Risk of bias assessment of clinical trials referenced in the technical notes on direct-acting oral anticoagulants available on e-NatJus

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ABSTRACT:

Objective: Assess and classify the risks of bias in the clinical trials (CTs) that make up the technical notes (TNs) referring to direct-acting oral anticoagulants (DOAC) requests. **Methods:** The TNs related to the DOAC requests of apixaban, dabigatran, edoxaban, and rivaroxaban were selected on the e-NatJus website and, after excluding duplicate references, an analysis of the CT used for their writing was carried out. The CT risk of bias (low, high, or uncertain bias) was assessed using the Cochrane Risk of Bias tool, and the results were added to Review Manager 5.4. **Results:** 181 TNs were selected, 236 articles were analyzed and after applying the inclusion criteria, 28 CTs were analyzed in full. None of the CTs were free of bias. Most CTs, 71% (20/28), had a low risk of bias regarding attrition bias and reporting bias. In contrast, 61% (17/28) of the studies did not control for selection, performance, and detection bias, as they present uncertainties and a high risk of bias. In addition, it was observed that 21% (6/28) of the CTs had a high risk of bias for conflict of interest. **Conclusion:** The biases present in the CT cited as a reference for the TN referring to the DOAC request are significant and compromise their quality.

Keywords: Technical notes, Judicialization, Anticoagulants, Clinical trial, Bias

INTRODUCTION

Health in Brazil is safeguarded by the Federal Constitution of 1988, in which Article 196 recognizes health as "a right of all and a duty of the state"[1]. Thus, faced with a health risk, the citizen prevails over this right and demands against the state to obtain the necessary assistance, giving rise to the process of judicialization[2]. According to Machado[3], judicialization of health refers to a socio-legal event that is notably expressed in judicial processes aimed at granting procedures, treatments, and medications and which was implemented in Brazil from 1990 onwards.

The judicialization of health has been growing significantly and the drugs most requested in court are for the treatment of rare diseases and non-communicable chronic diseases (NCDs)[4]. Among the NCDs, thromboembolic diseases stand out. The treatment of thromboembolic diseases is through therapeutic anticoagulation, and warfarin, made available by the Public Health Service (*Sistema Único de Saúde* – SUS), is considered the mainstay of oral anticoagulant therapy for the treatment. However, its use requires strict laboratory monitoring, as it interacts with other drugs and some foods, which can cause poor adherence to therapy[5]. Thus, direct-acting oral anticoagulants (DOACs) have been prescribed for the treatment of venous thromboembolism since they have fixed doses without the need for monitoring. Due to the high cost, many patients who need to use DOACs go to court[6-7].

As a way to rationalize and minimize judicialization, the National Health Council, the Ministry of Health of Brazil, and the Sírio Libanês Hospital created the "e-NatJus" website, which holds technical notes (TNs), which are scientific documents formulated by a technical team from the Judiciary Support Centers (NATJus), composed of health professionals from the Court of Justice and at the request of magistrates to assist in the decisions of health processes[4-8]. To exercise this objective, the contents of the TN must be based

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on references, which include clinical trials (CTs) of relevance and technical-experimental quality. Given the lack of studies that assess the quality of the CTs that are used to prepare these TNs, the purpose of this study was to evaluate and classify the risks of bias in the CTs that make up the TN referring to the DOAC requests of apixaban, dabigatran, edoxaban, and rivaroxaban.

METHODS

This is a descriptive documentary study developed in two stages:

1. Selection of technical notes and analysis of the references used

The study used secondary data contained in the e-NatJus platform (https://www.cnj.jus.br/e-natjus/pesquisaPublica.php). The search for all TNs published since the implementation of the system (2018) was carried out by two researchers (N.A.A and M.L.P.D) from May to June 2020, using as inclusion criteria all TNs referring to the DOAC request (apixaban, dabigatran, edoxaban, and rivaroxaban). To identify them in the system, the following keywords were used: anticoagulantes, anticoagulante, rivaroxabana, rivaroxaban, dabigatrana, apixabana, apixaban, edoxabana, edoxaban, lixiana, lixian, xarelto, pradaxa and eliquis. Subsequently, a detailed analysis of the TN was carried out by a researcher (N.A.A) to exclude duplicates and TNs that did not fit the inclusion criteria. The analysis of the CTs used as a reference for writing the TN was performed individually by a researcher (M.L.P.D), excluding duplicates. The CTs inserted in the work were allocated into a Microsoft Excel® spreadsheet, separated by active ingredient.

