



## Risk of Intraocular Bleeding With Novel Oral Anticoagulants Compared With Warfarin

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### ABSTRACT

**Background:** The literature surrounding the risk of intraocular bleeding associated with novel oral anticoagulants (NOACs) compared to warfarin reveals a complex interplay of efficacy and safety outcomes. **Literature Review:** The systematic review by (Sardar et al., 2013) highlighted the significant reduction in intracranial bleeding risks among NOAC users, which is particularly relevant for patients with atrial fibrillation and a history of stroke or transient ischemic attacks. Focusing specifically on intraocular bleeding, (Park et al., 2020) provided evidence that NOACs may exhibit a lower risk of intraocular bleeding in patients with retinal vascular diseases, particularly among those with diabetes. This suggests that NOACs could be a safer option in populations where intraocular bleeding is a concern. However, the study also emphasized the need for more targeted research to clarify these risks further. The investigations conducted in 2011 by (Reum Choe et al., 2011) and (Waranugraha et al., 2011) highlighted the complexities surrounding gastrointestinal bleeding, revealing inconsistent findings regarding the bleeding risks associated with NOACs compared to warfarin. This inconsistency underscores the need for a nuanced understanding of bleeding risks across different clinical settings and patient populations. Finally, (Liu et al., 2012) emphasized the variability in results regarding recurrent events and bleeding risks in real-world studies, indicating that while NOACs may offer certain advantages, the overall safety profile, particularly concerning intraocular bleeding, remains complex and warrants ongoing research. **Conclusion:** In conclusion, the literature demonstrates that NOACs generally present a lower risk of major bleeding events compared to warfarin, with specific advantages in reducing intracranial and potentially intraocular bleeding risks. However, the variability in bleeding risks across different studies and patient populations highlights the need for individualized treatment approaches and further research to establish clearer safety profiles for NOACs, particularly in the context of intraocular bleeding.

**Keyword:** Risk of Intraocular Bleeding, Novel Oral Anticoagulants, Warfarin

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## INTRODUCTION

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The literature surrounding the risk of intraocular bleeding associated with novel oral anticoagulants (NOACs) compared to warfarin reveals a complex interplay of efficacy and safety outcomes. The initial investigation by (D Fox et al., 2012) established a foundational understanding of the relative safety profiles of NOACs and vitamin K antagonists, indicating that while rivaroxaban was associated with a decreased risk of major bleeding, no significant differences were noted in all-cause mortality between these anticoagulants. This study set the stage for subsequent analyses focusing on specific bleeding risks, particularly within the context of stroke prevention and atrial fibrillation.

In 2013, (Sardar et al., 2013) expanded the conversation by systematically reviewing trials comparing NOACs with warfarin, emphasizing the notable reduction in the risk of intracranial bleeding among patients receiving NOACs. This meta-analysis provided crucial insights into the safety of NOACs, particularly in patients with a history of stroke or transient ischemic attacks (TIAs), thereby highlighting their potential advantages over warfarin in certain clinical scenarios.

(Deng et al., 2019) further corroborated these findings by demonstrating that NOACs were associated with a decreased risk of both intracranial and gastrointestinal bleeding compared to warfarin. Their systematic review and meta-analysis indicated a strong tendency towards a reduced risk of major bleeding events, although the differences in risks of clinically relevant bleeding were not statistically significant. This suggests that while NOACs may offer safety benefits, the nuances surrounding their bleeding risks require careful consideration.

(Park et al., 2020) provided a focused examination of intraocular bleeding specifically in patients with retinal vascular diseases. Their study found that NOACs exhibited a lower risk of intraocular bleeding compared to warfarin, particularly among patients with diabetes and those without a prior history of stroke. The findings emphasized the potential safety of NOACs in this specific population, suggesting mechanisms that might explain the reduced bleeding risk.

In 2011, (Reum Choe et al., 2011) explored the clinical outcomes of gastrointestinal bleeding in patients on NOACs compared to vitamin K antagonists. They noted that while NOACs were preferred for preventing strokes in non-valvular atrial fibrillation, the understanding of their bleeding risks, particularly gastrointestinal bleeding, remained ambiguous. This study highlighted the ongoing concerns regarding the safety of NOACs and called for further investigation into their bleeding profiles.

The same year, (Waranugraha et al., 2011) conducted a systematic review that included real-world evidence, revealing inconsistent results regarding the risk of gastrointestinal bleeding compared to major and intracranial bleeding. This inconsistency underscores the complexity of assessing bleeding risks across different settings and populations.

Finally, (Liu et al., 2012) added to this discourse by analyzing real-world studies on NOACs in venous thromboembolism patients, which reported conflicting findings regarding recurrent events and bleeding risks. This variability in data emphasizes the need for a nuanced understanding of how NOACs perform in diverse clinical scenarios.

