Review

Interventional Cardiology

Review of anticoagulation options for mechanical valve prosthesis

Clinical guidelines recommend lifelong oral anticoagulation (OAC) with warfarin in all patients with mechanical valves with variance in the target INR for patient associated risk factors, type of mechanical valve or implant position of the valve. Recent randomized controlled trials have demonstrated that clinicians may consider a lower OAC strategy (INR: 1.5–2.5) in low (thrombogenic) risk patients undergoing bileaflet mechanical valve replacement thereby achieving similar thromboprophylaxis yet minimizing bleeding events. Likewise, physicians may also consider a lowered OAC option in high (thrombogenic) risk patients undergoing bileaflet mechanical valve replacement yielding similar efficacy (avoidance of thromboembolic events) and improving safety (bleeding events). Finally, while advancement of novel oral anticoagulants (NOACs) has been swift in the realm of atrial fibrillation anticoagulation management, NOACs for mechanical valves are currently contraindicated due to evidence of increased thromboembolic and bleeding risk. Future studies comparing NOACs and warfarin along with newer mechanical valve construction are eagerly being awaited.

Keywords: anticoagulation • antiplatelet • mechanical valve • valve surgery

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Treatment strategies for valvular heart disease include surgical replacement, surgical repair and more recently catheter-based interventions [1]. The optimal heart valve prosthesis should be durable, nonthrombogenic, resistant to infection, easy to implant, readily available and yield normal hemodynamics. While this 'perfect' valve has not yet been identified, valve repair, when applicable, achieves excellent long-term clinical outcomes, maintains structural integrity and avoids the use of anticoagulants [2–6]. When valve repair is not an option, valve replacement with either a bioprosthetic or mechanical valve can be considered. Although long-term oral anticoagulation is not generally required in bioprosthetic valve replacement, the major short-coming is valve deterioration typically requiring reintervention [7,8]. Despite this, there are an increasing number of patients under 65 years of age undergoing bioprosthetic valve replacement with long-term results mimicking that of mechanical valve replacement [9,10]. Ultimately, to avoid oral anticoagulation (OAC) and structural valve deterioration, a valve repair strategy should be considered [5]. Patients who undergo mechanical valve replacement are at major risk for thrombus formation on the prosthetic valve and subsequent arterial thromboembolic events [11]; thus, OAC for thromboprophylaxis is considered standard therapy after mechanical valve implantation with varying intensity based on valve location, prosthesis type and patient risk factor [12,13]. The Achilles heel of mechanical valve replacement is lifetime OAC which may lead to significant bleeding events. Attempts to improve thromboprophylaxis with the addition of antiplatelet drugs (i.e., aspirin, dipyridamole) have demonstrated mixed results [14,15]. A recent meta-analysis for mainly mechanical valve prosthesis demonstrated a significant reduction in thromboembolic events with OAC and addition of one antiplatelet drug, but the perceived benefit was challenged with

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a significant increased risk of major bleeding [16]. At mid-term follow-up, contemporary (2005+) incidence of thromboembolic events has been relatively low ranging from 0 to 3.6% [17,18]. With the advent of newer generation mechanical valves, there is potential for achieving even lower rates of thromboembolic and bleeding events with either less intense OAC, antiplatelet therapy alone or potentially novel OACs (NOAC). Therefore, this review is aimed at discussing current practice trends, novel strategies and future endeavors for postoperative thromboprophylaxis for mechanical valves.

