Novel oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation after transcatheter aortic valve replacement: A systematic review and meta-analysis

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Abstract

Background: The efficacy and safety of novel oral anticoagulants (NOACs) compared to the current guideline-recommended vitamin K antagonists (VKAs) in atrial fibrillation (AF) patients undergoing transcatheter aortic valve replacement (TAVR) has not been well established. We pooled evidence from all available studies to assess the risks and benefits of this drug class.

Methods: We queried electronic databases (MEDLINE, Scopus, and Cochrane central) up until January 28th, 2022 for studies comparing NOACs to VKAs in AF patients undergoing TAVR. Results from studies were presented as risk ratios (RR) and pooled using a random-effects model. Subgroup analysis by study design and meta-regression analysis were performed to explore heterogeneity.

Results: A total of 12 studies (3 RCTs and 9 observational) containing 12,203 patients (mean age 81.2 years; 50.5% men) were identified and included in the analysis. Pooled analysis revealed no significant difference between NOACs and VKAs in terms of stroke or systemic embolism (RR: 0.78; \( p = 0.18 \)), major bleeding (RR: 0.84; \( p = 0.32 \)), intracranial hemorrhage (RR 0.61; \( p = 0.06 \)), all-cause mortality (RR: 0.69; \( p = 0.07 \)), and myocardial infarction (RR: 1.60; \( p = 0.24 \)) at a mean length of follow-up of 15.1 months. RCTs and observational studies did not significantly differ across outcomes on subgroup analysis. Meta-regression analysis found heterogeneity in all-cause mortality to be significantly explained by percentage of males (coefficient: 0.049, \( p = 0.007 \)), mean age (coefficient: 0.221, \( p < 0.001 \)), and CHA2DS2-VASc score (coefficient: −1.657, \( p < 0.001 \)).

Conclusions: This meta-analysis suggests that outcomes with NOACs do not significantly differ compared to VKAs following TAVR in patients with AF.

Keywords
atrial fibrillation, novel oral anticoagulants, transcatheter aortic valve replacement, vitamin K antagonists, Warfarin
1 | INTRODUCTION

Atrial fibrillation (AF) is one of the most clinically significant cardiac arrhythmias, and is a major cause of morbidity and mortality, especially in the United States. AF patients are at increased risk for thromboembolic events, particularly in the presence of valvular heart disease (VHD). Since both conditions primarily affect the elderly, many AF patients also have concomitant aortic stenosis (AS). While most AS patients of all risk strata (low, intermediate, and high) are candidates for TAVR, the older patients with medium to high-risk AS are preferably treated via the minimally invasive transcatheter aortic valve replacement (TAVR) procedure. Reportedly, 16%–59% of patients undergoing TAVR have pre-existing AF, that is, the presence of AF at or before the time of TAVR. These patients are frequently prescribed anticoagulants, namely vitamin K antagonists (VKAs) like warfarin, and novel (i.e., non-vitamin K antagonist) oral anticoagulants (NOACs), to reduce the risk of thromboembolic events.

The efficacy of NOACs for AF in the absence of valvular disease has already been well established, with multiple studies demonstrating their superiority to VKAs. However, the data are still unclear for AF with VHD though, despite these patients being more in need of anticoagulants. Most AF NOAC trials enrolled small numbers of AS patients relative to patients with other valvular defects, limiting the reliability of the results obtained. Currently, AS patients who have undergone TAVR are typically prescribed VKAs or antplatelet therapy, regardless of whether they have AF or not, to mitigate the risk of thrombus formation on the TAVR valve. NOACs are currently not recommended, mainly because the studies cited were stopped prematurely due to high rates of bleeding in the NOAC arms. However, newer trials compared the efficacy and safety of VKAs and NOACs in TAVR patients with AF. A prior meta-analysis compared the effects of warfarin and NOACs in post-TAVR patients. However, it did not specifically study patients with AF, that is, the indication for anticoagulation, was limited by a relatively small sample size, and assessed only a handful of adverse outcomes. In particular, there was no mention of intracranial hemorrhage (ICH), one of the most dreaded complications of antithrombotic therapy. Since this publication there have been several important trials present and published in this field, thereby necessitating an updated review and analysis.

2 | METHODS

This systematic review and meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines.

