacokinetics and pharmacodynamics have emerged as possible targets for optimised integrated therapeutic approaches [18]. Overall, we like to re-call and use for a provocative conclusion a recent sentence by Thoralf Sundt stating that “Properly applied, standard medications with up-to-date monitoring technologies shift the balance today” in favour of mechanical valves [24].

P2Y12 is a Gi-protein coupled receptor expressed on platelet membranes, which regulates ADP-induced aggregation [25]. Considering the importance of P2Y12 receptor in platelet activation, anti-platelet drugs have been designed which antagonize this receptor hence reduce the risk of anti-thrombotic events [25]. Nowadays, P2Y12 receptor antagonists have a well-established role as anti-thrombotic agents in the treatment of PCI and acute coronary syndromes [25]. Despite their recognized anti-thrombotic effects, this class of drugs is

not currently recommended per se in patients with mechanical valve replacement by the current international guidelines. However, the second cohort of the Prospective Randomized On-X Anticoagulation Clinical Trial (PROACT) will compare current oral anticoagulant therapy versus aspirin and clopidogrel only in selected lower risk patients requiring AVR. The enrolment of this cohort has been finished in May 2013 and we are awaiting the outcome of this strategy in the near future.

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