Current practice for anticoagulation

Current international guidelines generally recommend the following: low dose aspirin (74–100 mg) for all patients, OAC in mechanical aortic valves with target INR 2.0–3.0 at low-risk for thromboembolic events and OAC with target INR 2.5–3.5 in mechanical mitral valves and high-risk aortic valve patients (Table 1) [12–13,19–20]. High-risk patients are considered to be those with concomitant atrial fibrillation, previous thromboembolism, hypercoagulable state or depressed left ventricular function [21,22]. These recommendations have been partially based on older studies using more thrombogenic mechanical valves (i.e., Starr–Edwards ball and cage, Bjork–Shiley tilting disc) [23–25] along with a landmark meta-analysis by Cannegieter and colleagues [20]. Moreover, based on Massel and Little's meta-analysis, the European guidelines advise caution with the addition of an antiplatelet medication due to the increased risk of bleeding with an odds ratio of 1.58 (95% CI: 1.14–2.18) [16,26]. Several groups have demonstrated similar effectiveness with reduced OAC therapy (compared with historically target INR of 3.0–4.5 in patients with bileaflet St. Jude Medical [St. Jude Medical, Inc., Saint Paul, MN, USA]) mechanical valves, mostly in the aortic position [21,27]. These results along with previously performed meta-analyses [16,20,26] have led to the universal recommendation of targeting INR between 2.0 and 2.5 for the aortic position and 3.0–3.5 for the mitral position [12,13]. A recent randomized clinical trial by Dong and colleagues evaluated the safety and efficacy of combined low dose aspirin (<100 mg) and OAC to OAC alone in mechanical valve patients [17]. A total of 1500 patients were randomized to either low dose aspirin plus OAC to OAC alone with target INR between 1.8 and 2.5 which were both commenced within 48 h after surgery, assuming hemodynamic stability and low chest tube output. The average age for this cohort was very young at 34.5 ± 7.3 years of age with a majority of male patients (60%) requiring valve replacement for rheumatic valve disease. The bileaflet St. Jude Medical mechanical prosthesis was used in just over one third of patients (36%) while the remaining being tilting disk mechanical prostheses. With a mean follow-up period of 24 ± 9 months, there was no significant difference in the number of deaths or bleeding events between the two groups; however, there was a slightly significant reduction in overall thromboembolism in the aspirin + OAC group (2.1%) versus OAC alone (3.6%; p-value = 0.044) (Table 2). Since there was no apparent increased risk of bleeding with the addition of aspirin in the study group, this justifies the addition of an antiplatelet medication for thromboprophylaxis. While this investigation may have good internal validity and a sound research protocol, the external validity and generalizability of these results is poor. The etiology for mitral or aortic valve replacement in most western and industrialized nations includes degenerative valve disease. Thus, while the addition of aspirin to OAC may improve thromboprophylaxis in the 36-year-old rheumatic disease patient, the bleeding risk may be detrimental in patients over the age of 50 (Table 2). This has been demonstrated in an updated meta-analysis where after including all randomized studies (majority of studies with mean age >50 years of age) the odds ratio for bleeding with the addition of aspirin to OAC was 1.58 (95% CI: 1.14–2.18) [16]. This updated meta-analysis by Massel and Little [16] has not provided any additional information regarding optimal postoperative anticoagulation compared with their previous work in 2003 [26], which was the framework for several national recommendations [12,13]. Since that time there has been little research in determining alternatives for postoperative

Table 1. Current national guidelines† surrounding oral anticoagulation and their target INR for mechanical valve thromboprophylaxis.

Patient characteristic and valve location	OAC (INR 2.0–3.0)	OAC (INR 2.5–3.5)	Aspirin (75–100 mg)
Low-risk aortic position	++	-	++
High-risk aortic position	+	++	++
Mitral position	-	++	++

++ Strong recommendation; + Weak recommendation; - No recommendation.
†Data taken from [12,13].
INR: Internationalized ratio; OAC: Oral anticoagulation.

Table 2. Summary table of contemporary randomized controlled trials discussed in detail in this review.

