There is Still No Alternative to Warfarin for Mechanical Valves……. It Remains the Most Effective Anticoagulant

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Title: There is Still No Alternative to Warfarin for Mechanical Valves……. It Remains the Most Effective Anticoagulant

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Central Message: Despite the development of direct oral anticoagulants, warfarin remains the most effective and only approved anticoagulant for prevention of thromboembolic events after mechanical valve replacement.

Central Picture Legend: Coagulation cascade with mechanisms of action of VKA, DOAC, and Factor XI/XIa inhibitors.
Recent technological developments and the advent of transcatheter aortic valve replacement technology (TAVR) have completely altered the landscape of aortic valve interventions in the current era. Although the volume of surgical aortic valve replacement (SAVR) has become increasingly small since TAVR was approved for use in moderate/low-risk patients, SAVR remains the preferred option in several patient populations, such as young patients, calcified bicuspid valves, and those with aortic insufficiency. In this subgroup, the choice of a mechanical versus bioprosthetic valve is of vital importance since these are often younger patients who will outlive the durability of a bioprosthesis but are also concerned about lifestyle limitations related to anticoagulation with warfarin. Fortunately, technology continues to advance with improvements in tissue engineering for increased durability\textsuperscript{1} while novel oral anticoagulants are being developed as alternatives to warfarin.\textsuperscript{2,3}

**Rationale for Direct Oral Anticoagulants**

Each year \textasciitilde300,000 prosthetic heart valves are implanted worldwide.\textsuperscript{4} Despite advances in technology, premature valve failure and structural deterioration still necessitate repeat valve procedures. Mechanical valves are a more durable alternative to bioprosthetic valves but require lifelong anticoagulation with Vitamin K antagonists (VKAs) such as warfarin to prevent valve thrombosis and thromboembolic complications.\textsuperscript{5,6} However, disadvantages of warfarin include requiring frequent phlebotomy, dose adjustments to maintain a relatively narrow therapeutic window, drug/food interactions, and associated health care costs.\textsuperscript{7,8} With long-term VKA therapy, a considerable time is spent out of the narrow therapeutic window thereby lowering the preventive effect and increasing bleeding.\textsuperscript{9,10} These challenges have hastened the development of direct oral anticoagulants (DOACs) which include dabigatran, rivaroxaban, apixaban and endoxaban. DOACs are at least as effective as warfarin in treating deep venous thrombosis...
(DVT) and preventing thromboembolic stroke with atrial fibrillation. They have a wider therapeutic window and better safety profile with lower incidence of hemorrhagic complications compared to warfarin. Importantly, frequent monitoring and phlebotomy are not required due to their predictable bioavailability.

### Use of DOACs After Bioprosthetic Valve Replacement

Recently, DOACs have been used as an alternative to warfarin after bioprosthetic valve replacement but risk of early thrombosis is also a concern with these valves, especially on the exposed sewing cuff. The River trial randomized 1005 patients to rivaroxaban or warfarin (target INR 2.0-3.0) in patients with atrial fibrillation undergoing bioprosthetic MVR. The incidence of stroke was 0.6% with rivaroxaban and 2.4% with warfarin (HR 0.25; 95%CI 0.07-0.88). Major bleeding occurred in 1.4% vs 2.6% (HR 0.54; 95%CI 0.21-1.35). Rivaroxaban was non-inferior to warfarin for death, major cardiovascular events, or major bleeding. Less than 20% of patients were enrolled within 3 months following MVR but among them, the incidence of primary-outcome event was 6.4% vs 18.9% (HR 0.31; 95%CI 0.12-0.79). This subgroup analysis must be interpreted with caution as it consisted of <200 patients.

The Enavle study randomized 220 patients to receive endoxaban (n=109) or warfarin (target INR 2.0-3.0) (n=109) for the first 3 months following surgical bioprosthetic valve replacement. The primary efficacy outcome (death, thromboembolic events, intracardiac thrombus) occurred in 3.7% taking warfarin and none taking edoxaban (RR -0.0367; 95%CI –0.0720 to –0.0014; P<.001). The primary safety outcome occurred 0.9% taking warfarin and 2.8% taking edoxaban (RR 0.0183; 95%CI –0.0172 to 0.0539; P = .013). The authors concluded that endoxaban was non-inferior to warfarin for preventing thromboembolic events and was
comparable for risk of major bleeding. Notably, 60% of patients had atrial fibrillation and valve
type was heterogeneous with aortic valves comprising the majority (51% of endoxaban group vs
47% of warfarin group), mitral valve replacement in 22% vs 19% and mitral valve repair in 38%
vs 41%. The small study size heterogeneity of the population make it difficult to draw
meaningful conclusions. Larger, randomized controlled trials are needed to determine the
efficacy and safety of DOACs in this setting.