2. Risk of bias analysis of clinical trials contained in the technical notes references

The risk of bias of the selected CTs was assessed using the Risk of Bias tool from the Cochrane Collaboration[9], which comprises the seven domains (Dom):

- Selection bias:
  - Dom1: Random sequence generation,
  - Dom2: Allocation concealment,
- Performance bias:
  - Dom3: Blinding of participants and professionals,
- Detection bias:
  - Dom4: Blinding of outcome assessors,
- Attrition bias:
  - Dom5: Incomplete outcomes,
- Reporting bias:
  - Dom6: Reporting of selective outcome,
- Other biases:
  - Dom7: Other sources of bias.

This analysis was performed by two researchers (M.L.P.D and N.A.A), independently, and each one categorized the CTs contained in the Excel spreadsheet as: high risk of bias, low risk of bias, and uncertain risk of bias according to the criteria established in the Cochrane Manual (HIGGINS et al., 2011)[9], according to the items below:

1. Random sequence generation: Low risk of bias is considered when the method used to generate the sequence was coin tossing, dice, raffle, table of random numbers, random numbers by computer, or shuffling of envelopes. A high risk of bias is considered if generating the sequence used the date of birth (even or odd), date or day of admission, test results, hospital medical record number, participant preference, or professional judgment. Uncertain risk of bias is considered if the study does not have enough information about the random sequence generation process to allow judgment.
2. Allocation concealment: A low risk of bias is considered if the process to conceal the allocation was carried out centrally, by sealed and opaque envelopes, or if the medicine containers were numbered in sequence with identical appearance. A high risk of bias is verified when the allocation was made by date of birth, envelopes without security criteria, or another process that does not hide the allocation. Uncertain risk of bias occurs when the study does not have enough information about the blinding process to allow judgment.

3. Blinding of participants and professionals: This is classified as low risk of bias when the blinding of participants and professionals is assured, impossible to be broken, or when the study is unblinded or incomplete blinding, but the outcomes are not altered by the lack of blinding. When there is an attempt to blind the participants and professionals, but it is likely to have been broken and this influences the outcome, or the study is unblinded or the blinding is incomplete and the outcome is influenced by the absence of blinding, the study is classified as having a high risk of bias. Uncertain risk of bias happens when the study does not present enough information to judge as high or low risk of bias or the study does not report this information.
4. Blinding of outcome assessors: Low bias is considered when there is blinding of outcome assessors and it is unlikely that the blinding was broken or the outcome assessors were not blinded, but the outcomes cannot be influenced by the lack of blinding. A high risk of bias is verified when there was no blind assessment of the outcomes and this influences the evaluated outcomes or there was blinding of the outcome evaluators, but it is likely that it was broken, and the verified outcome may have been influenced due to the lack of blinding. Uncertain risk of bias happens when the study does not present enough information to judge as high or low risk of bias, or the study does not report this information.
5. Incomplete outcomes: The study is classified as low risk of bias when there is no loss of outcome data, or the losses are not related to the outcome of interest, or the missing data were imputed by appropriate methods. A high risk of bias occurs when the reasons for data loss may be related to the investigated outcome with a difference in the number of patients or the imputation of data was performed improperly. When there is insufficient reporting of losses and exclusions to permit judgment, the study is at an uncertain risk of bias.
6. Selective outcome reporting: A study is classified as being at low risk of bias if the study protocol is available and all pre-specified primary and secondary outcomes that are of interest to the review were reported as proposed, or even though it is not available by the study protocol, it is understandable that the published study included all relevant outcomes. A risk of bias is considered high if one or more primary outcomes were reported using a measurement, method of analysis, or a subset of data that were not prespecified, or one or more reported primary outcomes were not prespecified, or the study did not include results from important outcomes that would be expected in this type of study. The uncertain risk of bias is verified when the information is insufficient to allow the judgment. It is expected that most studies will fall into this category.
7. Other biases: there is a low risk of bias if the study appears to be free from other sources of bias. A high risk of bias is related to the specific design of the study or it was alleged to be fraudulent or had some other problem. When the information is insufficient to assess whether an important risk of bias exists or insufficient rationale that an identified problem could introduce bias, the study is classified as an uncertain risk of bias.

