


## Original Investigation

# Risk of Substantial Intraocular Bleeding With Novel Oral Anticoagulants

## Systematic Review and Meta-analysis

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**IMPORTANCE** In noninferiority trials, novel oral anticoagulants (NOACs), also known as non-vitamin K oral anticoagulants, were at least noninferior to standard care in the prevention of most prothrombotic conditions. However, differences exist in the safety profile of antithrombotic drugs, and little is known about their intraocular bleeding risk.

**OBJECTIVE** To evaluate the risk of substantial intraocular bleeding associated with NOACs.

**DATA SOURCES** MEDLINE, Cochrane Library, SciELO collection, and Web of Science databases were searched from inception to November 2014, as well as other systematic reviews and regulatory agencies documentation.

**STUDY SELECTION** All phase 3 randomized clinical trials (RCTs) comparing NOACs with any other control that reported intraocular bleeding events.

**DATA EXTRACTION AND SYNTHESIS** Data were extracted independently by 2 of the authors and pooled using random-effects meta-analysis. Heterogeneity was assessed with the  $I^2$  test.

**MAIN OUTCOMES AND MEASURES** Substantial intraocular bleeding was evaluated with pooled risk ratios (RRs) and 95% CIs.

**RESULTS** Seventeen RCTs were included. In patients with atrial fibrillation, no difference was identified between NOACs and vitamin K antagonists (RR, 0.84; 95% CI, 0.59-1.19;  $I^2 = 35%$ ; 5 RCTs), and no increased risk was identified compared with acetylsalicylic acid (RR, 14.96; 95% CI, 0.85-262.00; 1 RCT). In patients with venous thromboembolism, no increased risk of substantial intraocular bleeding compared with sequential treatment with low-molecular-weight heparin and a vitamin K antagonist (RR, 0.67; 95% CI, 0.37-1.20;  $I^2 = 0%$ ; 5 RCTs) was identified. Regarding patients who underwent orthopedic surgery, the risk was not different between NOACs and low-molecular-weight heparin (RR, 2.13; 95% CI, 0.22-20.50;  $I^2 = 0%$ ; 5 RCTs).

**CONCLUSIONS AND RELEVANCE** Randomized data suggest that no differences exist in the risk of substantial intraocular bleeding between NOACs and other antithrombotic drugs. However, the number of events was scarce so that additional studies from larger databases that monitor patients under conditions of ophthalmologic routine clinical practice should be performed to better characterize the safety profile of NOACs.

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The novel oral anticoagulants (NOACs), also called non-vitamin K oral antagonist anticoagulants,<sup>1</sup> are still relatively new agents on the market, and reports describing their risks for patients are still uncommon. The NOACs are safer than existing anticoagulation therapies, significantly reducing intracranial hemorrhage risk compared with vitamin K antagonists (VKAs) and sequential treatment with low-molecular-weight heparin (LMWH) and VKAs.<sup>2</sup> However, safety concerns remain, especially when taking into account that no reversal agent is systematically available. Intraocular hemorrhage is a serious adverse event for patients taking antithrombotic drugs (<1%).<sup>3</sup> Although rare,<sup>4</sup> substantial intraocular hemorrhages can cause severe visual acuity impairment, and in some cases, surgery is needed for complete resolution.<sup>5</sup> Therefore, we aimed to better estimate the risk of substantial intraocular bleeding, a bleeding event defined by default as major bleeding,<sup>6</sup> associated with NOACs through a systematic review and meta-analysis of phase 3 randomized clinical trials (RCTs).

## Methods

This systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as a guideline.<sup>7</sup>

### Eligibility Criteria

For this systematic review, we considered published RCTs that evaluated patients treated with NOACs, such as dabigatran etexilate, apixaban, edoxaban, or rivaroxaban, compared with any other active or placebo control. We considered all trials with prothrombotic conditions eligible for anticoagulation treatment, irrespective of patients' baseline disease, drug treatment duration, or follow-up. Only phase 3 RCTs were included to obtain robust data without the bias associated with statistical effects of small, underpowered studies on meta-analysis results.<sup>8-11</sup> Furthermore, we were interested in determining the risk associated with approved NOACs and their commonly used doses.