Evaluating the Use of DOACs for Mechanical Valves

The first clinical trial evaluating the use of DOACs with mechanical valves was the RE-
ALIGN trial which compared dabigatran, a direct thrombin inhibitor to warfarin in patients who
received mechanical aortic or mitral valves either within 7 days or after 3 months. Table 1 This
trial was terminated early after enrolling only 252 patients due to significantly more
thromboembolic and bleeding events with dabigatran. The incidence of strokes (5% vs 0) and
major bleeding (4% vs 2%) were significantly higher with dabigatran. Interestingly, a majority of
thromboembolic events in the dabigatran group occurred in those enrolled within 7 days of
surgery. This was attributed to early thrombus formation prior to endothelialization of the sewing
ring. The major bleeding events all occurred in patients enrolled within 7 days of surgery.
Notably, this study included mitral valve replacements and double valve replacements, which are
at increased risk for thrombotic complications.

Warfarin is believed to be more effective than dabigatran at preventing thrombus formation
because it inhibits tissue factor induced coagulation by inhibiting production of factor VII. It also
suppresses contact pathway coagulation by inhibiting synthesis of factor IX, factor X and thrombin.\textsuperscript{15} In contrast, dabigatran solely inhibits thrombin. (see Figure 1)

**Prior Success Leading to the PROACT Series**

Previous trials found that reducing the level of anticoagulation is acceptable in some patients. The Lowering-it trial randomized 396 patients after isolated mechanical AVR to low INR (1.5 – 2.5) or standard INR (2-3).\textsuperscript{16} With mean follow-up of 5.6 years, thromboembolic events were similar and there were less hemorrhagic events in the Low-INR group. Another randomized trial of 1,137 patients assessed lower INR targets after mechanical AVR, MVR or double valve replacement (DVR).\textsuperscript{17} After 6 months patients were selected to continue low target INR or switch to very low dose groups (target INR 1.6-2.1 for AVR and 2.0-2.5 for MVR/DVR). There was no difference in thromboembolic events, bleeding or mortality among the three groups.

These successes led to the original PROACT trial (Prospective Randomized On-X Anticoagulation Clinical Trial) using the On-X Aortic Valve, a bileaflet mechanical valve designed specifically to reduce thrombogenicity. Characteristics include a graphite composition coated with pure unalloyed pyrolytic carbon, creating an extremely smooth surface, flared inlet orifice, 90° leaflet opening, shorter leaflet closing angle, 2-point leaflet contact and actuated pivot. These features improved hemodynamics and reduced hemolysis and thrombogenicity, offering potential to reduce anticoagulation.\textsuperscript{18}

The PROACT trial demonstrated that the On-X aortic valve can be maintained with lower INR. It randomized patients at 3 months following AVR into the low-risk or high-risk arm.\textsuperscript{19} Patients without risk factors for thromboembolism were placed in the low-risk arm and randomized to dual antiplatelet therapy (DAPT) (aspirin 325mg and clopidogrel 75mg) or
standard warfarin and aspirin. This arm was terminated early due to increased thromboembolic events in the DAPT arm, demonstrating the inadequacy of antiplatelet therapy alone.\textsuperscript{20} Patients with thromboembolic risk factors were placed in the high-risk arm and received aspirin 81mg plus either standard warfarin (INR goal 2.0-3.0) or lower dose warfarin (INR goal 1.5-2.0).

While thromboembolic events were similar (2.67\% vs 1.59\%/patient-year, p=0.164) major bleeding events were less in the lower INR group (1.48\%/patient-year vs 3.26 \%/patient-year, p=0.047). These data suggested that patients with an On-X aortic valve can be safely anticoagulated to an INR of 1.5-2.0.\textsuperscript{20}

**Study Design of the PROACT Xa Trial**

In the PROACT Xa study, patients with On-X Aortic Valves (Artivion, Kennesaw, GA) were randomized at a minimum of three months following implantation to receive apixaban or warfarin (target INR 2.0-3.0) plus aspirin 75-100mg daily. The lower target INR from PROACT was not used. The favorable results of PROACT were primarily due to a lower rate of bleeding despite having a higher incidence of thromboembolic events. Additionally, in PROACT the number of patients was small and minimized the composite outcomes. Therefore, to determine if apixaban was noninferior to warfarin in the prevention of thromboembolism and valve thrombosis without giving apixaban an additional advantage, the standard warfarin INR target of 2-3 was utilized. The primary endpoint was valve thrombosis or valve-related thromboembolism.\textsuperscript{21,22}

