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Factors associated with non-adherence to the use of oral anticoagulants: a systematic review protocol

Fatores associados à não adesão ao uso de anticoagulantes orais: protocolo de revisão sistemática

Factores asociados a la no adherencia al uso de anticoagulantes orales: un protocolo de revisión sistemática

RESUMO

Objetivo: Descrever fatores associados à não adesão ao uso de derivados cumarínicos e anticoagulantes orais de ação direta. Método: Serão elegíveis os estudos observacionais e experimentais, com pacientes ≥ 18 anos em anticoagulação oral. A busca de artigos será nas bases MEDLINE (via PubMed), EMBASE, CINAHL e Literatura Latino-Americana e do Caribe, além de busca manual nas listas de referência dos estudos selecionados. As duplicatas serão removidas. Será feita leitura do título/resumo dos artigos para pré-seleção daqueles que serão lidos na íntegra para definir sobre sua inclusão na revisão. As informações serão extraídas, tabuladas e descritas de forma narrativa. Resultado: Na busca preliminar foram encontrados 1270 estudos, sendo selecionados 21 artigos para a revisão sistemática após realização das etapas metodológicas. Conclusão: O conhecimento dos fatores associados à não adesão à anticoagulação oral pode melhorar o entendimento sobre aspectos do tratamento. Cadastro de registro da revisão sistemática (PROSPERO): CRD 42020223555.

DESCRITORES: Anticoagulantes; Cumarínicos; Inibidores do fator Xa; Revisão sistemática; Tromboembolismo

ABSTRACT

Objective: To describe factors associated with non-adherence to the use of coumarin derivatives and direct acting oral anticoagulants. Method: Observational and experimental studies with patients ≥18 years on oral anticoagulation will be eligible. The search for articles will be conducted in MEDLINE (via PubMed), EMBASE, CINAHL and Latin American and Caribbean Literature, as well as a manual search of the reference lists of the selected studies. Duplicates will be removed. The title/summary of the articles will be read to pre-select those that will be read in full to define their inclusion in the review. The information will be extracted, tabulated and described in narrative form. Result: In the preliminary search 1270 studies were found, and 21 articles were selected for the systematic review after the methodological steps. Conclusion: Knowledge of factors associated with non-adherence to oral anticoagulation may improve understanding of treatment aspects. Systematic review registration (PROSPERO): CRD 42020223555.

DESCRIPTORS: Anticoagulants; Coumarins; Factor Xa inhibitors; Systematic review; Thromboembolism

RESUMEN

Objetivo: Describir los factores asociados a la falta de adherencia al uso de derivados cumarínicos y anticoagulantes orales de acción directa. Método: Serán elegibles los estudios observacionales y experimentales con pacientes ≥18 años en anticoagulación oral. La búsqueda de artículos se realizará en las bases de datos MEDLINE (a través de PubMed), EMBASE, CINAHL y Literatura Latinoamericana y del Caribe, además de una búsqueda manual en las listas de referencias de los estudios seleccionados. Se eliminarán los duplicados. Se leerá el título/resumen de los artículos para preseleccionar los que se leerán en su totalidad para definir su inclusión en la revisión. La información se extraerá, se tabulará y se describirá en forma de relato. Resultados: En la búsqueda preliminar se encontraron 1270 estudios, siendo seleccionados 21 artículos para la revisión sistemática tras realizar los pasos metodológicos. Conclusión: El conocimiento de los factores asociados a la no adherencia a la anticoagulación oral puede mejorar la comprensión de los aspectos del tratamiento. Registro de revisión sistemática (PROSPERO): CRD 42020223555.