### Information Sources

MEDLINE, Cochrane Library (CENTRAL), SciELO collection, and Web of Science databases (inception to November 8, 2014) were searched to retrieve RCTs evaluating the intraocular bleeding risk of NOACs. The search strategy is outlined in the eMethods in the Supplement. There were no language restrictions.

Reference lists of systematic reviews, as well as the reference list of each included study, were comprehensively searched. Because the conventional search may not detect intraocular bleeds not mentioned in the title or abstract in the electronic record (even though they appear in the full report),<sup>12,13</sup> we sought bleeding data of all published phase 3 RCTs and available public reports of these drugs in the websites of regulatory entities (US Food and Drug Administration, European Medicines Agency, and Australian Therapeutic Goods Administration), similarly to previous work,<sup>14,15</sup> irrespective of the initial search.

### Study Selection

After study deduplication, the references obtained in the electronic search were screened independently by 2 authors (D.C. and M.B.) through title and abstract for full-text assessment eligibility. Irrespective of the results of this search, these authors retrieved independently intraocular bleeding estimates of all published and previously identified phase 3 RCTs.

Study characteristics and results were extracted into a standardized form. Included studies were appraised for methodologic bias risk with Cochrane Collaboration's Risk of Bias Tool.<sup>16</sup> Studies were not excluded a priori based on quality reporting assessment.

### Outcome Measures

The primary outcome was substantial intraocular bleeding considered by the International Society on Thrombosis and Hemostasis as critical organ bleeding and therefore classified as major bleeding.<sup>6</sup>

### Statistical Analysis

We used RevMan software, version 5.3.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), for statistical analysis and to derive a forest plot showing the results of individual studies and pooled analysis. We compared NOACs with controls (active drugs or placebo) through random-effects meta-analysis to estimate pooled risk ratios (RRs) and 95% CIs. The effect measurement estimate chosen was RR because relative measures are more similar across studies with different designs, populations, and lengths of follow-up compared with absolute measures, such as risk difference.<sup>17</sup>

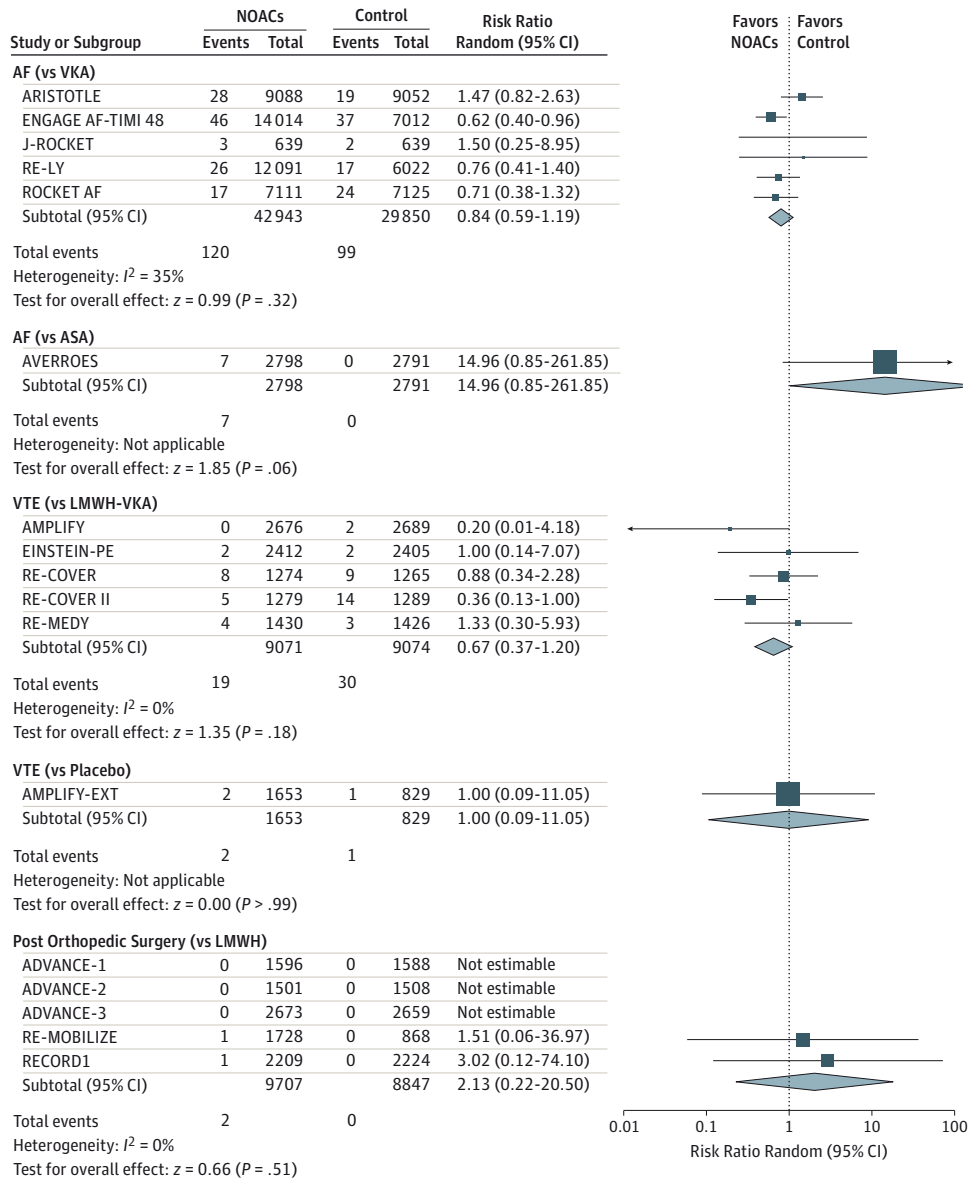
Heterogeneity measured as the percentage of total variation between studies due to heterogeneity was assessed through the  $I^2$  test.<sup>18</sup> We used a Mantel-Haenszel random-effects model irrespective of the existence of substantial heterogeneity between the study results ( $I^2 > 50%$ ) because we pooled results of studies with different designs and patient characteristics. When differences were found ( $P < .05$ ), we planned to determine the number needed to treat and 95% CI, taking into account the control baseline risk.