2.1 | Data sources and search strategy

Two reviewers (AAS and MMM) independently searched through the MEDLINE, Embase, and Cochrane central databases through January 28th, 2022. No time or language restrictions were set. The search strategy involved using MeSH terms to determine the different keywords for TAVR and AF coupled with the Boolean operators, "AND" and "OR." We also went through other data sources, namely bibliographies of editorials and relevant reviews from major medical journals, conference proceedings for indexed abstracts, and databases of grey/unpublished literature. The detailed search strategy for both databases is provided in Table S1.

2.2 | Study selection

The predefined eligibility criteria for our study were: (1) randomized controlled trials (RCTs) or observational studies; (2) patients with AF who underwent TAVR; (3) compared outcomes after anticoagulant therapy with NOACs versus VKAs; (4) included at least one of the following outcomes: major bleeding, stroke or systemic embolism (SSE), myocardial infarction (MI), all-cause mortality, and/or ICH. The definition of major bleeding was accepted as reported by individual studies. We had planned to also include major adverse cardiovascular event (MACE) as an outcome; however, the definition of MACE varied widely across studies and hence could not be compared.

All studies retrieved were compiled in Endnote Reference Library (Version X7.5; Clarivate Analytics) software where the duplicates were identified and removed. All the remaining articles were then thoroughly reviewed to ensure that they met our predefined eligibility criteria.

2.3 | Data extraction and assessment of study quality

Data were extracted and verified by two reviewers (AAS and MMM). The original reference articles were reviewed in the event of any discrepancies. Summary events and totals were extracted and used to calculate risk ratios (RRs) with 95% confidence intervals (CIs). In cases where summary events were not available (\(n=2\)), hazard ratios with 95% CIs were extracted and approximated to RRs. Additionally, other study characteristics like the number of participants, percentage of participants with a history of diabetes mellitus, baseline CHA2DS2-VASc score, publication year, length of follow-up, and mean/median ages were also extracted. The Newcastle-Ottawa scale was used to assess the quality of observational studies based on selection, comparability, and outcome/exposure criterion of included studies. For RCTs, the Cochrane Risk of Bias Tool (CRBT) was employed to evaluate study quality across six domains (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias).
Outcomes of interest were presented as RRs with 95% CIs, and were pooled using an inverse variance weighted random-effects model. The pooled analyses were visually represented with forest plots. Higgins $I^2$ was used to evaluate heterogeneity across studies. A value of 25%–50% was deemed mild, 50%–75% moderate, and >75% severe. Outcomes were stratified into subgroups based on study design (RCT or observational) to reduce the risk of bias. Multivariate random-effects meta-regression analysis was carried out using Open Meta-Analyst (Brown University School of Public Health Providence) to further explore heterogeneity. Outcomes with ≥10 studies (SSE, major bleeding, all-cause mortality) were included in the meta-regression analysis with the covariates of age (years), follow-up duration (days), proportion of males (%), history of diabetes mellitus (%), and baseline CHA2DS2-VASc score. Publication bias was assessed using a funnel plot and Egger’s regression test for the outcome of SSE. A $p < 0.05$ was considered significant in all cases.

3 | RESULT

3.1 | Literature search results

The complete literature search and study selection process has been outlined in the PRISMA flow diagram (Figure 1). The initial search yielded 782 potential articles. After exclusion based on title and abstract ($n = 765$), we screened 17 full-text studies, of which 12 studies (3 RCTs and 9 observational) containing 12,203 patients were finalized for this analysis.

3.2 | Study characteristics and quality assessment

Study characteristics and baseline demographics have been summarized in Table 1. Mean age of patients ranged from 71.2 to 84.4 years with an average of 81.2 years. The percentage of males varied from