DESCRIPTORES: Anticoagulantes; Cumarina; Inhibidores del factor Xa; Revisión sistemática; Tromboembolismo

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Waleska Jaclyn Freitas Nunes de Sousa
Graduação completa em farmácia. Mestrado incompleto em Ciências de Saúde. Hospital das Clínicas da Universidade Federal de Minas Gerais.
ORCID: 0000-0002-6454-7983

Nathália Sernizon Guimarães
Doutora. Faculdade de Medicina da Universidade Federal de Minas Gerais.
ORCID: 0000-0002-0487-0500

Catiane Costa Viana
Mestre. Faculdade de Farmácia, Universidade Federal de Minas Gerais.
ORCID: 0000-0001-6237-8541

Amanda Fonseca Medeiros
Bacharel em farmácia. . Faculdade de Farmácia, Universidade Federal de Minas Gerais
ORCID: 0000-0002-6747-6172

Mayara Sousa Vianna
Enfermeira. Faculdade de Farmácia, Universidade Federal de Minas Gerais
ORCID: 0000-0003-1427-2149

Caryne Margotto Bertollo
Hospital das Clínicas da Universidade Federal de Minas Gerais. Faculdade de Farmácia, Universidade Federal de Minas Gerais
ORCID: 0000-0003-1427-2149

INTRODUCTION

Oral anticoagulants are used for primary and secondary prevention of thromboembolism in individuals with risk factors such as atrial fibrillation (AF). 1,2 In people diagnosed with AF there is an increased risk of developing stroke, 3 which is the third leading cause of death worldwide. 4 Despite the benefits of oral anticoagulation, some patients are more likely to develop adverse drug events, mainly represented by thromboembolism and bleeding, which are related to therapeutic failure and excessive anticoagulant effect, respectively. 5

Coumarin derivatives have been used for decades as oral anticoagulants. 1,6,7 For some indications, these drugs have been gradually replaced by direct acting oral anticoagulants, and both therapeutic options are effective in preventing stroke. 6,7,8,9,10,11,12 However, direct acting oral anticoagulants have limitations for use in patients with mechanical heart prostheses, severe renal failure, and AF with rheumatic heart disease associated with severe mitral stenosis. In addition, evidence to support the use of direct acting oral anticoagulants in people with moderate and severe liver dysfunction is lacking. 13

Warfarin is a widely used coumarin derivative with recognized benefits, although its disadvantages are the narrow therapeutic index, 7 wide dose-response variability, 14 potential to interact with medicinal plants, 15 various medications 6,16,17 and foods high in vitamin K. 6 Monitoring the International Normalized Ratio (INR), obtained from the prothrombin time, is necessary to guide warfarin dose adjustments and increase the safety of the drug. 18

Direct acting oral anticoagulants are represented by direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (edoxaban, rivaroxaban and apixaban). 19,20,21,22 These, unlike warfarin, do not require individualized dose adjustment 6 and have fewer interactions with food and other medications. 23 However, the high cost presents itself as a disadvantage 24 and the shorter half-life compared to coumarin derivatives may increase the risk of thromboembolic events in patients with poor adherence to treatment. 20

Obtaining optimal control of oral anticoagulation is a challenge in clinical practice and adherence is crucial for treatment success. 25,26,27 According to the World Health Organization (2003), the concept of adherence concerns the administration of medication by the patient and the adoption of behaviors, such as changes in lifestyle and diet, in accordance with recommendations based on evidence given by professionals responsible for the care of the patient. Thus, especially for those who need prolonged treatment, non-adherence becomes an important problem to be considered 28 and that needs to be addressed to ensure effectiveness and safety of oral anticoagulation.

To measure adherence, direct and indirect methods can be used. Direct methods comprise measurements of the concentration of drug or metabolites in fluids such as blood and urine or of biological markers in the blood. 29 Indirect methods include electronic monitoring devices, assessment of clinical response, pill counting, application of questionnaires and self-report of treatment adherence. The latter has the advantages of being simple, low cost and very useful in the clinical setting due to its ease of application. Both methods have disadvantages, with direct methods having a high cost and indirect methods having the possibility of overestimating adherence when interviewing the patient. 30

Knowledge about the factors associated with non-adherence to treatment with oral anticoagulants can improve the understanding of aspects of the care process aimed at this profile of patients. Thus, knowing these factors can be useful for the clinical practice of pharmacists and other professionals to support interventions aimed at improving

medication adherence and treatment outcomes. This review aims to describe the factors associated with non-adherence to oral anticoagulation with coumarin derivatives and direct acting oral anticoagulants.

METHODS

This protocol will be conducted in accordance with the PRISMA-P 31 checklist and is registered with PROSPERO, under the code CRD 42020223555.