Pooled analyses were performed according to control groups, which reflect the baseline conditions. Publication bias was assessed through visual inspection of funnel plot asymmetry.

## Results

After study selection process (eFigure 1 in the Supplement), 17 RCTs fulfilled the inclusion criteria<sup>19-35</sup>; 6 trials included 78 382 patients with nonvalvular atrial fibrillation (AF) (5 of them were VKA-controlled trials,<sup>19-23</sup> and 1 compared a NOAC [apixaban] with acetylsalicylic acid<sup>24</sup>), 6 RCTs enrolled 20 627 patients with venous thromboembolism (5 trials with LMWH-VKA control<sup>25,27-29,36</sup> and 1 placebo-controlled trial<sup>35</sup>), and 5 trials included 18 554 patients who underwent orthopedic surgery (with LMWH control).<sup>30-34</sup> Further details on included studies are given in the eTable in the Supplement. Overall, the included studies had a low risk of bias (eFigure 2 in the

Figure 1. Forest Plot: Risk Ratios for Intraocular Bleeding With NOACs



ADVANCE indicates Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation; AF, atrial fibrillation; AMPLIFY, Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; AMPLIFY-EXT, Apixaban After the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis With First-Line Therapy-Extended Treatment; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ASA, acetylsalicylic acid; AVERROES, Apixaban vs Acetylsalicylic Acid to Prevent Strokes; EINSTEIN-PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; ENGAGE AF-TIMI 48, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; J-ROCKET, Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; LMWH, low-molecular-weight

heparin; NOACs, novel oral anticoagulants; RECORD1, Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 1; RE-COVER, Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-COVER II, Phase III Study Testing Efficacy & Safety of Oral Dabigatran Eteixilate vs Warfarin for 6 months Treatment for Acute Symptomatic Venous Thromboembolism; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; RE-MEDY, Secondary Prevention of Venous Thrombo Embolism; RE-MOBILIZE, Oral Thrombin Inhibitor Dabigatran Eteixilate vs North American Enoxaparin Regimen for Prevention of Venous Thromboembolism After Knee Arthroplasty; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Supplement). Pooled analysis for the different clinical conditions and controls did not identify an increased risk of substantial intraocular bleeding with NOACs (Figure 1).

Among patients with nonvalvular AF, no difference was identified between NOACs and VKA (RR, 0.84; 95% CI, 0.59-1.19;  $I^2 = 35\%$ ). The incidence of intraocular bleeding events

reported in patients treated with NOACs and VKAs was 0.28% (n = 120/42 943) and 0.33% (n = 99/29 850), respectively.

