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MANAGEMENT OF ANTICOAGULATION IN ATRIAL FIBRILLATION: MINIMIZING DRUG INTERACTIONS WITH DOACS

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ABSTRACT

Introduction: Atrial fibrillation (AF) is a common cardiac arrhythmia that elevates the risk of thromboembolic events, necessitating effective anticoagulation strategies. Direct oral anticoagulants (DOACs) have become the preferred choice due to their safety profiles; however, drug interactions can compromise their efficacy and safety. Objective: This study aims to assess the impact of drug interactions on the efficacy and safety of DOACs in patients with AF. Method: A literature review was conducted using databases such as the Virtual Health Library, LILACS Plus, and Medline, focusing on articles published from 2019 to 2024. Inclusion criteria emphasized studies related to drug interactions involving DOACs and AF, resulting in the selection of 13 relevant articles. Results: The analysis revealed a significant prevalence of drug interactions among patients treated with DOACs. Co-prescription with CYP3A4 inhibitors and P-glycoprotein modulators was linked to increased bleeding risks. Factors such as age, renal function, and the presence of comorbidities were crucial in determining appropriate dosing and the risk of adverse events. Conclusion: Careful management of AF patients on DOACs is vital to mitigate risks associated with drug interactions. Personalized treatment approaches that consider individual clinical profiles and ongoing education for healthcare providers are essential to optimize anticoagulation therapy.

Keywords: Atrial Fibrillation. Direct Oral Anticoagulants. Drug Interactions.

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1 INTRODUCTION

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia that significantly increases the risk of thromboembolic events, necessitating effective anticoagulation strategies (Van et al., 2024). Direct oral anticoagulants (DOACs) have emerged as a preferred choice due to their ease of use and favorable safety profiles compared to traditional vitamin K antagonists (Khalife et al., 2024).

However, the management of anticoagulation in AF patients is complicated by potential drug interactions that can compromise the efficacy and safety of DOACs (Douketis et al., 2024). Understanding the implications of these interactions is crucial for optimizing treatment outcomes and minimizing adverse effects in this vulnerable population (Wong et al., 2024).

The prevalence of drug interactions among elderly patients with AF, who often present with multiple comorbidities, poses a substantial challenge for clinicians (Chobanov et al., 2024). Studies have highlighted the frequency of co-prescriptions that may lead to harmful interactions, particularly with medications that influence metabolic pathways such as CYP3A4 and P-glycoprotein (Stöllberger et al., 2023; Shurrab et al., 2022). Identifying these interactions is essential for clinicians to make informed decisions regarding anticoagulant therapy, ensuring that patients receive appropriate and effective treatment while minimizing the risk of bleeding and other adverse events (Gulikers et al., 2024).

Furthermore, clinical conditions such as age and renal function play a significant role in determining appropriate dosing of DOACs (Lee et al., 2024). Inadequate dosing due to overlooked drug interactions or altered pharmacokinetics can lead to serious complications, including major hemorrhages or thrombotic events (Cormier & Siegal, 2024). Therefore, this study aims to assess the impact of drug interactions on the efficacy and safety of DOACs in patients with AF, focusing on the prevalence of such interactions, their association with adverse events, and the influence of clinical factors on prescribing practices. By addressing these key areas, we aim to provide valuable insights for improving anticoagulation management in AF patients.

2 METHOD

This study conducts a literature review on the impact of drug interactions on the efficacy and safety of direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF). The research was carried out in databases such as the Virtual Health Library, LILACS Plus, and Medline, using the following descriptors: "Direct Oral Anticoagulants" (DOACs), "Atrial Fibrillation," and "Drug Interactions." Boolean terms "AND" and "OR" were employed to refine the search results. Initially, a total of 4.495 articles were found in the selected databases.

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The search process involved applying these descriptors in the chosen databases, filtering the results to ensure that only articles meeting the inclusion criteria were considered. To achieve this objective, we established inclusion criteria that encompass articles published in Portuguese, Spanish, and English, which are freely accessible online and published in the last five years, from 2019 to 2024. A total of 43 articles met the criteria, focusing on the relationship between atrial fibrillation and drug interactions with DOACs.