Study	Population	Results	Implications	Ref.
Dong *et al.* (2011): – Control: Warfarin (INR 2.5–3.0) – Treatment: Warfarin + ASA – Follow-up: 24 ± 9 months	n = 1 496 Mean age = 35 ± 8.5 years Mitral valve = 83% Aortic valve = 43%	TE events (p = 0.044): – Warfarin = 3.6% – Warfarin + ASA = 2.1% Hemorrhage (p > 0.05): – Warfarin = 3.7% – Warfarin + ASA = 3.5%	Low risk patients with either mechanical aortic or mitral valves should take ASA in addition to warfarin	[17]
PROACT study: – Control: Warfarin + ASA (INR 2.0–3.0) – Treatment: Warfarin + ASA (INR 1.5–2.0) – Follow-up: 3.82 years	n = 375 Mean age = 55.2 ± 12.5 years Aortic valve = 100% Elevated risk for TE events	TE events (p = 0.164): – Control = 1.59%/pt-year – Treatment = 2.67%/pt-year Hemorrhage (p < 0.001): – Control = 6.62%/pt-year – Treatment = 2.67%/pt-year	Mechanical aortic valve patients with elevated risk for TE events can benefit from a lower target INR strategy (INR 1.5–2.0) with ASA	[30]
LOWERING-IT trial: – Control: Warfarin (INR 2.0–3.0) – Treatment: Warfarin (INR 1.5–2.5) – Follow-up: 5.6 years	n = 396 Mean age = 49.7 ± 8.8 years Aortic valve = 100%	TE events (p = 0.62): – Control = 1.5% – Treatment = 0.5% Hemorrhage (p = 0.04): – Control = 3% – Treatment = 8.0%	Mechanical aortic valve patients can benefit from a lower target INR strategy (INR 1.5–2.5) without ASA	[31]

ASA: Aspirin; INR: Internationalized ratio; TE: Thromboembolic.

anticoagulation. Despite these recommendations, perioperative anticoagulation strategies practiced in the real word are still quite variable [28,29].

Modified anticoagulation strategies

The On-X (On-X Life Technologies, Inc., TX, USA) mechanical valve was approved by the US FDA in 2002 for clinical use [32–34]. This pyrolytic carbon bileaflet valve has been reported to achieve excellent *in vitro* and *in vivo* [33–35] hemodynamics along with low adverse clinical event rates at long-term follow-up (mean follow-up 5.2 years) [36,37]. Anticoagulation therapy for On-X valves follows the general recommended INR targets yet mid-term thromboembolic event rates in a poorly anticoagulated cohort of patients in South Africa were acceptable [38].

Under the FDA investigational device exemption, a multicenter prospective randomized controlled trial entitled, Prospective Randomized On-X Clinical Trial (PROACT) began enrollment in 2007. This work includes three separate cohorts with each group of patients being subjected to various antithrombotic treatments. The first cohort compares high-risk mechanical aortic valve patients with OAC targeting INR 1.5–2.0 versus standard OAC (INR 2.0–2.5) while the second cohort compares low-risk mechanical aortic valve patients with aspirin or clopidogrel with standard OAC therapy. The third cohort will compare low-risk mechanical mitral valve patients with lower OAC (INR 2.0–2.5) versus standard OAC therapy (INR 3.0–3.5). The last two cohorts have undergone enrollment with results to be reported over the next 2 years. Recently, Puskas and colleagues reported the 5-year results from the first cohort of PROACT, the high-risk aortic mechanical vales with low OAC target (INR 1.5–2.0) versus standard treatment (INR 2.0–2.5) [30]. This study included 33 centers across North America and consisted of 425 patients undergoing aortic valve replacement. This was an intention-to-treat noninferiority experiment. They excluded patients with right sided valve replacement, double (aortic and mitral) valve replacement, and those with active endocarditis at implantation. All patients received OAC with target INR 2.0–3.0 plus aspirin (81 mg daily) for 3 months postsurgery. All patients received a home INR monitor at randomization with weekly testing. Patients in the lower OAC group resulted in a mean INR of 1.89 ± 0.50 (target INR 1.5–2.0) as compared with the standard OAC group with mean INR 2.50 ± 0.64 (target INR 2.0–3.0; p-value < 0.0001) (Table 2). The primary composite end point including thromboembolic events, bleeding and death was significantly reduced in the lower OAC group (INR 1.5–2.0) with incidence rate 5.63%/pt-year compared with the standard OAC group (INR 2.0–3.0) with 8.47%/pt-year (rate ratio of 0.66; 95% CI: 0.44–0.99; p-value = 0.046). This reduction in the composite end point was mainly driven by the significant reduction in both major and minor bleeding with rate ratio for total bleeding in the lower OAC group of 0.40 (95% CI: 0.24–0.69; p-value < 0.001). Thus, it is clear that after a blanket period of 3 months with standard OAC in high-risk patients with mechanical aortic valve replacement, a