The studies of interest are those that evaluated the factors associated with non-adherence to treatment with coumarin derivatives or direct acting oral anticoagulants in patients ≥18 years old, of both genders, on oral anticoagulation for any indication of thromboprophylaxis. Direct and indirect methods will be considered relevant for obtaining non-adherence data.

Observational (cross-sectional, case-control and cohort) and experimental studies in humans (clinical trials) will be evaluated for eligibility. There will be no language or publication date restrictions.

Systematic reviews with or without meta-analysis, integrative or narrative reviews, case series or case reports and experimental studies with animals will be excluded.

To improve the sensitivity of the research strategies, terms cited by the Medical Subject Heading (MeSH) will be used, as well as non-MeSH terms, characterized as clinical practice jargon. The initial search strategy will be adapted and replicated for each database using keywords and indexed terms related to the topic of interest, comprising Emtree for Embase and DeCS for Latin American and Caribbean Literature (LILACS). Indexed terms were defined to compose search strategies in April 2021 (Appendix A).

Following the PICO strategy (P: patients; I: intervention; C: control; O: outcome), the domains defined for the search strategies will be the study population (patients ≥18 years old, both sexes), the methods used for measure non-adherence to oral anticoagulation (use of direct or indirect methods) and the variables of interest (factors associated with non-adherence to oral anticoagulation) (Appendix B). The control criteria are not applicable for the purpose of the review.

The databases considered for electronic searches will be MEDLINE (via PubMed), Embase, CINAHL and LILACS. In addition, a manual search will be performed to find relevant studies in the reference lists of selected articles. Gray literature (Google Scholar, MedNar, OpenGray and ProQuest Dissertations and Theses) will also be considered for the article search.

All selected articles will be exported to the Rayyan QCRI program (Doha, Qatar, 2016), 32 where duplicates will be detected and removed prior to screening for eligibility. The selection of studies will occur with the initial reading of the title and abstract by two independent reviewers (WJFNS and NGS), followed by the full reading of the articles selected at this stage by two reviewers (WJFNS and NGS).

Articles that do not meet the inclusion criteria after full reading will be excluded. The reason for the exclusion of studies at each stage will be presented in a flowchart indicated by the PRISMA Statement: an Updated Guideline for Reporting Systematic Reviews 33 (Appendix C). A third reviewer (MAPM) will resolve any disagreements that may have occurred in the previous steps, carried out independently by the two reviewers.

Data extraction will be performed by two reviewers (WJFNS and NGS) and differences will be resolved through discussion with a third reviewer (MAPM). To ensure that the data extraction tools capture all the necessary information, a pilot study will be carried out including three randomly selected articles until the two authors are able to record the extracted information without discrepancies.

The selected studies will be read and the information of interest extracted as follows: study information (title, author, year, country, study design, number of participants, non-adherence measurement method (direct methods or indirect methods), oral anticoagulant evaluated (coumarin derivatives and direct acting oral anticoagulants), tested variables, evaluated duration of use, association measures and factors associated with non-adherence), sociodemographic and behavioral data (age, male gender, education, alcohol consumption and smoking), clinical and pharmacotherapeutic data (indication of oral anticoagulation, comorbidities, occurrence of events (thromboembolism or hemorrhage) and other medications in chronic use) (Appendix D).

Study authors will be contacted to request missing information if necessary. Those studies with no response from the corresponding authors will have the information identified as "missing" in the presentation of results.

Data will be extracted and described in tables. Factors associated with non-adherence to treatment with coumarin derivatives and direct acting oral anticoagulants are the variables of interest and will be discussed. The results of this systematic review will provide data on factors associated with non-adherence to oral anticoagulation and may be useful for decision-making in patient care.

Case-control and cohort studies will have their methodological quality assessed using the Newcastle-Ottawa Quality Assessment Scale. 34 This checklist contains eight items, with three domains in each. The maximum score that can be obtained is nine points. The scores determine the level of study quality, with cutoff points indicating high (7-9 points), moderate (4-6 points), and low (0-3 points) quality. The Agency for Research and Health Quality (ARHQ) Methodology Checklist for Cross-Sectional/Prevalence Studies 35 will be used to assess the methodological quality of cross-sectional studies. This scale has 11 items with three domains ("yes", "no" and "not clear") to be completed and the results are scored with the answer "yes". The final score is categorized as low (0-3 points), moderate (4-7 points), and high (8-11 points) quality.

