# Efficacy and Safety of Nonvitamin K Oral Anticoagulants following Cardiac Valve Replacement

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**Objective:** To compare the efficacy and safety of nonvitamin K oral anticoagulants (NOACs) and vitamin K antagonists (VKAs) following bioprosthetic cardiac valve replacement.

**Methods:** This was a retrospective analysis conducted at a community teaching hospital in the southeastern United States between August 2015 and August 2018. Patients 18 years of age and older who underwent cardiac valve replacement and were prescribed oral anticoagulation were screened for inclusion. Patients were excluded if they had a mechanical valve replacement, experienced a venous thromboembolism, cerebrovascular accident, or acute coronary syndrome within 1 month before valve replacement, changed oral anticoagulation during the study period, were lost to follow-up, or declined to participate in the follow-up survey. The primary outcome was a composite of thromboembolic events within 90 days following bioprosthetic cardiac valve replacement. The safety outcome was major bleeding within 180 days of bioprosthetic cardiac valve replacement.

**Results:** The primary outcome of a composite of thromboembolic events within 90 days following bioprosthetic cardiac valve replacement occurred in 1 patient (4.3%) in the VKA group and 4 patients (7.4%) in the NOAC group. Major bleeding occurred in 2 patients (8.7%) in the VKA group and 0 patients in the NOAC group.

**Conclusion:** Our study is the first to report the efficacy and safety of NOACs compared with VKA therapy following bioprosthetic cardiac valve replacement irrespective of an atrial fibrillation diagnosis. Notably, two of the thromboembolic events in the NOAC group occurred while therapy was held or inappropriately dosed; when these events are removed, the rate of thromboembolism is 3.8%. This rate is consistent with the VKA group. Our study adds to a small pool of literature regarding the use of NOACs following bioprosthetic cardiac valve replacement and suggests that NOACs may have similar efficacy and improved safety as compared with VKA therapy. Large randomized controlled trials are warranted to confirm our observations.

**Key Words:** anticoagulant, bleeding, cardiac valve, thromboembolism, treatment efficacy

Valvular heart disease is a growing health problem, with an estimated 2.5% of the US population affected.[1] The disease often is degenerative and progressive in nature, causing a disproportionate rise in incidence in those older than 65 years. Many patients deteriorate and require surgical or transcatheter intervention to reestablish valve function and improve prognosis. Cardiac valve repairs and replacements account for 10% to 20% of all cardiac surgical procedures.[1,2] There is an increased risk of thromboembolic complications following cardiac valve replacement, with a peak incidence during the first 3 months after surgery. Thrombotic potential varies based on valve type and position; however, many patients require either short- or long-term anticoagulation.[3]

As a result of the ease of dosing and improved safety profiles, nonvitamin K oral anticoagulants (NOACs) are preferred over vitamin K antagonists (VKAs) in several disease states requiring oral anticoagulation, including atrial fibrillation (AF) and venous thromboembolism (VTE)[4,5]; however, current guidelines do not recommend the use of NOACs following cardiac valve replacement. Both the American College of Chest Physicians (ACCP) and the

## Key Points

- Rates of venous thromboembolism following bioprosthetic cardiac valve replacement were comparable between nonvitamin K oral anticoagulants (NOACs) and vitamin K antagonists.
- NOACs and vitamin K antagonists appeared to have similar rates of major bleeding following bioprosthetic cardiac valve replacement.
- Large randomized controlled trials are warranted to formally assess the safety and efficacy of NOACs following bioprosthetic cardiac valve replacement.

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The article includes unlabeled/investigational uses of apixaban, rivaroxaban, and dabigatran used for anticoagulation following cardiac valve replacement, and the status of these is disclosed herein.