One trial<sup>24</sup> compared a NOAC (apixaban) with acetylsalicylic acid in 5599 patients with nonvalvular AF. The incidence of intraocular bleeding events reported in the apixaban and acetylsalicylic acid groups was 0.25% (n = 7/2798) and 0% (n = 0/2791), respectively (RR, 14.96; 95% CI, 0.85-262.00).

Among patients with venous thromboembolism, no difference was identified between NOACs and sequential LMWH-VKA (RR, 0.67; 95% CI, 0.37-1.20; *I*<sup>2</sup> = 0%). The incidence of intraocular bleeding events reported in patients treated with NOACs and LMWH-VKA was 0.21% (n = 19/9071) and 0.33% (n = 30/9074), respectively. In the venous thromboembolism extended-treatment placebo-controlled trial,<sup>35</sup> no increased risk of intraocular bleeding was detected.

A total of 18 554 patients undergoing orthopedic surgery were enrolled in 5 RCTs evaluating anticoagulation drugs for thromboprophylaxis. Only 2 of these RCTs reported intraocular bleeding events (one event in patients treated with NOACs and no events in the LMWH control group in each trial), yielding no differences in the risk of intraocular bleeding (RR, 2.13; 95% CI, 0.22-20.50; *I*<sup>2</sup> = 0%).

Figure 2 shows the risk of intraocular bleeding according to each NOAC and the respective control. With the exception of the comparison between edoxaban and VKAs in nonvalvular AF (RR, 0.62; 95% CI, 0.40-0.96; 1 RCT),<sup>20</sup> all comparisons between individual NOACs and controls were nonsignificant. A funnel plot does not suggest a publication bias toward a specific treatment (eFigure 3 in the Supplement).

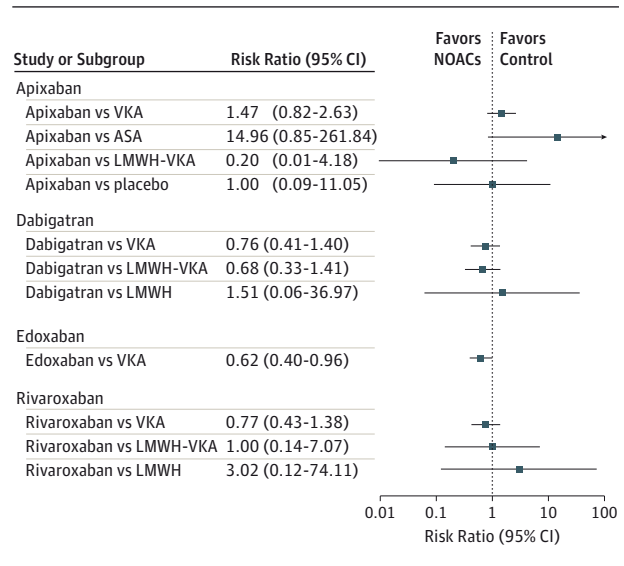
## Discussion

Our study highlights the absence of evidence about differences in the risk of substantial intraocular bleeding between NOACs and other antithrombotic drugs, namely, VKAs and LMWH. This information is clinically relevant for ophthalmologists treating patients undergoing intraocular procedures while receiving anticoagulation. The information available comparing NOACs and antiplatelet agents is scarce, and only one trial<sup>24</sup> (Apixaban vs Acetylsalicylic Acid to Prevent Strokes) reported data for this comparison in patients with nonvalvular AF. The differences reported between apixaban and acetylsalicylic acid failed to reach statistical significance. It remains unknown whether this risk could be by chance because the trial was not powered for intraocular bleeding risk estimation. It is also unknown whether baseline characteristics were balanced for intraocular bleeding risk factors.

In the RCTs considered in this systematic review and meta-analysis, only substantial intraocular bleeding (ie, hyphema, vitreous hemorrhage, subretinal hemorrhage, and suprachoroidal hemorrhage) was considered a major bleeding event. This definition respects the criteria established by the International Society on Thrombosis and Hemostasis,<sup>6</sup> excluding minor uncomplicated bleedings, such as subconjunctival hemorrhages.