The second version of RoB 2 will be used to evaluate experimental studies. This Cochrane tool was validated to verify the methodological quality of experimental studies and contains five domains of bias

assessment: (1) bias resulting from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to lack of outcome data; (4) bias in the measurement of results and (5) bias in the selection of reported results. The options for answering the questions are "yes", "probably yes", "probably no", "no" and "no information". The risk of bias for each domain is assessed as "low risk of bias", "some concerns" and "high risk of bias". 36

RESULTS

1270 articles were found in the preliminary search (Appendix A), with the exclusion of 188 duplicates. The stage of reading the title and abstract with application of the exclusion criteria was carried out with the remaining 1082 studies, of which 91 were considered eligible and had the content read in full. Of these, 21 studies were included in the review for data extraction and description.

DISCUSSION

Understanding that adherence is related to multiple factors that need to be identified to enable intervention measures, 37 this theme is of relevance to public health, since failure to reach therapeutic goals with the use of oral anticoagulants can lead to adverse events due to therapeutic failure and exacerbation of the anticoagulant effect, represented by thromboembolism and bleeding, respectively, or even death.

Therefore, it is necessary to build pillars to support the health care process and produce knowledge that provides the development of measures to benefit the patient, with the approach of non-adherence to treatment being an extremely relevant subject in the patient care scenario.

The results of this review will indicate factors associated with non-adherence to treatment with coumarin derivatives and direct acting oral anticoagulants. A critical analysis of the collected information will be carried out and the findings may be relevant to produce new knowledge that can promote the effectiveness and safety in the use of the medicine in clinical practice. The results will be published in a narrative way through scientific articles, with a description of the methods used and a critical evaluation of the results.

CONCLUSION

Knowledge of the factors associated with non-adherence to oral anticoagulation can favor the planning of actions to improve patient care. Thus, it is expected that the review will contribute to the identification of these factors and that their approach in clinical practice will result in improved adherence and the achievement of therapeutic goals, contributing to the implementation of an effective and safe treatment.

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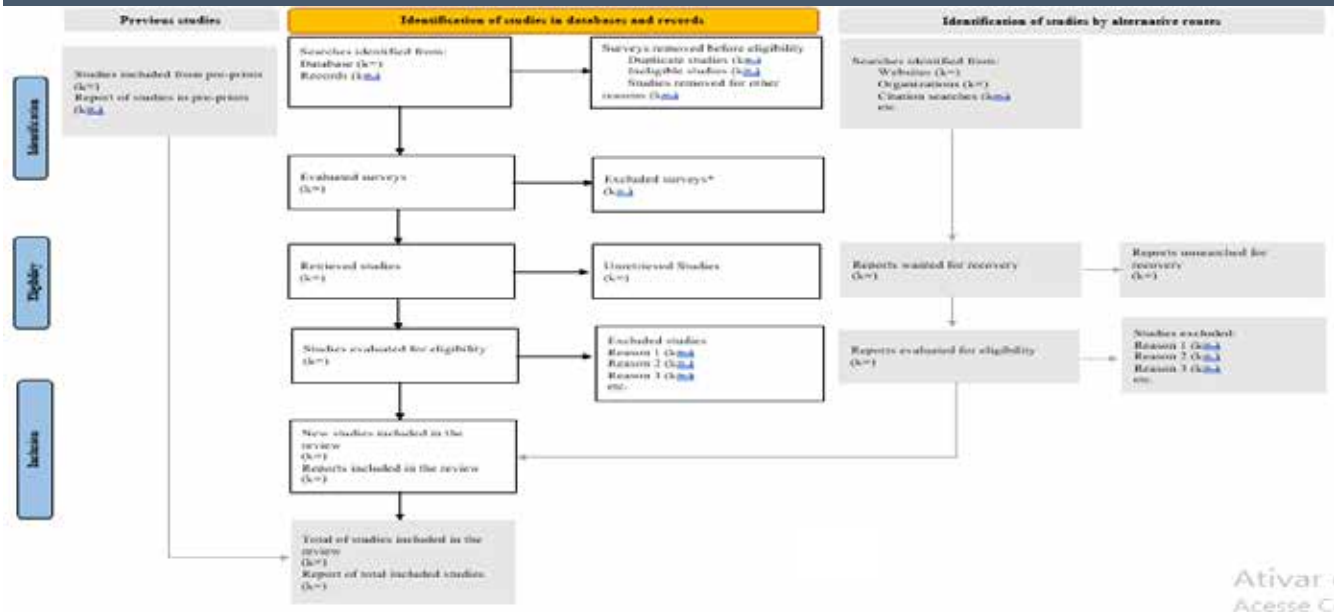
Appendix A: Search strategies and registration of studies in April 2021, without filtering by language or publication date