lower OAC strategy (INR 1.5–2.0) is noninferior to standard OAC (INR 2–3) for prevention of thromboembolic events; moreover, the lower OAC strategy (INR 1.5–2.0) achieves significantly less bleeding events (Table 2). This work along with the outcomes from the two other cohorts, will potentially change the recommendations toward a lower OAC strategy (INR 1.5–2.0) in the higher risk subgroup undergoing mechanical aortic valve replacement with the On-X valve. Even though this work was underpowered to determine whether lower OAC strategy is better than conventional OAC to prevent thromboembolic events, which generally has a low event rate, national guidelines may still evolve, since previous recommendations were based on older more thrombogenic valves [12–13,16,20]. This study also optimized patient adherence to warfarin with the implementation of home INR monitoring.

Several studies have demonstrated improved clinical end points with self-testing or self-dosing based on home INR monitoring including lower risk of death, thromboembolic events and bleeding [39,40]. In addition to ease of use, patients using the self-testing option reported less stress with warfarin management and improved quality of life [41,42]. To improve these outcomes further, internet-based systems are being implemented in self-testing and self-dosing of warfarin. Thus, when financially feasible, patients after mechanical valve replacement should consider self-testing or self-dosing.

Torella and colleagues also investigated lower OAC target (INR 1.5–2.5) versus standard OAC target (INR 2.0–3.0), in patients undergoing bileaflet mechanical aortic valve replacement. This prospective, single center, randomized controlled trial titled, Lowering the Intensity of Oral Anticoagulant Therapy in Patients with Bileaflet Mechanical Aortic Valve Replacement (LOWERING-IT Trial) aimed to evaluate the safety and feasibility of lowered OAC target. This experiment enrolled 420 patients with low-risk for thromboembolic events, undergoing isolated aortic valve replacement to either the LOW-INR group (target INR 1.5–2.5) or the Conventional-INR group (target INR 2.0–3.0) (Table 2). Over 75% of patients received a Sorin Bicarbon prosthesis (Sorin Group, Milan, Italy) and the remaining group received a St. Jude Medical prosthesis. Unlike Puskas and colleagues with a 3-month blanket period of conventional OAC (INR 2.0–3.0) after surgery [30], this study immediately aimed for their respective target INRs. Moreover, patients did not receive aspirin and underwent more traditional INR monitoring with assessments occurring every 3 weeks [31]. The primary end point, which included all thromboembolic events, was found to be similar between OAC groups (OR comparing LOW-INR to conventional-INR = 0.33; 95% CI: 0.006–4.20; p-value = 0.62). Again, since the rates of thromboembolic events in contemporary studies are low (<2.0%), a very large sample size (>2000) would be needed to deduce superiority. Their secondary end points, which included all bleeding events, were marginally lower in the LOW-INR group (OR: 0.36; 95% CI: 0.11–0.99; p-value = 0.04) (Table 2). This study further challenges the potential benefit of lower OAC strategy (even without concomitant aspirin) in lower thrombogenic risk patients with respect to maintaining acceptable thromboprophylaxis yet simultaneously reducing the incidence of bleeding. While both these studies have demonstrated similar safety and efficacy, further observational and clinical trials will be required before concrete changes can be made in general practice.