Apixaban (a factor Xa inhibitor) was chosen given its effectiveness in preventing stroke and systemic thromboembolism with improved safety profile and less bleeding events in patients with atrial fibrillation.\textsuperscript{3} Apixaban has enhanced bioavailability and superior safety profile compared to dabigatran, which was used in the RE-ALIGN trial.\textsuperscript{21,22} Furthermore, Lester and
colleagues reported that in a swine heterotopic mechanical valve model, apixaban groups had valve thrombus burdens similar to or less than the warfarin group.\textsuperscript{23}

The On-X valve was chosen for its beneficial design characteristics that render it less thrombogenic than other mechanical valves. The study was limited to only aortic valve replacements, which demonstrate higher flow velocity and are less predisposed to thrombus formation and thromboembolic complications compared to other valves. Patients were randomized after a minimum 3 months from implantation, allowing for endothelialization of the sewing ring to mitigate early thrombogenicity of the exposed fabric.\textsuperscript{18,21,22}

Outcomes of the PROACT Xa Trial

At the 103\textsuperscript{rd} Annual Meeting of the American Association for Thoracic Surgery, results of the PROACT Xa trial, which compared apixaban to warfarin anticoagulation for the prevention of valve thrombosis and valve-related thromboembolism in patients with an On-X Aortic Valve, were presented.\textsuperscript{4} The design of this study was predicated on the success of novel direct oral anticoagulants in preventing thrombotic complications for non-valvular indications\textsuperscript{2,3}, as well as previous trials showing that reduced levels of anticoagulation are acceptable for On-X mechanical aortic valves.\textsuperscript{19,20}

Despite a study design that capitalized on the beneficial characteristics of apixaban and On-X mechanical valve design, apixaban failed to demonstrate non-inferiority compared to warfarin in preventing thromboembolic events. As a result of a significant increased incidence of events in the apixaban group the trial was stopped after enrolling 863 patients. There were 20 valve thrombosis or valve-related thromboembolism in the apixaban group (4.2%/patient-year) and 6 events in the warfarin group (1.3%/patient-year) (figure 2). This resulted in a difference in
primary endpoint rates of 2.9 (95% CI, 0.8 to 5.0). Furthermore, 14 thromboembolic strokes occurred with apixaban compared to none with warfarin.\textsuperscript{21}

Prosthesis characteristics are likely to play an important role in thrombotic event rates. In both groups, 21mm or smaller valves had more events than those >21mm. Patients in the apixaban group who underwent aortic root replacement with the On-X AAP composite valve-graft had a higher event rate (8.79%/patient-year) compared to AVR alone (3.4%/patient-year), but the difference was not seen with warfarin. This is quite a discrepancy considering that larger size valves are usually utilized in patients undergoing root replacement. The On-X AAP includes a Dacron graft with prefabricated sinuses of Valsalva. Alterations in blood flow dynamics and vortical motion of blood in the aortic root can potentially affect the degree of stasis near the sewing cuff.\textsuperscript{24} Although the prefabricated graft has sinus-like bulges, it does not emulate the native root anatomy perfectly and lacks the dynamic motion of living aortic tissue. These differences potentially lead to increased thrombus formation if anticoagulation is inadequate.

So why did PROACT Xa fail to demonstrate non-inferiority of apixaban compared to warfarin in a well-designed trial that utilized the strengths of several optimized mechanisms to prevent thrombosis? Interestingly, whether patients were judged to be high risk or low risk for thromboembolic events, based on preoperative risk factors such as atrial fibrillation, low ejection fraction, enlarged left atrium, or previous cerebral emboli, did not make a notable difference in the within-group comparison. Although apixaban had more events compared to warfarin in both high-risk and low-risk patients, the risk level did not affect the within-group event rate significantly in either apixaban or warfarin patients. This could potentially indicate that there may be a deficiency in the mechanism of action of apixaban, in which a necessary part of the coagulation cascade is not adequately inhibited when it comes to thrombus formation with
mechanical valves. Further understanding of the mechanisms and factors which contribute to mechanical valve thrombus formation may help to explain the ineffectiveness of DOACs, which target specific later-stage steps in the coagulation cascade. Figure 1

Jaffer and colleagues studied thrombin generation induced by mechanical valve leaflets and sewing ring segments and evaluated the effectiveness of dabigatran, apixaban, rivaroxaban and warfarin in inhibiting thrombin formation. These in vitro studies demonstrated that mechanical valves induce thrombin generation at concentrations that overwhelm thrombin inhibitors and factor Xa inhibitors at clinically relevant doses. They showed that inhibition of both factor Xa and thrombin is necessary to prevent thrombus formation. Warfarin is effective at preventing thrombus formation by inhibiting both factor Xa and thrombin. This is unlikely to be achieved safely utilizing a combination of dabigatran and rivaroxaban or apixaban at clinically relevant doses.

Is There Any Hope for an Alternative to Warfarin?