We read the abstracts of the selected articles to ensure their relevance to the proposed topic. After this screening, we chose 20 articles and read them in full, as they provided a comprehensive review of the subject. Finally, we selected the 13 articles that best supported the discussion of this research. For data analysis, we compiled the 13 selected articles into a table 1 and synthesized the main results of each, identifying common themes and divergences in the authors' approaches and recommendations, thereby enriching the discussion of this study.

3 RESULT

Table 1 – Summary of the reviewed results

Year	Authors	Objective	Conclusion
2024	Sudhan, M., Janakiraman, V., Ahmad, S. F., Attia, S. M	To assess the impact of DOACs on PON1 through a combination of computational and experimental analyses.	Overall, our computational and experimental results clearly show the higher inhibitory effect of dabigatran than rivaroxaban. Hence, rivaroxaban will be a better drug candidate for improving the outcome of AF.
2023	Stöllberger, C., Schneider, B., & Finsterer, J.	To evaluate the pharmacokinetic and pharmacodynamic drug-drug interactions (DDIs) involving direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF).	Co-medications affecting platelet function consistently increase the risk of bleeding in patients taking DOACs, the interactions involving metabolic enzymes present a more complex and ambiguous picture.
2023	Ersoy, I., & Ersoy, P	To evaluate the effect of drug interactions with chronic direct oral anticoagulants (DOAC) on mortality in older atrial fibrillation (AF) patients during the Coronavirus disease 2019(COVID-19) pandemic.	Most co-medications do not have significant interactions with DOACs, few serious drug interactions contribute to mortality in elderly patients with AF during the pandemic.
2023	Shurrab, M., Jackevicius, C. A., Austin, P. C., Tu, K et al.	To evaluate the bleeding risk associated with the co-prescription of amiodarone and direct oral anticoagulants (DOACs) in older adults with atrial fibrillation (AF).	The findings indicate that among patients aged over 66 years with AF on DOACs, current use of amiodarone is linked to 53% increased odds of experiencing major bleeding. In contrast, past use of amiodarone did not show a significant association with bleeding risk.
2022	Shurrab, M., Jackevicius, C. A., Austin, P. C., Tu, K et al.	To determine the association between the use of diltiazem and the occurrence of major bleeding in older adults with atrial fibrillation (AF who are prescribed direct oral anticoagulants (DOACs).	Among patients over 66 years old with AF on DOACs, current use of diltiazem is significantly linked to an increased risk of major bleeding, with an adjusted odds ratio of 1.37. However, recent use of diltiazem did not show a significant association with bleeding risk.