After analysis according to eligibility criteria, 28 CTs were included for risk of bias assessment. Overall, the largest amount of study involved the DOAC rivaroxaban (19/28), followed by apixaban (4/28), edoxaban (3/28), and dabigatran (2/28).

It was observed, in agreement of 85% among the researchers, that all the included studies presented some kind of bias, and 17 presented selection, performance, and detection bias, since they present uncertainties and a high risk of bias, compromising the methodological quality. In contrast, in the analysis by domain (Dom1), it was observed that the domain related to random sequence generation had a low risk of bias in 11 studies.

The second domain, allocation concealment, presented uncertainties in similar proportions to Dom1 with 11 studies. Regarding the

blinding of participants and professionals (Dom3) and blinding of outcome assessors (Dom4) the uncertain risk of bias was verified in 10 and 11 of the studies, respectively.

Similarly, 20 trials had a low risk of bias regarding the incomplete outcome (Dom5) and selective outcome reporting (Dom6) domains. Finally, considering Dom7, referring to conflict of interest, six of the studies showed a high risk of bias. A summary of the risk of bias of the CTs included in the study, considering the seven domains pre-established by the Cochrane tool, are presented in Figure 2a and 2b.

Rivaroxaban was the DOAC for which the largest number of CTs was found (Figure 2a), mainly from 2010. It was observed that there was a predominance of a low risk of bias in rivaroxaban studies, more specifically, related to incomplete outcome (14/19) and random sequence generation (8/19). However, other biases and conflicts of interest were observed in nine rivaroxaban studies. The uncertainties reflected by the studies ranged from 7 regarding allocation concealment, blinding of participants and professionals, 6 regarding blinding of outcome assessors, 5 regarding random sequence generation, and 5 regarding incomplete outcome and incomplete outcome reporting. It should be noted that the highest percentage of a high risk of bias in the included studies occurred in the domain blinding of outcome assessors, in 7 studies[11-29].

When analyzing the CTs related to the apixaban DOAC (Küpper et al., 1989; Keren et al., 1990; Fleddermann et al., 2018; Robinson et al., 2020)[30-33], it was found that concerning selection bias, 3 of the studies presented uncertainties regarding random sequence generation (Dom1) and 2 of uncertainties regarding allocation