Data base	Research Strategy	Records retrieved
MEDLINE	#1 Adult [Mesh Terms] OR (Adults) OR Aged [Mesh] OR (Elderly) #2 Coumarins [Mesh Terms] OR (Coumarines) OR (1,2-Benzopyrone Derviatives) OR (1,2 Benzopyrone Derviatives) OR (Derviatives, 1,2-Benzopyrone) OR (Benzopyran-2-ones) OR (Benzopyran 2 ones) OR (Coumarin Derivatives) OR (Derivatives, Coumarin) OR (1,2-Benzopyrones) OR (1,2 Benzopyrones) OR (1,2-Benzo-Pyrones) OR (1,2 Benzo Pyrones) OR "Factor Xa Inhibitors" [Mesh Terms] OR (Direct Factor Xa Inhibitors) OR (Direct-Acting Oral Anticoagulants) OR (Anticoagulants, Direct-Acting Oral) OR (Direct Acting Oral) OR (Anticoagulants) OR (Oral Anticoagulants, Direct-Acting) #3 "Medication Adherence" [Mesh Terms] OR (Medication Non-Adherence) OR (Medication Non Adherence) OR (Non-Adherence, Medication) OR (Medication Nonadherence) OR (Medication Non-Compliance) OR (Medication Non Compliance) OR (Non-Compliance, Medication) #1 AND #2 AND #3	**574**
EMBASE	#1 'Adult'/syn OR (Adult/exp) OR Aged/syn OR (Aged/exp) AND [embase]/lim #2 'coumarin derivative'/syn OR ('coumarin derivative'/exp) OR 'blood clotting factor 10a inhibitor'/syn OR ('blood clotting factor 10a inhibitor'/exp) AND [embase]/lim #3 'medication compliance'/syn OR ('medication compliance'/exp) AND [embase]/lim #1 AND #2 AND #3	653
CINAHL (EBSCO)	(Adult [Mesh Terms] OR (Adults) OR Aged [Mesh] OR (Elderly)) AND (Coumarins [Mesh Terms] OR (Coumarines) OR (1,2-Benzopyrone Derviatives) OR (1,2 Benzopyrone Derviatives) OR (Derviatives, 1,2-Benzopyrone) OR (Benzopyran-2-ones) OR (Benzopyran 2 ones) OR (Coumarin Derivatives) OR (Derivatives, Coumarin) OR (1,2-Benzopyrones) OR (1,2 Benzopyrones) OR (1,2-Benzo-Pyrones) OR (1,2 Benzo Pyrones) OR "Factor Xa Inhibitors" [Mesh Terms] OR (Direct Factor Xa Inhibitors) OR (Direct-Acting Oral Anticoagulants) OR (Anticoagulants, Direct-Acting Oral) OR (Direct Acting Oral) OR (Anticoagulants) OR (Oral Anticoagulants, Direct-Acting)) AND ("Medication Adherence" [Mesh Terms] OR (Medication Non-Adherence) OR (Medication Non Adherence) OR (Non-Adherence, Medication) OR (Medication Nonadherence) OR (Medication Non-Compliance) OR (Medication Non Compliance) OR (Non-Compliance, Medication))	43
LILACS	#1 "Adult" OR "Adults" OR mh:"Idoso" OR "Aged" OR "Anciano" #2 "Cumarínicos" OR "Coumarins" OR "Cumarinas" OR "1,2-Benzopironas" OR "Benzopiran-2-Onas" OR "Cumarinas" OR "Inibidores do Fator Xa" OR "Factor Xa Inhibitors" OR "Inhibidores del Factor Xa" OR "Anticoagulantes Orais de Ação Direta" OR "Inibidor do Fator Xa" OR "Inibidores Diretos do Fator Xa" #3 "Adesão à Medicação" OR "Medication Adherence" OR "Cumplimiento de la Medicación" OR "Não Aderência ao Medicamento" OR "Não Adesão ao Medicamento Submissão ao Medicamento" #1 AND #2 AND #3	0