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2022	Sanborn, D., Sugrue, A., Amin, M., Mehta, R et al.	To examine the prevalence of co-prescription of direct oral anticoagulants (DOACs) with interacting medications and assess their impact on outcomes such as stroke, major bleeding, and minor bleeds in patients with atrial fibrillation.	30.4% of atrial fibrillation patients on DOACs were co-prescribed medications with potential interactions. However, these interactions did not result in an increased risk of major bleeding or embolic events.
2021	Wang, C., Victor Chien-Chia Wu, Tu, H., Huang, Y et al.	To evaluate the risk of major bleeding associated with the concurrent use of direct oral anticoagulants (DOACs) and anticancer drugs (ACDs) in patients with atrial fibrillation (AF) and cancer, particularly focusing on those ACDs that share metabolic pathways with DOACs.	Co-prescription of DOACs with 15 different ACDs did not increase the risk of major bleeding compared to DOAC use alone in patients with AF and cancer.
2021	Gandhi, S. K., Reiffel, J. A., Boiron, R., & Wieloch, M.	To evaluate the risk of major bleeding associated with the concurrent use of dronedarone and direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF).	The study found no increased risk of major bleeding with dronedarone and apixaban, a modestly increased risk of gastrointestinal bleeding with dabigatran, and an overall increased risk of bleeding with rivaroxaban.
2021	Gronich, N., Stein, N., & Muszkat, M	To evaluat the risk of serious bleeding and thromboembolic events in patients with atrial fibrillation (AF) and venous thromboembolism using direct oral anticoagulants (DOACs) alongside P-glycoprotein (P-gp) and CYP3A4 inhibitors or inducers.	Co-prescribing DOACs, particularly dabigatran and rivaroxaban, with verapamil or amiodarone significantly increased the risk of serious bleeding. Additionally, using DOACs with phenytoin or carbamazepine raised the risk of stroke or systemic embolism in AF patients.
2020	Lee, J. Y., Oh, I.-Y., Lee, J.-H., Kim, S.-Y et al.	To evaluate the risk of bleeding associated with the simultaneous use of direct oral anticoagulants (DOACs) and drugs known to cause drug-drug interactions (DDIs) in patients with non-valvular atrial fibrillation (AF) and venous thromboembolism (VTE).	Physicians prescribing DOACs for AF or VTE should be aware of the increasing risk of bleeding associated with drugs having potential DDIs regardless of comorbidities.
2020	Sanghai, S., Wong, C., Wang, Z., Clive, P et al.	To evaluate the prevalence and factors related to inappropriate dosing of direct-acting oral anticoagulants (DOACs) in older atrial fibrillation patients, focusing on age, renal function, body weight, and drug-drug interactions.	More than 20% of older patients on DOACs received inappropriate doses, mostly underdosed. Common drug-drug interactions were noted, with older age, higher CHA2DS2VASc scores, and renal failure linked to these inappropriate prescriptions.
2020	Maria, Darze, E. S., & Rocha, P. N	To evaluate trends and predictors of oral anticoagulants utilization in patients with AF.	Between 2011 and 2016, DOACs were rapidly incorporated into clinical practice, replacing AVKs and antiplatelets, and contributing to greater use of anticoagulation in patients with AF.
2020	Ferrari, F., da Silveira, A. D., Martins, V. M., Franzoni	To evaluate the efficacy and safety of direct oral anticoagulants (DOACs) in preventing stroke in patients with atrial fibrillation, comparing them to vitamin K antagonists, and to discuss their indications and limitations in various clinical conditions.	DOACs demonstrate comparable efficacy to warfarin with a lower risk of intracranial bleeding, making them an attractive option for stroke prevention in elderly patients with atrial fibrillation.

4 DISCUSSION

4.1 IMPACT OF DRUG INTERACTIONS ON THE EFFICACY AND SAFETY OF DOACS IN ATRIAL FIBRILLATION

The use of direct oral anticoagulants (DOACs) to prevent thromboembolic events in patients with atrial fibrillation (AF) is widely recognized, but drug interactions pose a significant challenge.

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The literature indicates that the safety and efficacy of DOACs can be compromised by interactions with other medications. For instance, the study by Shurrab et al. (2022) suggests that the co-prescription of diltiazem, a CYP3A4 inhibitor, with DOACs is associated with an elevated risk of bleeding. The research identified that patients currently using diltiazem experienced a significant increase in the risk of major bleeding compared to those not exposed, underscoring the need for vigilance in polymedicated patients (Shurrab et al., 2022).

Gandhi et al. (2021) also addressed drug interactions, focusing on dronedarone and its association with an increased risk of bleeding in patients treated with rivaroxaban and dabigatran. The authors found that the use of dronedarone resulted in a heightened risk, particularly for gastrointestinal bleeding, illustrating the complexity of treating patients with AF requiring multiple medications (Gandhi et al., 2021). These studies emphasize the importance of careful assessment of interactions and patient risk profiles before introducing new medications.

4.2 PREVALENCE OF DRUG INTERACTIONS

The prevalence of drug interactions in patients with AF treated with DOACs is alarming. Sanborn et al. (2022) reported that among a cohort of 8,576 patients treated with DOACs, 30.4% were using at least one interactive agent, with a predominance of enzymatic inhibitors such as diltiazem and amiodarone. These medications not only increased the likelihood of suboptimal DOAC dosing but also heightened the risk of adverse events such as bleeding (Sanborn et al., 2022).

Additionally, the research by Sanghai et al. (2020) identified that 23% of patients with AF receiving DOACs were on inadequate doses, often due to unmonitored drug interactions. The authors noted that interactions led to dosing errors, indicating that a deeper understanding of these interactions is crucial for optimizing anticoagulant therapy (Sanghai et al., 2020). The work of Lee et al. (2020) corroborates these findings, showing that 66.1% of major bleeding events were associated with the concurrent use of drugs with potential interactions, highlighting the need for rigorous monitoring to prevent complications (Lee et al., 2020).