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American College of Cardiology/American Heart Association Task Force (ACC/AHA) recommend VKA therapy for patients with mechanical valve prostheses.[6,7] In addition, the ACC/AHA recommends against the use of NOACs in this population, citing harm.[7] This recommendation is based on results of the RE-ALIGN (Dabigatran Etexilate in Patients with Mechanical Heart Valves) trial comparing dabigatran with VKA therapy in patients following mechanical valve replacement, which was stopped prematurely because of excessive rates of thromboembolism and bleeding in the dabigatran group.[8] These negative data have been extrapolated to all NOACs, as RE-ALIGN is the only major trial to date to evaluate the use of a NOAC in patients with prosthetic valves. In contrast, the optimal antithrombotic regimen following a bioprosthetic cardiac valve replacement is more variable. The ACCP recommends VKA therapy for the first 3 months after bioprosthetic mitral valve replacement and aspirin over VKA therapy for the first 3 months following bioprosthetic aortic valve replacement.[6] The ACC/AHA suggests anticoagulation with a VKA for at least 3 months following either bioprosthetic mitral or aortic valve replacement.[7] Notably, there are no recommendations for the use of NOACs following bioprosthetic cardiac valve replacement from either ACCP or ACC/AHA.[6,7]

Despite the paucity of data regarding the safety and efficacy of NOACs following bioprosthetic cardiac valve replacement, there is an apparent increase in NOAC prescribing in this population. Beller et al[9] reviewed >30,000 cardiac surgery patients, 11,632 of whom received bioprosthetic cardiac valve replacement. Anticoagulation patterns were compared during two 3-year periods, 2011–2014 and 2015–2018. Although there was no difference in overall rates of anticoagulation between the two periods (31.9% vs 31.6%), the rate of NOAC prescribing increased nearly sixfold during the second time frame (from 6.6% to 32.1%, $P < 0.001$).[9]

At our institution an average of 550 cardiac surgeries were performed per year from August 2015 to August 2018, with cardiac valve replacements accounting for approximately 25% of these cases. Similar to the findings of Beller et al,