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**FIGURE 1** PRISMA flow diagram outlining literature search and study selection process
<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Study design</th>
<th>Country of study</th>
<th>NOAC used</th>
<th>Concomitant antiplatelet therapy</th>
<th>Total study population, (N)</th>
<th>(N) (NOAC)</th>
<th>(N) (Warfarin)</th>
<th>Male sex (%)</th>
<th>Age (years)</th>
<th>Follow-up</th>
<th>CHA2DS2-VASc score</th>
<th>History of diabetes mellitus, (N) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geis (2018)</td>
<td>Retrospective observational</td>
<td>Germany</td>
<td>Dabigatran, rivaroxaban, apixaban, or edoxaban</td>
<td>-</td>
<td>326</td>
<td>154</td>
<td>172</td>
<td>47.2</td>
<td>Mean = 83.05</td>
<td>6 months</td>
<td>Mean 4.7</td>
<td>104 (31.9%)</td>
</tr>
<tr>
<td>Butt (2019)</td>
<td>Retrospective observational</td>
<td>Denmark</td>
<td>Dabigatran, rivaroxaban, apixaban, or edoxaban</td>
<td>90 days: DOAC = 15.7%, VKA = 14.0%; 182 days: DOAC = 6.5%, VKA = 3.9%; 365 days: DOAC = 4.0%, VKA = 2.8%</td>
<td>735</td>
<td>219</td>
<td>516</td>
<td>53.7</td>
<td>Median = 82 (77–85 IQR)</td>
<td>Median = 369 days (CI: 299–485)</td>
<td>Mean (SD) = 4.9 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Kawashima (2020)</td>
<td>Retrospective observational</td>
<td>Japan</td>
<td>-</td>
<td>SAPT: DOAC = 60.4%, VKA = 67.0%; DAPT: DOAC = 3.5%, VKA = 8.0%</td>
<td>403</td>
<td>227</td>
<td>176</td>
<td>33.3</td>
<td>Mean (SD) = 84.4 (4.7)</td>
<td>Mean (SD) = 568 days (IQR: 367–819 days)</td>
<td>5.1 (1.1)</td>
<td>98 (24.3%)</td>
</tr>
<tr>
<td>Okoh (2019)</td>
<td>Retrospective observational</td>
<td>US</td>
<td>Rivaroxaban</td>
<td>-</td>
<td>151</td>
<td>31</td>
<td>121</td>
<td>-</td>
<td>-</td>
<td>36 months</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Moon (2019)</td>
<td>Retrospective observational</td>
<td>Korea</td>
<td>Dabigatran, rivaroxaban, apixaban, or edoxaban</td>
<td>VKA = 76.0%, NOAC = 78.9%</td>
<td>5729</td>
<td>3058</td>
<td>2671</td>
<td>53.4</td>
<td>Mean = 71.2</td>
<td>Mean = 1.4 years</td>
<td>3.9</td>
<td>18.45%</td>
</tr>
<tr>
<td>Mangner (2019)</td>
<td>Retrospective observational</td>
<td>Germany</td>
<td>Dabigatran, rivaroxaban, apixaban, or edoxaban</td>
<td>All patients received clopidogrel for 6 months after TAVI</td>
<td>598</td>
<td>182</td>
<td>-</td>
<td>43.8</td>
<td>Median = 80</td>
<td>30 days</td>
<td>5.7 (49.7%)</td>
<td>239</td>
</tr>
<tr>
<td>Kosmidou I [PARTNER II] (2019)</td>
<td>Observational (RCT substudy)</td>
<td>Multinational</td>
<td>-</td>
<td>VKA = 58.5%, NOAC = 57.4%</td>
<td>933</td>
<td>155</td>
<td>778</td>
<td>65.6</td>
<td>Mean = 82.8</td>
<td>Median (IQR) = 2.8 (1.6–3.3 years)</td>
<td>5.6 (35.8%)</td>
<td></td>
</tr>
<tr>
<td>Jochheim (2019)</td>
<td>Retrospective observational</td>
<td>Multinational</td>
<td>Dabigatran, rivaroxaban, or apixaban</td>
<td>NOAC = 81.9%, VKA = 83.5%</td>
<td>962</td>
<td>326</td>
<td>636</td>
<td>47.5</td>
<td>Mean (SD) = 81.3 (6.3)</td>
<td>1 year</td>
<td>311 (32.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Seeger 2017 [CSI-TAVR]</td>
<td>RCT</td>
<td>Germany</td>
<td>Apixaban</td>
<td>100% for all patients for 4 weeks after TAVR</td>
<td>272</td>
<td>141</td>
<td>131</td>
<td>50.7</td>
<td>Mean (SD) = 81.3 (5.9)</td>
<td>30 days</td>
<td>4.9 (1.2)</td>
<td>88 (32.4%)</td>
</tr>
<tr>
<td>First author (year)</td>
<td>Study design</td>
<td>Country of study</td>
<td>NOAC used</td>
<td>Concomitant antiplatelet therapy</td>
<td>Total study population, N</td>
<td>N (NOAC)</td>
<td>N (Warfarin)</td>
<td>Male sex (%)</td>
<td>Age (years)</td>
<td>Follow-up</td>
<td>CHA2DS2 VASc score</td>
<td>History of diabetes mellitus, N (%)</td>
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<tr>
<td>Kalogeras (2019)44</td>
<td>Retrospective observational</td>
<td>Multinational</td>
<td>Dabigatran, rivaroxaban, apixaban or edoxaban</td>
<td>VKA = 98.8%, NOAC = 100%</td>
<td>217</td>
<td>115</td>
<td>102</td>
<td>57.7</td>
<td>Mean = 83.25</td>
<td>Median = 15.1 (6.2–29.1) months</td>
<td>-</td>
<td>20.15%</td>
</tr>
<tr>
<td>Van Mieghem NM [ENVISAGE-TAVI AF] (2021)22</td>
<td>RCT</td>
<td>Multinational</td>
<td>Edoxaban</td>
<td>NOAC = 46.0%, VKA = 50.4%</td>
<td>1426</td>
<td>713</td>
<td>713</td>
<td>52.5</td>
<td>Mean = 82.1</td>
<td>6–36 months</td>
<td>Mean = 4.5</td>
<td>527 (37.0%)</td>
</tr>
<tr>
<td>Collet JP [ATLANTIS] (2021)20</td>
<td>RCT</td>
<td>Multinational</td>
<td>Apixaban</td>
<td>VKA = 88.6%, NOAC = 0%</td>
<td>451</td>
<td>223</td>
<td>228</td>
<td>46.9</td>
<td>Mean = 81.95</td>
<td>1 year</td>
<td>4.35</td>
<td>435 (29%)</td>
</tr>
</tbody>
</table>