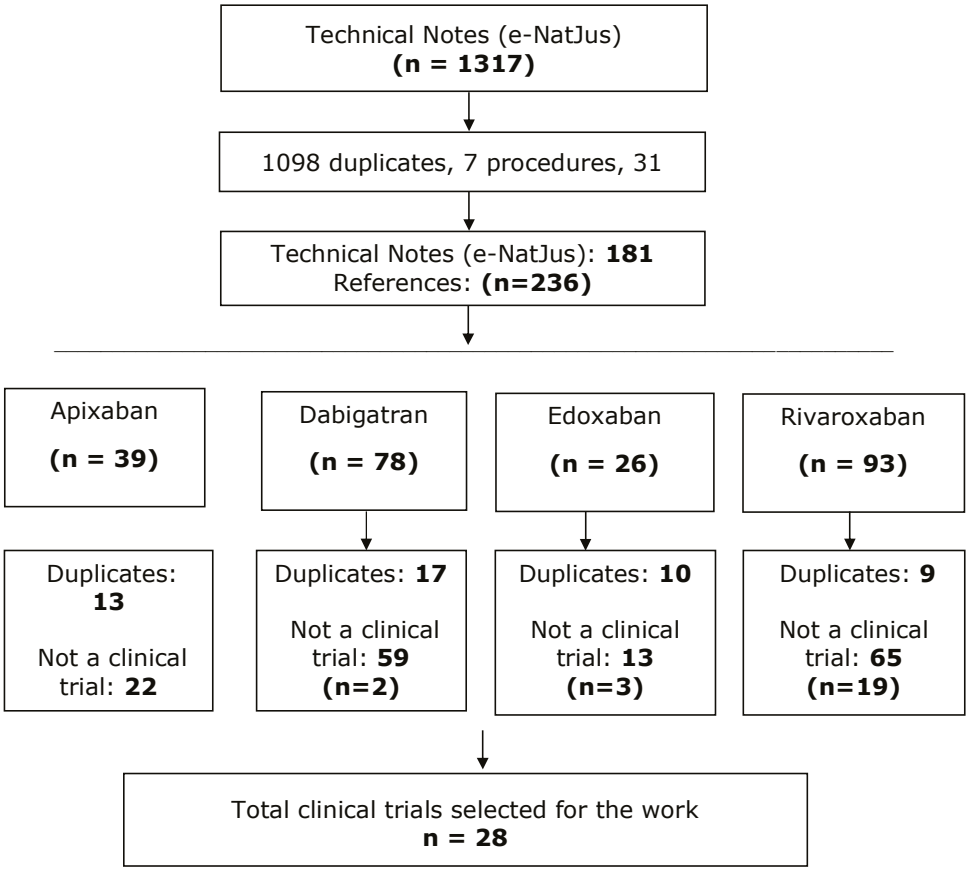

Figure 1: Flowchart for the selection of CTs, n=28, cited in the references in the TNs regarding the request for DOACs.

concealment (Dom2). As for the blinding of participants and professionals (Dom3), performance bias, the uncertainties totaled 3. For Dom4, blinding of outcome assessors, detection bias, 100% of uncertainties were observed in the studies. Regarding attrition bias, incomplete outcome (Dom5), and reporting bias, report of selective outcome (Dom6) there was a predominance of a low risk of bias in 2 studies. In the domain, other sources of bias (Dom7) 3 of uncertainty were observed.

In the analysis of dabigatran (Cantu et al., 2004; Ferro et al., 2019)[34-35], it was observed in both studies that the low risk of bias was predominant (greater than or equal to 50% in six of the seven domains analyzed (random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome, selective outcome reporting, and other biases). The high risk of bias was verified considering four domains, specifically: selection bias (allocation concealment), detection (blinding of outcome evaluators), and other biases (conflicts of interest), at 50% and, in performance bias (blinding of participants and professionals), 100%.

Finally, regarding edoxaban (Sardi et al., 2011; Giugliano et al., 2013; Monte et al., 2014)[36-38], a low risk of bias could be perceived in most domains (random sequence generation, blinding of participants and professionals, blinding of outcome assessors, incomplete outcome, report of selective outcome, and other biases) with a percentage above 67% (n=2). The percentage of uncertainties was observed in 33% (n=1) concerning blinding of outcome assessors, incomplete outcome, report of selective outcome, and 67% (n=2) studies regarding concealment of allocation.

DISCUSSION

This study evaluated the quality of the CTs cited as reference in the TNs referring to DOAC requests (apixaban, dabigatran, edoxaban, and rivaroxaban) and the results obtained showed that none of the included studies showed no risk of bias. This result was already expected, since, in the analyzed CTs, sometimes the information

Figure 2: Summary of risk of bias of CTs of DOACs (DOACs) included in the study, considering the seven domains pre-established by the Cochrane tool. a) classification by authors; b) distribution of the percentages of risk of bias in the studies.

was insufficient to classify the bias, and sometimes they presented data that led to a high risk of bias classification. Therefore, most of the analyzed domains presented the sum of high risk of bias and uncertainties higher than the low risk of bias.

The lack of sufficient information to allow judgment was a problem found in the description of the CTs. Without proper information, research can be considered incomplete, of scientific misconduct, and contributes to bias[39]. An alternative to remedy this problem is the use of reporting quality tools, such as the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network, which aims to improve reliability, based on the promotion of transparent and accurate research reports[40-41]. One example is the Consolidated Standards of Reporting Trials (CONSORT), the first scientific writing guide available to guide the writing of CTs. The publication of CONSORT was triggered by the growing evidence that reports of CTs needed to be more complete, providing essential information for their interpretation and application of their results[39].

As for the quality of CTs, the first domain analyzed, random sequence generation, showed that CTs do not describe in detail the method used to idealize the random sequence, or the method used is classified as having a high risk of bias. The same happens concerning the second domain, allocation concealment, where CTs do not detail the method used to conceal the random sequence or the method performed, which configures a high risk of bias, compromising the methodological quality of the study, since the bias selection is not controlled. Random sequence generation reduces, but by itself, it is not enough to prevent selection bias, and allocation concealment should be used to more efficiently protect against these biases[42]. Studies show that the creation of equivalent groups in CTs contributes to more reliable results[43]. It is noteworthy that randomization and allocation aim to create comparable groups, which minimizes bias[44]. Another way to reduce systematic errors, in the generation of random sequence and allocation concealment, is to train the teams participating in the trials, resorting to software and protocols that ensure the random allocation of training[45].