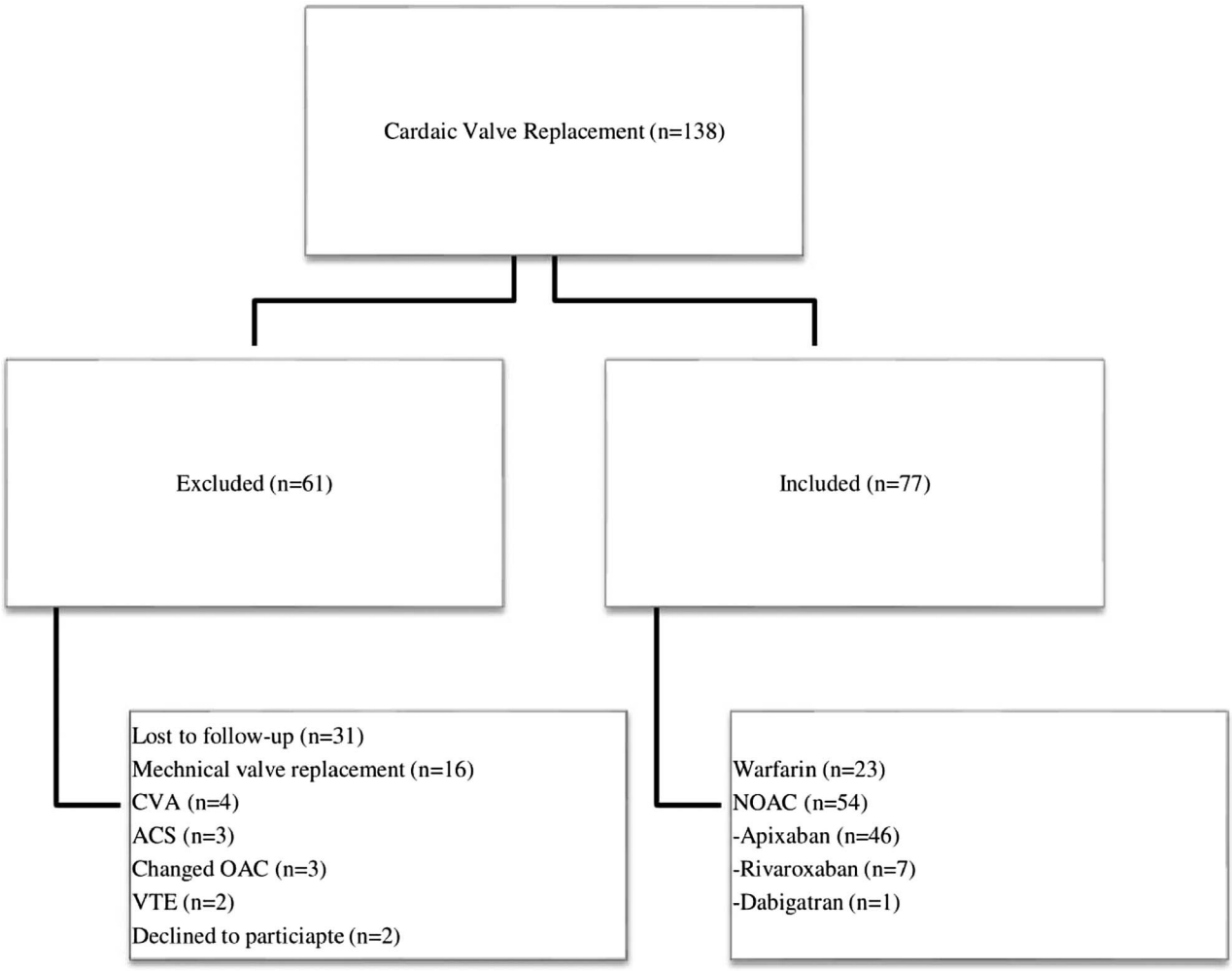


**Fig. Flow diagram of the patient selection process ACS, acute coronary syndrome; CVA, cerebrovascular accident; NOAC, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulant; VTE, venous thromboembolism.**

an increase in the prescription of NOACs following cardiac surgery was noted, especially after bioprosthetic cardiac valve replacement.[9] Despite an increase in use, data on safety and efficacy outcomes for NOACs following bioprosthetic cardiac valve replacement are lacking. The purpose of this study was to compare the efficacy and safety of NOACs versus VKA following bioprosthetic cardiac valve replacement.

## Methods

This retrospective analysis was conducted at a 505-bed community teaching hospital located in the southeastern United States between August 2015 and August 2018. The study protocol was approved by the institution's review board. Patients 18 years of age and older who underwent surgical or minimally invasive cardiac valve replacement and were prescribed oral anticoagulants following valve replacement were identified and reviewed. Patients were excluded if they had a mechanical valve replacement, experienced a VTE, cerebrovascular accident (CVA), or acute coronary syndrome within 1 month before valve replacement, changed oral anticoagulants during the study period, were lost to follow-up, or declined to participate in the follow-up survey. Patients were considered lost to follow-up after three failed attempts at telephone contact.

The primary outcome was a composite of thromboembolic events within 90 days following bioprosthetic cardiac valve replacement. Thromboembolic events included CVA, transient ischemic attack, acute coronary syndrome, VTE, valve thrombosis, or other vascular occlusion. Secondary outcomes included the individual components of the primary outcome, a composite of thromboembolic events within 180 days following bioprosthetic cardiac valve replacement, and all-cause mortality within 90 and 180 days following bioprosthetic cardiac valve replacement. The safety outcome was major bleeding within 180 days of bioprosthetic cardiac valve replacement, defined by a World Health Organization bleeding scale score of ≥3, indicating severe or debilitating gross blood loss. The electronic medical record was reviewed for all outcomes. Patients without follow-up in the electronic medical record were surveyed via telephone for all outcomes.

Patients were placed into either the NOAC or the VKA group based on the prescribed anticoagulant. Categorical variables were represented with descriptive statistics. Because of the descriptive nature of the primary outcome, a power analysis was not performed. A subgroup analysis was defined a priori to assess the primary composite outcome based on aortic versus mitral valve position.

## Results

A total of 138 patients underwent open or minimally invasive cardiac valve replacement within the specified time frame. Sixty-one patients were excluded, with the majority being lost to follow-up or having mechanical valve replacements (Fig). Seventy-seven patients were included for analysis, with 23 in the VKA group and 54 in the NOAC group.

**Table 1. Baseline characteristics**

| Characteristic | VKA (n = 23) | NOAC (n = 54) |
|---|---|---|
| Age, y, mean (SD) | 65 (8.5) | 68 (1.4) |
| Male sex, n (%) | 14 (61) | 29 (54) |
| Race, n (%) | | |
| White | 18 (74) | 45 (83) |
| African American | 5 (22) | 9 (17) |
| Hispanic | 1 (4) | 0 |
| Medical history, n (%) | | |
| AF | 9 (39) | 19 (35) |
| CVA | 2 (9) | 6 (11) |
| ACS | 2 (9) | 0 |
| VTE | 1 (4) | 1 (2) |
| BMI, kg/m$^2$, mean (SD) | 29.1 (7.2) | 31 (2.2) |
| Creatinine clearance, mL/min, mean (SD) | 64.1 (8.5) | 63.1 (35) |
| Concomitant antithrombotic agents, n (%) | | |
| Aspirin | 21 (91) | 50 (93) |
| P2Y12 inhibitor | 0 | 4 (7) |
| Dual antiplatelet therapy | 2 (9) | 0 |
| Duration of therapy, n (%) | | |
| <3 mo | 8 (19) | 19 (35) |
| ≥3 mo | 34 (81) | 35 (65) |