4.3 RISK OF ADVERSE EVENTS

Analyzing the risks associated with the co-prescription of DOACs and other medications is vital for patient safety. Wang et al. (2021) focused on the concomitant use of DOACs and anticancer drugs, noting that despite theoretical concerns about increased bleeding risk due to overlapping metabolic pathways, the data indicated that co-prescription was not significantly associated with an

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increase in bleeding (Wang et al., 2021). This result suggests that clinical approaches should be adaptive, considering both potential risks and the benefits of combined treatment.

Conversely, Gronich et al. (2021) reported that the co-prescription of DOACs with drugs that inhibit or induce CYP3A4 or P-glycoprotein is associated with an increased risk of bleeding events. The authors observed that specific interactions, such as the combination of rivaroxaban with verapamil or amiodarone, were particularly concerning, resulting in a significant increase in bleeding rates (Gronich et al., 2021). This evidence underscores the need for continuous monitoring and therapy adjustment in patients using multiple medications.

4.4 CLINICAL CONDITIONS AND ASSOCIATED COMORBIDITIES

Patients' clinical conditions play a crucial role in determining the safety of using DOACs. Sudhan et al. (2024) investigated how clinical characteristics, such as the presence of renal failure, can affect the efficacy of DOACs. The study showed that the presence of comorbidities not only increases the risk of complications but also complicates the choice of appropriate therapy (Sudhan et al., 2024). Therefore, assessing clinical conditions should be an essential part of the decision-making process in treating patients with AF.

Maria et al. (2020) also emphasized the importance of considering factors such as hypertension and a history of prior AF in selecting anticoagulant treatment. Their data suggested that these factors significantly influence the decision to initiate anticoagulation and the choice of anticoagulant agent (Maria et al., 2020). A comprehensive evaluation of the patient, including their clinical conditions and comorbidities, is critical for minimizing the risk of drug interactions and ensuring effective therapy.

Finally, the study by Ferrari et al. (2020) reviewed the safety and efficacy of DOACs, highlighting the importance of an individualized approach that considers comorbidities and drug interactions. They warned that while DOACs offer several advantages over traditional anticoagulants, drug interactions and clinical conditions must be closely monitored to prevent complications (Ferrari et al., 2020).

4.5 BIAS IN THE RESEARCH

One of the main limitations of this research pertains to selection bias, which can influence the representativeness of the collected data. The studies analyzed, such as those by Ersoy & Ersoy (2023) and Shurrab et al. (2023), utilize specific cohorts of patients that may not reflect the general population with atrial fibrillation, especially in diverse contexts, such as different healthcare systems or demographic variations. Additionally, recruitment in tertiary centers may introduce bias, as these

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patients often present more complex clinical characteristics or more advanced stages of the disease, which may not apply to patients treated in primary care settings.

Another significant bias is confounding bias, where uncontrolled variables can impact the observed results. Although many studies, such as those by Wang et al. (2021) and Lee et al. (2020), have attempted to adjust for confounding factors like age, comorbidities, and type of DOAC, there may still be unmeasured variables affecting the occurrence of drug interactions and their outcomes. For instance, the presence of underlying conditions or adherence to treatment may not have been adequately documented, which could lead to an underestimation or overestimation of the risks associated with using DOACs. Thus, the interpretation of the results should be approached with caution, recognizing these potential biases and their implications on the overall findings.

5 CONCLUSION

The analysis of the interaction between atrial fibrillation (AF), the use of direct oral anticoagulants (DOACs), and potential drug interactions reveals the critical need for careful patient management. The studies indicate that co-prescribing DOACs with medications that affect metabolic pathways, such as CYP3A4 and P-glycoprotein, may increase the risk of bleeding and complications, highlighting the importance of rigorous monitoring. Therefore, it is essential to emphasize the relevance of personalized treatment, taking into account individual clinical characteristics and health conditions, to ensure the efficacy and safety of anticoagulation.

Moreover, continuous education for healthcare professionals about drug interactions and the appropriate use of DOACs is fundamental to minimize associated risks. The literature underscores that even with the increased use of DOACs, many patients still receive inadequate doses, either due to underdosing or the failure to consider potential interactions, which can compromise treatment efficacy and increase the incidence of adverse events.

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