Appendix B: Description of the Pubmed search strategy

Pesquisa: ((Adult [Mesh Terms] OR (Adults) OR Aged [Mesh] OR (Elderly)) AND (Coumarins [Mesh Terms] OR (Coumarines) OR (1,2-Benzopyrone Derviatives) OR (1,2 Benzopyrone Derviatives) OR (Derviatives, 1,2-Benzopyrone) OR (Benzopyran-2-ones) OR (Benzopyran 2 ones) OR (Coumarin Derivatives) OR (Derivatives, Coumarin) OR (1,2-Benzopyrones) OR (1,2 Benzopyrones) OR (1,2-Benzo-Pyrones) OR (1,2 Benzo Pyrones) OR "Factor Xa Inhibitors" [Mesh Terms] OR (Direct Factor Xa Inhibitors) OR (Direct-Acting Oral Anticoagulants) OR (Anticoagulants, Direct-Acting Oral) OR (Direct Acting Oral) OR (Anticoagulants) OR (Oral Anticoagulants, Direct-Acting))) AND ("Medication Adherence" [Mesh Terms] OR (Medication Non-Adherence) OR (Medication Non Adherence) OR (Non-Adherence, Medication) OR (Medication Nonadherence) OR (Medication Non-Compliance) OR (Medication Non Compliance) OR (Non-Compliance, Medication)) ("adult"[MeSH Terms] OR ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields] OR "adult s"[All Fields]) OR "aged"[MeSH Terms] OR ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields])) AND ("coumarins"[MeSH Terms] OR ("coumarin"[Supplementary Concept] OR "coumarin"[All Fields] OR "coumarinic"[All Fields] OR "coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR "coumarine"[All Fields] OR "coumarines"[All Fields]) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR ("1 2"[All Fields] AND "benzopyrone"[All Fields] AND "derviatives"[All Fields])) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR ("1 2"[All Fields] AND "benzopyrone"[All Fields] AND "derviatives"[All Fields])) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR ("derviatives"[All Fields] AND "1 2"[All Fields] AND "benzopyrone"[All Fields])) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR "benzopyran 2 ones"[All Fields]) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR "benzopyran 2 ones"[All Fields]) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR ("coumarin"[All Fields] AND "derivatives"[All Fields]) OR "coumarin derivatives"[All Fields]) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR ("derivatives"[All Fields] AND "coumarin"[All Fields]) OR "derivatives coumarin"[All Fields]) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR ("1 2"[All Fields] AND "benzopyrones"[All Fields]) OR "1 2 benzopyrones"[All Fields]) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR ("1 2"[All Fields] AND "benzopyrones"[All Fields]) OR "1 2 benzopyrones"[All Fields]) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR ("1 2"[All Fields] AND "benzo"[All Fields] AND "pyrones"[All Fields])) OR ("coumarins"[MeSH Terms] OR "coumarins"[All Fields] OR ("1 2"[All Fields] AND "benzo"[All Fields] AND "pyrones"[All Fields])) OR "Factor Xa Inhibitors"[MeSH Terms] OR ("Factor Xa Inhibitors"[Pharmacological Action] OR "Factor Xa Inhibitors"[MeSH Terms] OR ("factor"[All Fields] AND "xa"[All Fields] AND "inhibitors"[All Fields]) OR "Factor Xa Inhibitors"[All Fields] OR ("direct"[All Fields] AND "factor"[All Fields] AND "xa"[All Fields] AND "inhibitors"[All Fields]) OR "direct factor xa inhibitors"[All Fields]) OR ("Factor Xa Inhibitors"[Pharmacological Action] OR "Factor Xa Inhibitors"[MeSH Terms] OR ("factor"[All Fields] AND "xa"[All Fields] AND "inhibitors"[All Fields]) OR "Factor Xa Inhibitors"[All Fields] OR ("direct"[All Fields] AND "acting"[All Fields] AND "oral"[All Fields] AND "anticoagulants"[All Fields]) OR "direct acting oral anticoagulants"[All Fields]) OR ("Factor