*AF, atrial fibrillation; ACS, acute coronary syndrome; BMI, body mass index; CVA, cerebrovascular accident; NOAC, nonvitamin K oral anticoagulant; SD, standard deviation; VKA, vitamin K antagonist; VTE, venous thromboembolism.*

Characteristics of the patient groups are summarized in Table 1. Thirty-nine percent of the VKA group had an AF diagnosis compared with 35% of the NOAC group. Patients in the VKA group were more likely to be anticoagulated for a longer duration, with 81% of patients receiving anticoagulation for ≥3 months versus 65% of patients in the NOAC group. In the NOAC group, 46 patients received apixaban (85%), 7 patients received rivaroxaban (13%), and 1 patient received dabigatran (2%). Of the 46 patients, 41 (89%) receiving apixaban were prescribed 5 mg twice daily and 5 patients were prescribed 2.5 mg twice daily (11%). Of the 7 patients receiving rivaroxaban, 4 patients (57%) received 20 mg/day, 2 patients (29%) received 15 mg/day, and 1 patient (14%) received 10 mg/day. The single patient prescribed dabigatran received 75 mg twice daily.

The primary outcome of the composite of thromboembolic events within 90 days following bioprosthetic cardiac valve replacement occurred in 1 patient (4.3%) in the VKA group and 4 patients (7.4%) in the NOAC group (Table 2). The single event in the VKA group was a VTE. Of the four events in the NOAC group, two (3.7%) were CVAs and two (3.7%) were VTEs. There were no additional thromboembolic events at 180 days in either group.

One patient (4.3%) in the VKA group and 2 patients (3.7%) in the NOAC group died within 90 days. There were no additional deaths at 180 days. Major bleeding occurred in 2 patients (8.7%) in the VKA group and 0 patients in the NOAC group.

**Table 2. Outcomes**

| Outcome, n (%) | VKA (n = 23) | NOAC (n = 54) |
|---|---|---|
| Composite of thromboembolic events | | |
| Within 90 d | 1 (4.3) | 4 (7.4) |
| Within 180 d | 1 (4.3) | 4 (7.4) |
| Individual components of the composite of thromboembolic events | | |
| CVA | 0 | 2 (3.7) |
| TIA | 0 | 0 |
| ACS | 0 | 0 |
| VTE | 1 (4.3) | 2 (3.7) |
| Valve thrombosis | 0 | 0 |
| Other vascular occlusion | 0 | 0 |
| All-cause mortality | | |
| Within 90 d | 1 (4.3) | 2 (3.7) |
| Within 180 d | 1 (4.3) | 2 (3.7) |
| Major bleeding | 2 (8.6) | 0 (0) |

*ACS, acute coronary syndrome; CVA, cerebrovascular accident; NOAC, nonvitamin K oral anticoagulant; TIA, transient ischemic attack; VKA, vitamin K antagonist; VTE, venous thromboembolism.*

A predefined subgroup analysis based on valve position was performed. The VTE in the VKA group occurred in a patient with a bioprosthetic mitral valve. In the NOAC group, three events one CVA occurred in patients with bioprosthetic aortic valves (two VTEs,), and one CVA occurred in a patient with a bioprosthetic mitral valve.

## Discussion

Data on the efficacy and safety of NOACs in the prosthetic valve population are lacking. Based on the results of the RE-ALIGN trial, NOACs are not recommended in the setting of mechanical valves.[7,8] The absence of guideline recommendations regarding the use of NOACs following bioprosthetic cardiac valve replacement can be explained by the extrapolation of the mechanical valve data and the lack of additional research.