Future therapies

With the advent of novel OACs including dabigatran (Boehringer Ingelheim GmbH, Ingelheim, Germany) [43], rivaroxaban (Bayer AG, Barmen, Germany) [44], apixaban (Bristol-Meyers Squibb, NY, USA) [45] and edoxaban (Daiichi-Sankyo Company, Chuo, Japan) [46] being approved for nonvalvular atrial fibrillation patients, there is no surprise that all NOACs have either undergone research or are planning to determine whether NOACs can achieve similar or improved thromboprophylaxis in mechanical valve patients.

Soon after approval of NOACs for nonvalvular indications, several cases reports emerged demonstrating valve thrombosis in patients in whom NOACs were used off-label for mechanical valve thromboprophylaxis. This was followed by the early interruption of the RE-ALIGN study (randomized, Phase II experiment to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement), the only published randomized trial comparing NOACs for mechanical valve thromboprophylaxis [47]. This was a Phase II clinical trial conducted across 39 centers in ten countries with two different cohorts. Population A were patients who underwent aortic, mitral or both aortic and mitral position mechanical valve replacement to receive dabigatran or warfarin within 7 days following surgery while population B differed only by starting dabigatran or warfarin 3 months following surgery. This was a 12-week trial following treatment allocation with potential for patients to enroll in the extension trial (RE-ALIGN-EX). The primary outcome of this Phase II study was the trough plasma level of dabigatran with secondary outcomes including incidence of

thromboembolic events, bleeding, myocardial infarction and death. Unfortunately, after planned interim review by the data and safety monitoring board, the investigation was stopped prematurely because of excess thromboembolic and bleeding events among dabigatran treated patients. To achieve the primary outcome (dabigatran trough plasma level of 50 ng/ml) 24% of patients required augmentation of their dabigatran dose along with 8% of patients who were discontinued per protocol (trough level <50 ng/ml despite on maximum dose of dabigatran, 300 mg twice daily). Thus, the dabigatran group in population A had an average of 84% of the time at the targeted plasma level. Despite this, there was a stroke incidence of 5% in the dabigatran group versus 0% in the warfarin group. Clinically silent valve thrombosis was found in 3% of dabigatran patients compared with 0% in control. Finally, the composite end points of stroke, transient ischemic attack, systemic embolism, myocardial infarction or death occurred in 9% of dabigatran patients and only 5% of control (p-value = 0.24). Moreover, the incidence of all bleeding events was significantly more prevalent in the dabigatran group compared with control (hazard ratio: 2.45; 95% CI: 1.23–4.86; p-value = 0.01). These results indicate that at doses of dabigatran used in this study were not as effective as conventional OAC for thromboprophylaxis along with a significant increased risk of bleeding.

The potential main arguments surrounded this terminated trial include: inadequate levels of dabigatran for maintaining anticoagulation during valve replacement, or major differences in the mechanism of anticoagulation for artificial, metal or carbon surface materials in blood. Thus, based on this clear observation along with several case reports and editorials [48–51] surrounding this issue, dabigatran should not be used for mechanical valve anticoagulation management [50].

Alternatively, the CATHAR (Comparison of Antithrombotic Treatments after Aortic Valve Replacement) study, investigating another NOAC (rivaroxaban) has begun enrollment [52]. The results of this Phase II randomized controlled trial comparing mechanical valve patients taking rivaroxaban (20 mg once daily) versus conventional OAC are expected over the next 2 years. Therefore, based on the aforementioned results from observational studies and the RE-ALIGN study, NOACs should not be given to any patient with a mechanical valve.