Xa Inhibitors"[Pharmacological Action] OR "Factor Xa Inhibitors"[MeSH Terms] OR ("factor"[All Fields] AND "xa"[All Fields] AND "inhibitors"[All Fields]) OR "Factor Xa Inhibitors"[All Fields] OR ("anticoagulants"[All Fields] AND "direct"[All Fields] AND "acting"[All Fields] AND "oral"[All Fields])) OR (("direct"[All Fields] OR "directed"[All Fields] OR "directing"[All Fields] OR "direction"[All Fields] OR "directional"[All Fields] OR "directions"[All Fields] OR "directivities"[All Fields] OR "directivity"[All Fields] OR "directs"[All Fields]) AND ("acted"[All Fields] OR "acting"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields])) OR ("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR "anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields]) OR ("Factor Xa Inhibitors"[Pharmacological Action] OR "Factor Xa Inhibitors"[MeSH Terms] OR ("factor"[All Fields] AND "xa"[All Fields] AND "inhibitors"[All Fields]) OR "Factor Xa Inhibitors"[All Fields] OR ("oral"[All Fields] AND "anticoagulants"[All Fields] AND "direct"[All Fields] AND "acting"[All Fields]))) AND ("Medication Adherence"[MeSH Terms] OR ("Medication Adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "Medication Adherence"[All Fields] OR ("medication"[All Fields] AND "non"[All Fields] AND "adherence"[All Fields]) OR "medication non adherence"[All Fields]) OR ("Medication Adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "Medication Adherence"[All Fields] OR ("medication"[All Fields] AND "non"[All Fields] AND "adherence"[All Fields]) OR "medication non adherence"[All Fields]) OR ("Medication Adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "Medication Adherence"[All Fields] OR ("non"[All Fields] AND "adherence"[All Fields] AND "medication"[All Fields]) OR "non adherence medication"[All Fields]) OR ("Medication Adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "Medication Adherence"[All Fields] OR ("medication"[All Fields] AND "nonadherence"[All Fields]) OR "medication nonadherence"[All Fields]) OR ("Medication Adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "Medication Adherence"[All Fields] OR ("medication"[All Fields] AND "non"[All Fields] AND "compliance"[All Fields]) OR "medication non compliance"[All Fields]) OR ("Medication Adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "Medication Adherence"[All Fields] OR ("medication"[All Fields] AND "non"[All Fields] AND "compliance"[All Fields]) OR "medication non compliance"[All Fields]) OR ("Medication Adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "Medication Adherence"[All Fields] OR ("non"[All Fields] AND "compliance"[All Fields] AND "medication"[All Fields]) OR "non compliance medication"[All Fields]))

Appendix C: Flowchart template for PRISMA 2020 systematic reviews



Appendix D: Data extraction table

Study Information											
Title	Author; year	Country	Study outline	No.of participants	Non-adherence measurement method		Evaluated oral anticoagulant		Tested variables	Rated usage time	Association Measures	Factors associated with non-adherence
					Direct Methods	Indirect Methods	Coumarin derivatives	Direct acting oral anticoagulants				

Appendix D: Data extraction table 2

Sociodemographic and behavioral data				
Age (mean ± SD*)	Male gender (n; %)	Education (n; %)	Alcoholic beverage consumption	Smoking habits

Appendix D: Data extraction table 3

Dados sociodemográficos e comportamentais				
Oral anticoagulation indication	Comorbidities	Event occurrence		Other medications in chronic use
		Thromboembolism	Hemorrhages	