Our study is the first to report the efficacy and safety of NOACs compared with VKA therapy following bioprosthetic cardiac valve replacement irrespective of an AF diagnosis. Unlike previously published studies, factor Xa inhibitors account for 98% of the prescribed agents in the NOAC group. One patient (4.3%) in the VKA group and 4 patients (7.4%) in the NOAC group experienced a thromboembolic event within 90 days following bioprosthetic cardiac valve replacement. There are notable circumstances surrounding two of the four thromboembolic events in the NOAC group. One of the patients with a CVA apixaban was discontinued approximately 1 month before the CVA because of a nonmajor gastrointestinal bleed. In addition, one of the patients experiencing a VTE was prescribed apixaban 2.5 mg twice daily without factors necessitating dose adjustment (age 41 years old, weight 87 kg, baseline serum creatinine 1.7 mg/dL, estimated creatinine clearance 50–60 mL/min). Although these two scenarios illustrate real-world variation in practice, they limit the ability to attribute these two thromboembolic events to the NOAC prescribed. If these 2 patients are removed from the analysis, then 2 (3.8%) of the remaining 52 patients in the NOAC group experienced a thromboembolic event within 90 days of bioprosthetic cardiac valve replacement, which is consistent with the event rate observed in the VKA group (4.3%). With regard to the safety outcome of major bleeding, 2 patients in the VKA group experienced a major bleeding event. The bleeding events in the VKA group consisted of a major gastrointestinal bleed and a pericardial effusion with tamponade physiology. There were no major bleeding events in the NOAC group.

Yadlapati et al investigated the efficacy and safety of NOACs following bioprosthetic cardiac valve replacement in 73 patients with AF, with dabigatran being prescribed most commonly (60.3%).[10] No significant thromboembolic events were identified; however, major bleeding occurred in 6.9% of patients and minor bleeding in 8.2%.[10] In addition, Russo et al described the efficacy and safety of NOACs following bioprosthetic cardiac valve replacement in 122 patients with AF, with apixaban being prescribed most commonly (53.1%).[11] Two thromboembolic events were observed (1.6%), along with four cases of major bleeding (3.3%). A meta-analysis was performed by Malik et al[12] in 2019 to compare the efficacy and safety of NOACs as a class with warfarin in AF patients with native valvular heart disease and with a bioprosthetic cardiac valve. A group of 300 patients with bioprosthetic cardiac valves were identified from subgroups of the ENGAGE-AF-TIMI-48 (Global Study to Assess the Safety and Effectiveness of Edoxaban [DU-176b] vs Standard Practice of Dosing with Warfarin in Patients with Atrial Fibrillation) and ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation) trials as well as the preliminary data of the DAWA (Dabigatran Versus Warfarin after Mitral and/or Aortic Bioprosthesis Replacement and Atrial Fibrillation Postoperatively) study. This meta-analysis showed similar rates of stroke and systemic embolization, major bleeding, and all-cause mortality when comparing NOACs and warfarin in patients with AF and bioprosthetic cardiac valves.[12]

The limitations of our study include the retrospective single-center study design with a relatively small sample size. The necessity of contacting patients via telephone to gather outcomes data could have introduced potential reporting bias. Patients also had limited international normalized ratios or anti-Xa levels available for interpretation, making assessment of regimens for therapeutic dosing unfeasible. It is important to note that although levels may have been subtherapeutic or supratherapeutic, this was likely inconsequential overall based on the number of events reported.

## Conclusions

The previous literature demonstrates rates of thromboembolism of between 2% and 5% during the first 90 days following bioprosthetic cardiac valve replacement.[10] The rate of thromboembolic events in the VKA group in our study is within this range, but the rate in the NOAC group was higher at 7.4%;

however, when the two events that occurred in the NOAC group while therapy was held or inappropriately dosed are removed, the rate is 3.8%. This rate is consistent with the rate in the VKA group as well as rates previously described in the literature.[10] It is interesting that three of the four thromboembolic events that occurred in the NOAC group occurred following bioprosthetic aortic valve replacements, which typically would be considered a lower risk of thromboembolism. Notably, there were no major bleeding events in the NOAC group. Our study adds to a small pool of literature regarding the use of NOACs following bioprosthetic cardiac valve replacements and suggests that NOACs may have similar efficacy and improved safety as compared with VKA therapy. Large randomized controlled trials are warranted to confirm our observations.

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