Abbreviations: ATLANTIS, anti-thrombotic strategy after trans-aortic valve implantation for aortic stenosis; CSI-TAVR, coronary and structural interventions-transcatheter aortic valve replacement; DAPT, dual antiplatelet therapy; ENVISAGE-TAVI AF, edoxaban compared to standard care after heart valve replacement using a catheter in patients with atrial fibrillation; IQR, interquartile range; NOAC, novel oral anticoagulant; PARTNER II, Placement of AoRTic TranScatheter Valves-II A; RCT, randomized controlled trial; SAPT, single antiplatelet therapy; SD, standard deviation.

The results of multivariate random-effects meta-regression analysis have been summarized in Table S3. Increasing mean age significantly contributed to the inter-study heterogeneity observed across all outcomes, namely SSE (coefficient: 0.105, p < 0.001), and all-cause mortality (coefficient: 0.103, p < 0.001), and all-cause mortality (coefficient: 0.023, p < 0.001) were significantly associated with between-study heterogeneity, whereas a pooled data on MI. Meta-analysis showed no significant difference between NOACs and VKAs with respect to MI (RR: 1.40 [95% CI: 0.72, 2.74]; p = 0.24, p = 0.05). Subgroup analysis showed no significant difference between NOACs and VKAs with respect to ICH (RR: 0.69 [95% CI: 0.46, 1.03]; p = 0.07, p = 0.88) at a mean duration of follow-up of 15.1 months. No significant difference was observed when separating the outcome by RCTs or observational studies (p value for interaction = 0.08).

**3.3 | Outcome analysis**

For the composite outcome of SSE, NOACs significantly reduced the risk of SSE compared to VKAs (RR: 0.79 [95% CI: 0.61, 0.99]; p = 0.03, p = 0.08). Similarly, a significant reduction in the risk of MI was observed when separating the outcome by RCTs or observational studies (RR: 0.51 [95% CI: 0.31, 0.82]; p = 0.02, p = 0.06). Subgroup analysis did not reveal any significant difference (p value for interaction = 0.28). Major bleeding (Figure 3) observed a significant difference on major bleeding. Pooling analysis did not show a significant difference between NOACs and VKAs (RR: 0.84 [95% CI: 0.59, 1.21]; p = 0.42, p = 0.81). Subgroup analysis by study design (RCT or observational) revealed no significant difference (p value for interaction = 0.07).