The analysis of blinding, evaluated in the third and fourth domains, shows that most of the CTs included in the evaluation presented performance bias and detection bias due to presenting uncertainties and high risk of bias. According to Higgins et al. (2011)[9], blinding consists of measures used to hide study participants, professionals related to the intervention, and outcome evaluators after the inclusion and randomization of participants. With effective blinding, the results can be attributed to the intervention itself and are not influenced by the behavior of participants, professionals, or outcome evaluators. The lack of blinding of study participants can cause errors in the outcome results; for example, participants in the intervention group may be more likely to produce positive results, and those in the control group may have lower results than if they did not know to which group they were assigned[46]. The lack of blinding of the professionals involved with the intervention can lead to changes in the clinical conduct once the group to which the participant is allocated is known[42]. Thus, it is inferred that any lack of blinding leads to bias.

Regarding the incomplete outcome, attrition bias, the findings demonstrate that most CTs describe whether the data related to the outcomes are complete for each main outcome, including losses and exclusion from the analysis, presenting a low risk of bias. In randomized CTs, attrition is common and one way to deal with missing values is imputation. The imputation technique is intended to generate a complete data set and the choice of the appropriate method will be directly linked to the reason for data loss in the studies, whether the loss is attributed to chance or not[47-48]. A well-conducted CT proceeds from adequate patient follow-up and caution with the collected data, as data loss can affect the effects of each outcome[49]. The results of the analyses confirm that most of the evaluated trials performed adequate follow-up and all losses and exclusions were duly reported, configuring study quality.

The sixth domain analyzed, selective outcome reporting, indicates the possibility that the CTs selected the outcomes when describing study results and what was identified. This happens when authors of a study report only positive and statistically relevant results and exclude statistically

irrelevant or negative results[50]. It should be noted that most CTs are controlled for reporting bias as they present a low risk of bias in this domain.

The last domain analyzed "other sources of bias", and consists of explaining another bias that does not fit in another previous domain of the tool[51]. Conflict of interest is an example that falls under the judgment of this domain. According to a study by Santos et al. (2014)[51], conflict of interest was present in most of the analyzed studies, and funding by the pharmaceutical industry was related to beneficial conclusions for the tested treatment. Of the evaluated CTs, half showed a low risk of bias, followed by uncertainties, showing that the conflict of interest for funding was little observed.

It is important to highlight the limitations found, such as the lack of sufficient information in CTs to allow the judgment of the risk of bias, and concerning the Cochrane Risk of Bias tool, which, despite being considered the gold standard for assessing quality, includes domains dependent on judgments, since the degree of agreement between evaluators may vary[52-53]. To minimize this limitation, all researchers involved in this work underwent training. To the best of our knowledge, this is the first study assessing the quality of CTs cited in the TN references referring to the DOAC request, which could contribute to improving the technical quality of TNs, making them more robust and safer.

This work reveals worrying data regarding the technical quality of the CTs analyzed in the TNs for the DOAC request. This is due to the fact that in the analyses of these CTs, many domains presented uncertainties and a high risk of bias stood out concerning a low risk of bias. The low quality of CTs has a direct impact on the fulfillment of the functions of the TNs, on the advice of magistrates, and public health costs[54]. Therefore, it is urgent that the technical teams of the judiciary, responsible for making the TNs, seek new studies and update the references used to write them.

CONCLUSION

There are significant biases in the CTs cited as references in the TNs that support decision-making in the context of the judicialization of DOACs, which can compromise the quality of collective and individualized health care, in addition to compromising the quality and rationality of judicial processes. The data from this study call attention to the need for new, more emphatic clinical studies and/or review and updating of the references used in writing the TNs, in order to make them more robust and promote greater safety in their use. It is worth mentioning, as a perspective for further studies, the importance of quality scientific communication that is understandable to judges, which will facilitate decisions in health-related processes.

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