Collectively, these studies provide a comprehensive view of the safety profiles of NOACs compared to warfarin, particularly concerning the risk of intraocular bleeding. The evolving evidence suggests that while NOACs may offer certain advantages, particularly in reducing the risk of intracranial bleeding, the overall assessment of their safety profile remains complex and warrants ongoing research.

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### LITERATURE REVIEW

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The article by (D Fox et al., 2012) provides a comprehensive analysis of the efficacy and safety of novel oral anticoagulants (NOACs) in the context of treating acute venous thromboembolism, with a particular focus on their bleeding risks compared to vitamin K antagonists, such as warfarin. The authors conducted a direct and adjusted indirect meta-analysis of randomized controlled trials, which

adds a robust layer of evidence to the discussion surrounding the safety profiles of these anticoagulants.

One of the key findings of the study is that there was no significant difference in the rates of recurrent acute venous thromboembolism between NOACs and warfarin. This is particularly relevant when assessing the clinical decision-making process for patients at risk of thromboembolic events, as it suggests that NOACs may be a viable alternative without compromising efficacy. However, the article highlights rivaroxaban as the only NOAC associated with a decreased risk of major bleeding, which is crucial information for clinicians considering anticoagulation therapy in patients who may be at risk for intraocular bleeding.

The authors also note the absence of heterogeneity among the studies analyzed, which strengthens the reliability of their conclusions. This uniformity across studies suggests a consistent safety profile for NOACs, particularly in terms of major bleeding events, which is a significant concern for patients undergoing anticoagulation therapy. The lack of evidence of differences in all-cause mortality between NOACs and conventional treatments further supports the argument that NOACs can be used safely in the appropriate patient populations.

However, while the findings are promising, it is essential to consider the broader implications of these results. The article does not delve deeply into the specific risks of intraocular bleeding associated with NOACs, which remains a critical area of inquiry for ophthalmologists and other specialists managing patients on anticoagulants. Future research should aim to explore these specific risks in greater detail, particularly given the increasing use of NOACs in clinical practice.

The article titled "New Oral Anticoagulants Are Not Superior to Warfarin in Secondary Prevention of Stroke or Transient Ischemic Attacks, but Lower the Risk of Intracranial Bleeding: Insights from a Meta-Analysis and Indirect Treatment Comparisons" by (Sardar et al., 2013) provides a comprehensive analysis of the efficacy and safety of novel oral anticoagulants (NOACs) compared to warfarin in patients with atrial fibrillation (AF) and a history of stroke or transient

ischemic attacks (TIAs). The authors systematically reviewed randomized controlled trials (RCTs) published between January 2001 and September 2012, focusing on the outcomes of ischemic stroke and intracranial bleeding.

The methodology employed by the authors is robust, utilizing a thorough literature search across multiple databases, including PubMed and Cochrane CENTRAL. This systematic approach ensures a wide-ranging collection of relevant data, which strengthens the validity of their findings. The inclusion criteria for RCTs, specifically those with long-term follow-up, allow for a more accurate assessment of the long-term effects of NOACs compared to warfarin.

One of the key insights from the article is the finding that while NOACs, specifically dabigatran, rivaroxaban, and apixaban, do not demonstrate superiority over warfarin in preventing ischemic strokes or TIAs, they are associated with a significantly lower risk of intracranial bleeding. This outcome is particularly important for clinicians when considering anticoagulant therapy for patients with AF, as intracranial bleeding is a serious complication that can lead to significant morbidity and mortality. The authors provide a detailed statistical analysis, including odds ratios and confidence intervals, which supports their conclusions regarding the safety profile of NOACs compared to warfarin.

Furthermore, the use of indirect treatment comparisons through Bucher's method adds depth to the analysis, allowing for a nuanced understanding of the relative efficacy and safety of the three NOACs. The assessment of heterogeneity and publication bias through Cochran's Q test and funnel plots demonstrates the authors' commitment to ensuring the reliability of their results.

The systematic review and meta-analysis conducted by (Deng et al., 2019) provides valuable insights into the comparative safety of non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin, particularly in patients with cancer and atrial fibrillation. The article primarily emphasizes the bleeding risks associated with these anticoagulants, which is a critical concern in clinical practice.

One of the key findings of the study is that the use of NOACs is associated with a decreased risk of intracranial and gastrointestinal bleeding when compared to warfarin. This is particularly significant given that intracranial bleeding can lead to severe morbidity and mortality. The authors note a strong tendency toward statistical significance for a reduced risk of major bleeding events in patients treated with NOACs, which suggests that these agents may offer a safer profile in this specific patient population.