Patients with neovascular age-related macular degeneration treated with antiplatelet and anticoagulant drugs have an increased risk of intraocular hemorrhage.<sup>37</sup> The clinical rel-

Figure 2. Intraocular Bleeding Risk With Each Novel Oral Anticoagulant (NOAC)



ASA indicates acetylsalicylic acid; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.

evance of these events relies on the possibility of the development of severe visual acuity impairment.<sup>38</sup> According to a retrospective case-control study, this risk was clearly associated with warfarin treatment and to a lesser extent with antiplatelet drugs,<sup>39</sup> which at least partially overlaps with our results.

In the Randomized Evaluation of Long-Term Anticoagulation Therapy trial,<sup>40</sup> approximately 800 patients treated with dabigatran (and 400 patients treated with VKAs) underwent minor surgery, and approximately one-third of these patients underwent cataract removal. Despite the absence of data specific for eye surgery, the overall estimate for minor surgery did not reveal a significant increased risk of major bleeding (dabigatran etexilate, 110 mg: RR, 1.03; 95% CI, 0.39-2.71; and dabigatran etexilate, 150 mg: RR, 1.75; 95% CI, 0.74-4.14).<sup>40</sup> Despite all this, to the best of our knowledge, no studies with detailed data about NOACs and intraocular bleeding, whether spontaneous or after surgery, have been published. Although cataract surgery appears to be an uneventful and safe surgery to perform in patients undergoing anticoagulation,<sup>41</sup> it is important to clarify the effect of VKAs and NOACs in some types of more invasive ophthalmic operations with greater risks.<sup>42</sup> Unfortunately, whether patients undergoing intraocular surgery are at increased risk of severe hemorrhage with the use of these drugs is not answered by our work. Our data support that existing guidance of other anticoagulations would also be appropriate for NOACs. Published consensus-based guidance specifically for the management of NOACs does not support the withdrawal of anticoagulation in patients undergoing cataract or glaucoma interventions.<sup>4</sup>

In the existing medical literature, there is one case report of intraocular bleeding in an 82-year-old patient who developed a spontaneous choroidal hemorrhage after taking dabigatran for stroke prophylaxis in the context of atrial fibrillation for approximately 1 year.<sup>43</sup>

With the convenience of not having to perform frequent blood draws to monitor the therapeutic international normalized ratio, NOACs are expected to become more popular among patients. The risk of intraocular hemorrhage has to be weighed in each case. Ensuring that an appropriate medication dosage is maintained and paying attention to potential risk factors and hemorrhagic symptoms should be a concern for the treating physician and health care staff.

This analysis is limited by methodologic issues associated with meta-analysis and individual studies. The results of our meta-analysis are based on study-level data and not on individual patient data. Most of these studies were powered for a cardiovascular or a vascular primary outcome and not for a rare specific source of major bleeding as we assess in this review.

Data for our outcomes were not available in some studies, which restrains our review for robust conclusions. In fact, details of intraocular bleeding events were mostly absent from studies. Substantial intraocular bleeding was an uncommon event regardless of the antithrombotic interventions. Our study did not identify intraocular bleeding risk differences, but the wideness of the CIs in some analyses preclude a definite answer.

Pooling data of studies with different designs should also be accounted for as a further methodologic limitation of our study. Nevertheless, it increases the power and external validity of the findings. We also pooled the different NOACs under the assumption of a class effect of these drugs in bleeding events. Despite the pharmacodynamic and pharmacokinetic differences among NOACs,<sup>4</sup> no significant differences were found among NOACs in the meta-analysis.

## Conclusions

Overall, NOACs do not increase the risk of substantial intraocular bleeding compared with other anticoagulants (VKAs and/or LMWH). The rate of these serious events was very low (<0.4%) and they were reported in studies that were underpowered for this purpose. Therefore, additional observational studies from larger databases monitoring patients under conditions of ophthalmologic routine clinical practice should be performed to better characterize the safety profile of NOACs.

### ARTICLE INFORMATION

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**Author Contributions:** Dr Caldeira had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Caldeira, Costa.

*Acquisition, analysis, or interpretation of data:* All authors.

*Drafting of the manuscript:* Caldeira, Canastro, Barra, Costa.

*Critical revision of the manuscript for important intellectual content:* All authors.

*Statistical analysis:* Caldeira, Canastro, Costa.

*Administrative, technical, or material support:*

Caldeira, Barra, A. Ferreira, Costa, J. Ferreira.

*Study supervision:* Caldeira, Costa, Pinto, J. Ferreira.

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