One other major field of potentially improving thromboprophylaxis in mechanical valves comes from further research in the architecture of the valve itself. First and second generation mechanical vales from the 1960 to 1970s are rarely used due to their significant thrombogenic surfaces [9,22]. The bileaflet mechanical valve was introduced by St. Jude Medical in 1977 with improved hemodynamics and a larger effective orifice area [53,54]. The Medtronic (ATS) OpenPivot bileaflet mechanical valve (Medtronic, Inc., MN, USA) was introduced in the mid-1990s which reported remarkable thromboresistance due to continuous passive washing over the leaflets for gentle treatment of red cells and thromboembolic events along with easy implantability [55–57]. The recently approved On-X valve possesses considerably less thrombogenic properties as expressed by the company along with some clinical evidence [37,58–60]. This has led to the commencement of the PROACT study aimed to determine the minimum amount of OAC required to maximally prevent thromboembolic and bleeding events. While the first cohort of patients has been reported, the cardiac community still awaits the remaining two cohorts' results.

Although mechanical valves are known for their durability supported by significantly less structural valve deterioration [7–8,61–62], there has been an increasing trend toward using bioprosthetic valves including patients under the age of 65 years [9,10]. This may be partially explained by studies demonstrating excess mortality in patients undergoing mechanical aortic valve replacement [63] and more recently similar 15 year survival observed between bioprosthetic and mechanical valve replacement with the latter group having more bleeding complications [64]. Thus, the dreaded pitfalls associated with mechanical valve replacement may eventually be abated with the use

Table 3. Revised oral anticoagulation recommendations based on contemporary studies reviewed herein.

Patient characteristic and valve location	OAC (INR 1.5–2.0)	OAC (INR 1.5–2.5)	OAC (INR 2.5–3.5)	Aspirin (75–100 mg)
Low-risk aortic position	++	++	-	+
High-risk aortic position	++[†]	++	+	++
Mitral position	-	-	++	++

++ Strong recommendation; + Weak recommendation; - No recommendation.
[†]Only with On-X valve.
INR: Internationalized ratio; OAC: Oral anticoagulation.

of newer mechanical valve design with less thrombogenic properties, lowered requirement for OAC and effective alternative anticoagulants.

Conclusion

Clinical guidelines recommend lifelong OAC in all patients with mechanical valves with variance in the target INR for patient associated risk factors, type of mechanical valve or implant position of the valve. Recent randomized controlled trials have demonstrated that clinicians may consider a lower OAC strategy (INR 1.5–2.5) in low (thrombogenic) risk patients undergoing bileaflet mechanical valve replacement thereby achieving similar thromboprophylaxis yet minimizing bleeding events (Table 3). Likewise, physicians may also consider a lowered OAC option in high (thrombogenic) risk patients undergoing certain types of bileaflet mechanical valve replacement yielding similar efficacy (avoidance of thromboembolic events) and improving safety (bleeding events) (Table 3); however, caution must be exercised since these lowered anticoagulation target recommendations arise from only a few studies. Finally, while advancement of NOACs has been swift in the realm of atrial fibrillation anticoagulation management, NOACs for mechanical valves are currently contraindicated. Future studies comparing NOACs and warfarin along with newer mechanical valve construction may reveal new insights on this issue.

Future perspective

In addition to the NOACs and their expanding list of indications, design and construction of less thrombogenic mechanical valves is also required. As reported by On-X Lifesciences Technologies, Inc. along with some clinical evidence [32,37–38], this new valve possesses considerably less thrombogenic properties justifying the commencement of the PROACT study aimed to determine the minimum amount of OAC needed. Preliminary results from the first cohort patients have been promising as discussed in previous sections in this review. The final remaining results will be reported over the next 2 years.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

Current practice for anticoagulation

- Guidelines for OAC include target INR 2.0–3.0 for mechanical aortic valve replacement (low-risk) and INR 2.5–3.5 for mechanical mitral valve replacement or high-risk aortic valve replacement.
- All patients, unless indicated otherwise, should receive low dose aspirin daily.

Modified anticoagulation strategies

- Bileaflet mechanical valves in low-risk patients: may consider INR 1.5–2.5.
- Certain types of bileaflet mechanical valves in high-risk patients: may consider INR 1.5–2.0 (with aspirin daily).

Future therapies

- NOACs should not be given to any patient with a mechanical heart valve.
- Great amount of research is still needed in mechanical valve design and type of anticoagulation.

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