Factor XI and Factor Xa inhibitors are a new class of anticoagulants that may provide promise as an alternative to warfarin. Factor XI antagonists inhibit both contact activation and propagation of thrombus formation through feedback activation of factor XI by thrombin, which is generated by tissue factor activation. Figure 1. Tissue factor exposed at surgical sites is a significant contributor to postoperative DVT. Current clinical trials are evaluating novel factor XI and Xa inhibitors in patients at risk for DVT.

Abelacimab, a monoclonal antibody that binds factor XI, Osocimab, a monoclonal antibody that inhibits factor Xia, and Milvexian, an oral factor Xa inhibitor, have been studied in phase 2 trials in patients who underwent knee arthroplasty. Each agent was as effective or superior
to enoxaparin at preventing venous thromboembolism and had low rates of bleeding.

Abelacimab and Osocimab have the added benefit of long half-lives and may require less frequent dosing compared to other anticoagulants.\textsuperscript{25,26} Further evaluation of these novel anticoagulants are needed to validate and establish efficacy and safety.\textsuperscript{27} While these novel anticoagulants may provide another alternative to warfarin for treatment and prevention of DVT, it is unknown whether they are a viable alternative to warfarin for mechanical valves.

Current ACC/AHA guidelines continue to recommend anticoagulation with VKAs and low-dose aspirin in patients with mechanical valves. These guidelines state that use of dabigatran is contraindicated and use of anti-Xa DOACs is not recommended due to lack of evidence.\textsuperscript{5} Although there is a general desire to avoid the quality of life issues associated with VKAs, they remain the safest available method of long-term anticoagulation for mechanical valves. Patients should be informed of the relative safety profile and technological advances that can improve quality of life and compliance, such as at-home fingerstick INR testing.

Acknowledgement: We would like to acknowledge Katherine Sokoloff for creating figure 1.


Figure 1: The intrinsic and extrinsic pathway of the coagulation cascade demonstrating the mechanisms of action of VKA’s, DOACs, Factor XI and Factor XIa inhibitors.

Figure 2: Cumulative incidence of valve thrombosis or valve-related thromboembolism in patients with On-X mechanical aortic valves randomized to receive either apixaban or warfarin. Reprinted with permission^4.
Table 1. Prospective randomized trials comparing direct acting oral anticoagulants with warfarin in patients with surgical valves

<table>
<thead>
<tr>
<th>Trial</th>
<th>RE-ALIGN</th>
<th>PROACT Xa</th>
<th>RIVER</th>
<th>ENAVLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOAC and Dose</td>
<td>Dabigatran (150mg, 220mg, or 300mg twice daily)</td>
<td>Apixaban (5mg twice daily)</td>
<td>Rivaroxaban (20mg daily)</td>
<td>Endoxaban (30mg or 60 mg daily)</td>
</tr>
<tr>
<td>N</td>
<td>252 (terminated early)</td>
<td>863 (terminated early)</td>
<td>1005</td>
<td>220</td>
</tr>
<tr>
<td>Valve Type</td>
<td>Bileaflet Mechanical</td>
<td>On-X Mechanical</td>
<td>Bioprosthetic</td>
<td>Bioprosthetic or Repair</td>
</tr>
<tr>
<td>Position</td>
<td>Aortic or/and Mitral</td>
<td>Aortic</td>
<td>Mitral</td>
<td>Aortic or/and Mitral</td>
</tr>
<tr>
<td>DOAC initiation</td>
<td>Within 7 days or after 3 months</td>
<td>After 3 Months</td>
<td>18.8% before 3 Months</td>
<td>79.6% after 3 months</td>
</tr>
<tr>
<td>Stroke</td>
<td>5% versus 0%</td>
<td>2.9 %/patient-year versus 0%/patient-year</td>
<td>0.6% versus 2.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>0% versus 0%</td>
<td>3.5% /patient-year versus 1.3%/patient-year</td>
<td>0% versus 0.2%</td>
<td>0% versus 0.92%</td>
</tr>
<tr>
<td>Valve Thrombosis</td>
<td>3% versus 0%</td>
<td>0.6%/patient-year versus 0%/patient-year</td>
<td>1% versus 0.6%</td>
<td>0% versus 0.92%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>4% versus 2%</td>
<td>3.6%/patient-year versus 4.5%/patient-year</td>
<td>1.4% versus 2.6%</td>
<td>2.75% versus 0.92%</td>
</tr>
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</table>

RE-ALIGN, Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement; PROACT Xa,
Prospective Randomized On-X Anticoagulation Clinical Trial Xa; RIVER, Rivaroxaban
for Valvular Heart Disease and Atrial Fibrillation; ENALVE, Explore the Efficacy and
Safety of Endoxaban in Patients after Heart Valve Repair or Bioprosthetic Replacement;
NA, Not Available