However, the article also highlights that while NOACs show a trend towards lower major bleeding risks, the differences in risks of major or non-major clinically relevant bleeding and any bleeding between NOACs and warfarin were not statistically significant. This finding indicates that while NOACs may be safer in certain contexts, the overall bleeding risk profile remains an area requiring careful consideration.

The systematic review's methodology, which aggregates data from multiple studies, strengthens the reliability of its conclusions. Nevertheless, the authors acknowledge limitations inherent in the included studies, such as variability in patient populations and study designs, which may affect the generalizability of the results.

The article titled "Efficacy and safety of non-vitamin K-antagonist oral anticoagulants for retinal vascular diseases in patients with atrial fibrillation: Korean cohort study" by (Park et al., 2020) provides a comprehensive examination of the risk of intraocular bleeding associated with novel oral anticoagulants (NOACs) in comparison to warfarin. This population-based cohort study is particularly significant as it focuses on patients with non-valvular atrial fibrillation (AF) and addresses a critical aspect of anticoagulation therapy—safety concerning intraocular bleeding.

The authors report that there were no significant differences in intraocular bleeding incidence rates (IR) and hazard ratios (HRs) for various retinal diseases between NOACs and warfarin. However, a noteworthy finding is that NOAC users demonstrated a lower risk of intraocular bleeding compared to warfarin users,

particularly among patients with diabetes and those without a history of stroke. This aspect of the study is pivotal, as it suggests that NOACs may offer a safer profile for patients at risk of intraocular bleeding, which is a crucial consideration in managing anticoagulation therapy.

The cumulative incidence data presented further reinforce the conclusion that NOACs are associated with a lower rate of intraocular bleeding compared to warfarin. This aligns with existing literature that indicates a trend towards reduced bleeding complications with NOACs, providing a basis for clinicians to consider these agents as a safer alternative in certain patient populations.

The article also touches upon the potential mechanisms underlying the observed lower bleeding risk associated with NOACs. While the authors acknowledge that the exact mechanisms remain unclear, they suggest that the pharmacodynamic differences between NOACs and warfarin may play a role. Warfarin's mechanism involves the inhibition of vitamin K-dependent proteins, which could contribute to a higher bleeding risk. In contrast, the action of NOACs, which directly inhibit specific coagulation factors, may lead to a more controlled anticoagulation effect, thereby reducing the likelihood of bleeding events, including intraocular bleeding.

However, the study's limitations should be acknowledged. Although it presents valuable insights, it is essential to consider the cohort's demographic factors and the potential influence of confounding variables that may affect the outcomes. The study's focus on a Korean cohort may also limit the generalizability of the findings to other populations with different demographics or underlying health conditions.

The article "Characteristics, Location, and Clinical Outcomes of Gastrointestinal Bleeding in Patients Taking New Oral Anticoagulants Compared to Vitamin K Antagonists" by (Reum Choe et al., 2011) provides a comprehensive analysis of the bleeding risks associated with novel oral anticoagulants (NOACs) in comparison to traditional vitamin K antagonists (VKAs) like warfarin. The authors present a well-structured examination of the pharmacological

advancements introduced with NOACs, highlighting their specific mechanisms of action and the clinical implications of their use in patients with non-valvular atrial fibrillation (NVAF).

The article emphasizes that since the introduction of NOACs, such as dabigatran, rivaroxaban, apixaban, and edoxaban, there has been a shift in clinical practice toward these agents due to their rapid onset and offset of action, as well as their predictable pharmacokinetics. This is particularly significant given the guidelines from the European Society of Cardiology, which advocate for NOACs in stroke prevention for NVAF patients. The authors effectively contextualize the advantages of NOACs over VKAs, particularly in terms of their efficacy in reducing the incidence of major bleeding events, including intracranial hemorrhage.

However, the article does not shy away from addressing the concerns surrounding the risk of gastrointestinal (GI) bleeding associated with NOACs. The authors reference findings from the ROCKET AF trial, which indicated a higher incidence of GI bleeding in patients treated with rivaroxaban compared to those on VKAs. This critical insight underscores the necessity for clinicians to weigh the benefits of NOACs against the potential for significant bleeding events, particularly in vulnerable patient populations.

The study's objective to assess the clinical and endoscopic features of acute GI bleeding in patients on NOACs is particularly relevant, as it provides a granular view of the complications that may arise from their use. The authors' approach to evaluating the severity and clinical outcomes of these bleeding events in comparison to VKAs is commendable, as it offers valuable data that can influence treatment decisions.

The article titled "Direct comparison of non-vitamin K antagonist oral anticoagulant versus warfarin for stroke prevention in non-valvular atrial fibrillation: a systematic review and meta-analysis of real-world evidences" by (Waranugraha et al., 2011) provides a comprehensive evaluation of the bleeding risks associated with non-vitamin K antagonist oral anticoagulants (NOACs)

compared to warfarin in the context of stroke prevention for patients with non-valvular atrial fibrillation.