Major bleeding (Figure 3) observed a significant difference on major bleeding. Pooling analysis did not show a significant difference between NOACs and VKAs (RR: 0.84 [95% CI: 0.59, 1.21]; p = 0.42, p = 0.81). Subgroup analysis by study design (RCT or observational) revealed no significant difference (p value for interaction = 0.07).
### DISCUSSION

This comprehensive systematic review and meta-analysis of 12 studies comprising of 12,203 patients compared outcomes with NOACs to VKAs in patients with AF undergoing TAVR. The use of NOACs was not significantly associated with a decrease in major bleeding, SSE, MI, all-cause mortality, or ICH compared to VKAs. This data significantly updates a prior attempt at meta-analysis by including data from five additional studies, including the recently completed ATLANTIS and ENVISAGE-TAVI AF trials, thus significantly increasing statistical power and subsequent confidence in the findings.

Although the noninferior safety and efficacy profile of NOACs to VKA has been well-established in patients with nonvalvular AF, barring few contraindications like advanced Chronic Kidney Disease, the choice of anticoagulant is still widely debated in the setting of AF with VHD, especially post-TAVR. Our analysis adds significant insight to the growing body of literature. Considering NOACs were not found to be more efficacious or safer than VKAs after TAVR, one possible explanation for this could be that patients selected for TAVR when compared to patients in non-TAVR settings tend to be relatively older and frailer. Consequently, such patients present an additional risk of suffering from a non-AF-related stroke, biasing the effect of NOACs in preventing cardioembolic stroke in AF.

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**FIGURE 2** Forest plot comparing NOACs with VKA for stroke or systemic embolism (SSE). CI, confidence interval; NOAC, novel oral anticoagulants; VKA, vitamin K antagonists [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 3** Forest plot comparing NOACs with VKA for major bleeding. CI, confidence interval; NOAC, novel oral anticoagulants; VKA, vitamin K antagonists [Color figure can be viewed at wileyonlinelibrary.com]
patients to the null. Indeed, our meta-regression results lend support to this hypothesis, showing increasing age to account for differences in outcomes between studies. Furthermore, our finding of no difference in SSE between NOACs and VKAs differs from the study by Liang et al.\textsuperscript{15} where VKAs significantly reduced the stroke outcome. This could be due to two reasons; first, we treated stroke and systemic embolism as a composite outcome as opposed to stroke only in Liang et al. study,\textsuperscript{15} thereby incorporating more data points. Second, VKAs reduced the risk of stroke in the prior study only when pooling data from observational studies, which are inherently prone to confounding and selection bias, and not RCTs. Our subgroup analysis, on the other hand, confirmed that both RCTs and observational studies were congruent for all outcomes.

Additionally, baseline CHA2DS2-VASc score was significantly associated with all-cause mortality in our meta-regression analysis. This is in agreement with studies by Hamid et al.\textsuperscript{33} and Orvin et al.,\textsuperscript{34} which suggests a significant association between increasing CHA2DS2-VASc scores and increased rate of stroke and mortality at 1 year, and raises the possibility of using CHA2DS2-VASc scores in quantifying risk for mortality in post-TAVR patients. Nevertheless, these results should be viewed as hypothesis-generating and need to be interpreted with caution.

### Table 4.1

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>NOAC Total</th>
<th>VKA Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seeger et al. [CSI-TAVR trial]</td>
<td>1.026</td>
<td>1.6283</td>
<td>141</td>
<td>131</td>
<td>2.6%</td>
<td>2.79 [0.11, 67.86]</td>
<td>2017</td>
</tr>
<tr>
<td>Van Mieghem et al. [ENVISAGE-TAVI AF trial]</td>
<td>-0.2719</td>
<td>0.3276</td>
<td>713</td>
<td>713</td>
<td>38.0%</td>
<td>0.76 [0.40, 1.45]</td>
<td>2021</td>
</tr>
</tbody>
</table>

Subtotal (95% CI)

| Heterogeneity: Tau² = 0.03; df² = 1 (P = 0.43); I² = 0% |
| Test for overall effect: Z = 0.69 (P = 0.49) |

### Figure 4

Forest plot comparing NOACs with VKA for intracranial hemorrhage (ICH). NOAC, novel oral anticoagulants; VKA, vitamin K antagonists [Color figure can be viewed at wileyonlinelibrary.com]