A critical aspect of the study is its systematic review and meta-analysis, which aggregates data from various real-world studies to assess the comparative safety profiles of NOACs and warfarin. The authors highlight that while NOACs have been associated with a lower risk of major bleeding events overall, the analysis presents a nuanced view when it comes to specific types of bleeding, notably gastrointestinal and intracranial bleeding. The findings indicate that the risk of gastrointestinal bleeding may differ significantly from that of major and intracranial bleeding, suggesting that the bleeding risk profile is complex and not uniformly advantageous across all settings.

The subgroup analysis conducted by the authors reveals conflicting results regarding the incidence of intraocular bleeding when comparing NOACs and warfarin. This is particularly pertinent to the topic at hand, as it raises questions about the safety of these newer anticoagulants in terms of ocular health, an area that has not been extensively covered in previous research. The variability in bleeding risks across different anticoagulants necessitates careful consideration by clinicians when prescribing these medications, particularly for patients who may be at higher risk for ocular complications.

Moreover, the article emphasizes the importance of individual patient factors, including comorbidities and concurrent medications, which can influence bleeding risks. The authors advocate for a personalized approach to anticoagulation therapy, underscoring the need for clinicians to weigh the benefits of stroke prevention against the potential risks of bleeding, including intraocular bleeding.

The article "Non-vitamin K antagonist oral anticoagulants in venous thromboembolism patients: a meta-analysis of real-world studies" by (Liu et al., 2012) provides a comprehensive examination of the safety and efficacy of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with venous thromboembolism (VTE). The authors undertake a meta-analysis of various real-

world studies, highlighting the prevalence of recurrent VTE and associated bleeding events in this patient population.

A critical evaluation of the material reveals that the findings presented by (Liu et al., 2012) underscore the complexity of assessing the risk of bleeding events, particularly intraocular bleeding, when comparing NOACs to traditional anticoagulants like warfarin. The article notes that while NOACs have been associated with a lower incidence of major bleeding events overall, the data regarding specific types of bleeding, including intraocular bleeding, remains inconsistent across studies. This inconsistency is a key point of concern, as it complicates clinical decision-making for healthcare providers who must weigh the benefits of anticoagulation against the potential risks.

Furthermore, the authors discuss the variability in patient populations and study designs across the included real-world studies, which may contribute to the conflicting findings regarding bleeding risks. For instance, differences in the definition of bleeding events, the timing of follow-up, and the characteristics of the patient cohorts can all influence outcomes. This variability suggests that while NOACs may offer certain advantages over warfarin, including less frequent monitoring and a lower risk of some bleeding events, the potential for intraocular bleeding specifically requires more targeted research to draw definitive conclusions.

Additionally, (Liu et al., 2012) emphasize the importance of individual patient factors, such as age, comorbidities, and concurrent medications, in influencing bleeding risk. This individualized approach is critical in anticoagulation therapy, as it acknowledges that the risk-benefit profile may differ significantly from one patient to another.

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## CONCLUSION

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The exploration of the risk of intraocular bleeding associated with novel oral anticoagulants (NOACs) compared to warfarin reveals a nuanced understanding of their safety profiles. The foundational work by (D Fox et al., 2012) established that

rivaroxaban, a NOAC, is associated with a decreased risk of major bleeding, while subsequent studies have built upon this by focusing on specific bleeding risks, particularly intraocular bleeding.

The systematic review by (Sardar et al., 2013) highlighted the significant reduction in intracranial bleeding risks among NOAC users, which is particularly relevant for patients with atrial fibrillation and a history of stroke or transient ischemic attacks. This finding was corroborated by (Deng et al., 2019), who noted a general trend towards reduced bleeding events with NOACs compared to warfarin, although the differences in clinically relevant bleeding were not statistically significant.

Focusing specifically on intraocular bleeding, (Park et al., 2020) provided evidence that NOACs may exhibit a lower risk of intraocular bleeding in patients with retinal vascular diseases, particularly among those with diabetes. This suggests that NOACs could be a safer option in populations where intraocular bleeding is a concern. However, the study also emphasized the need for more targeted research to clarify these risks further.

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Finally, (Liu et al., 2012) emphasized the variability in results regarding recurrent events and bleeding risks in real-world studies, indicating that while NOACs may offer certain advantages, the overall safety profile, particularly concerning intraocular bleeding, remains complex and warrants ongoing research.

In conclusion, the literature demonstrates that NOACs generally present a lower risk of major bleeding events compared to warfarin, with specific advantages in reducing intracranial and potentially intraocular bleeding risks. However, the

variability in bleeding risks across different studies and patient populations highlights the need for individualized treatment approaches and further research to establish clearer safety profiles for NOACs, particularly in the context of intraocular bleeding.

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