### Table 4.2

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>NOAC Total</th>
<th>VKA Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geis et al.</td>
<td>1.209</td>
<td>1.629</td>
<td>154</td>
<td>172</td>
<td>2.6%</td>
<td>3.35 [0.14, 81.60]</td>
<td>2018</td>
</tr>
<tr>
<td>Moon et al.</td>
<td>-0.7985</td>
<td>0.2151</td>
<td>3058</td>
<td>2671</td>
<td>56.9%</td>
<td>0.45 [0.30, 0.69]</td>
<td>2019</td>
</tr>
</tbody>
</table>

Subtotal (95% CI)

| Heterogeneity: Tau² = 0.67; df² = 3 (P = 0.22); I² = 33% |
| Test for overall effect: Z = 0.58 (P = 0.56) |

### Figure 5

Forest plot comparing NOACs with VKA for all-cause mortality. CI, confidence interval; NOAC, novel oral anticoagulants; VKA, vitamin K antagonists [Color figure can be viewed at wileyonlinelibrary.com]
perceive them to be more effective. The contrasting trends between RCTs and observational studies observed in major bleeding might be a result of possible selection bias introduced through observational studies due to reverse causation.

To the best of our knowledge, our study is the first to include data from the highly awaited ATLANTIS (Anti‐Thrombotic Strategy After Trans‐Aortic Valve Implantation for Aortic Stenosis; NCT02664649) and ENVISAGE‐TAVI AF (Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation) trials, two multi‐center open‐label RCTs with a combined sample size of 2936 patients. These trials add to the scant pool of RCTs investigating the optimal antithrombotic therapy following TAVR. The results of the trial outcomes corroborate our results of NOACs being equal to VKAs in all safety and efficacy endpoints. Although major bleeding was found to be significantly higher in the NOAC arm of ENVISAGE‐TAVI AF, this effect was mostly driven by an increased incidence of gastrointestinal bleeding in that arm and was not observed in any other trial. Nevertheless, these findings hold significance as they can translate into clinicians safely being able to switch patients from VKAs to NOACs without fear of posing any additional risk to the patient. It should be noted that warfarin use is limited by a narrow therapeutic index that necessitates frequent International Normalized Ratio monitoring and dose adjustments, thereby complicating treatment and reducing adherence, which can lead to poorer prognosis. NOACs are free of such limitations, and thus are more likely to lead to higher adherence and lower complications. Furthermore, assessment of platelet reactivity using assays such as Light Transmission Aggregometry can serve as a powerful tool for predicting thrombotic or bleeding outcomes and help to individualize patient risk. Considering the lack of a clearly superior antithrombotic agent, a reasonable approach would be to provide an individualized risk‐adjusted antithrombotic therapy. Ultimately, clinicians should carefully assess the preferences, quality of life, socioeconomic status, and most importantly, pre‐existing comorbidities for each patient to drive individualized treatment decisions.

Moreover, other avenues could also be targeted to reduce risk of thromboembolism, such as LAAC (left atrial appendage closure), as is being investigated by the ongoing WATCH‐TAVR trial (WATCHMAN for Patients With Atrial Fibrillation Undergoing Transcatheter Aortic Valve Replacement; NCT03173534). This intervention could prove to be a feasible substitute for long term anticoagulation in patients at high risk.

Our study is subject to certain limitations. First, most outcomes suffered from moderate to severe levels of heterogeneity. Therefore, we employed subgroup and meta‐regression analysis to address possible causes. Second, we pooled RCTs with observational studies, the latter of which may be subject to confounding and multiple forms of bias. However, subgroup analysis stratifying outcomes by RCTs and observational studies proved agreement between the two study designs in terms of statistical significance, strengthening the confidence of our results. Third, the exact NOAC used varied between each individual study and could be a source of potential heterogeneity. Fourth, while only patients in stratum 1 of the ATLANTIS trial were included in the present analysis, baseline demographics were reported for all strata combined and hence had to be used for meta‐regression analysis.

## CONCLUSION

In conclusion, in patients undergoing TAVR, NOACs were not significantly different from VKAs with regard to all‐cause mortality, major bleeding, SSE, MI, or ICH. Therefore, NOACs can serve as a reasonable alternative for patients after TAVR without incurring the drawbacks of VKAs. Future large‐scale clinical trials are warranted to establish a clinically superior anticoagulant regime post‐TAVR.

## ACKNOWLEDGMENTS

The abstract of this study has been accepted for presentation at the American Heart Association (AHA) Scientific Sessions 2021. The author(s) received no financial support for the research, authorship, and/or publication of this article.
CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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REFERENCES


**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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