Short Communication

Quality of Adverse Effect Reporting in the Clinical Trials of Comparing Direct Oral Anticoagulants versus Warfarin in Atrial Fibrillation

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Abstract

Drug classes such as direct oral anticoagulants (DOACs) are relatively new; therefore, it is imperative to report their adverse effects with transparent information, and the quality of these reports in the medical science needs to be assessed. This study aimed at evaluating the quality of adverse effect reporting of DOACs against warfarin in atrial fibrillation (AF) using the Consolidated Standards of Reporting Trials (CONSORT) Harms checklist. We searched MEDLINE and Drug@FDA and identified four Food and Drug Administration-approved drugs from DOACs class and their relevant clinical trials. The data extraction form was designed using the CONSORT Statement of Harms to include 18 items. Data extraction was conducted by the first three authors independently and any discrepancies were resolved with a discussion later. Descriptive analysis was employed to measure the rate and percentage of completion of all the items in our revised CONSORT Statement of Harms checklist. Data analysis was condicted using the SPSS software version 20.0 software. All included articles were multicentered. The median number of authors was 14.78 and the median impact factor was 26.48. Eligibility criteria, interventions, outcomes, sequence generation, and baseline data were the most reported items whereas estimating the outcomes and explaining any interim analyses and stopping guidelines were the least reported items. All articles from the New England Journal of Medicine had a higher percentage of completion of items on the CONSORT checklist compared to the articles from other journals. The quality of reporting adverse effects for DOACs against warfarin in AF was found to be adequate.

Keywords: Adverse effects, atrial fibrillation, consortium, direct oral anticoagulants, warfarin

Introduction

Since the discovery of warfarin in 1933, it has been widely used to prevent and treat thromboembolic complications but with a significant number of harmful adverse effects.[1] In the light of safety data published about direct oral anticoagulants (DOACs) in recent studies, many healthcare providers prefer DOAC to warfarin in atrial fibrillation (AF).[2-4]

With the introduction of drug classes such as DOACs, which include drugs such as edoxaban, apixaban, rivaroxaban, and dabigatran in the market, the responsibility of reporting adverse effects and having transparent information is even more important than ever.[5] Although identifying the adverse effects reported in the trials seems to be a sensible solution, it often fails due to authors not delivering clear and cohesive information about the adverse effects, especially in phase III trials.

In 1996, the Consolidated Standards of Reporting Trials (CONSORT) group, comprising of a number of medical journal editors, created the CONSORT Statement of Harms to help researchers improve the quality of reporting Randomized Clinical Trials (RCTs).[6,7] To take full advantage of this concept, the CONSORT statement was later modified to include harms-related items with the aim of improving the adverse effects reporting in RCTs when conducting a clinical trial.[8]

One of the best sources for testing the efficacy and safety of an intervention is RCT.[9] It is considered the gold standard for assessing health care interventions and a cornerstone for measuring the benefits and harms of medication in most

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cases.[10] For this reason, the analysis of these benefits and harms reported in these trials that may occur to the patient guides the clinical decision making in healthcare practice.

The quality of reporting the adverse effects of DOACs against warfarin in medical science has not been assessed to date. Therefore, there is a need to assess the quality of reporting the adverse effects of DOACs against warfarin in AF.

This study aimed at evaluating the quality of reporting adverse effects in RCTs that include DOAC as an intervention against warfarin in AF using the extended CONSORT Statement for Harms.

Materials and Methods

Identification and selection of articles

We searched MEDLINE and Drug@FDA on June 16, 2016, from inception for clinical trials that included DOACs and identified four drugs from the class, DOACs including rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa), and dabigatran (Pradaxa) [Table 1]. The search term we used was a randomized clinical trial, RCT, clinical trial, warfarin, rivaroxaban, Xarelto, apixaban, Eliquis, edoxaban, Savaysa, dabigatran, and Pradaxa.[11]

The first three authors assessed all the clinical trial reports independently by reading the abstracts. If deemed necessary, all the three authors discussed and came to a consensus about the inclusion and exclusion of the trials in this study.

Inclusion criteria

The inclusion criteria were RCTs wherein AF was the primary outcome, DOAC as intervention, and warfarin as control.

Exclusion criteria

The exclusion criteria were RCTs wherein AF was not the primary outcome (e.g. pulmonary embolism, deep vein thrombosis, venous thromboembolism, etc. were used as primary outcomes), and warfarin was not used as control [Table 2].

The CONSORT statements

The CONSORT statement originally consisted of 25 items. We revised it to include 18 items because we considered these items the most important and relevant for reporting adverse effects. The items we included were related to "Methods" and "Results" only, considering that "Introduction", "Background", "Discussion", and "Conclusion" sections may give an only little indication about how adverse effects were reported. Additional included items were the number of authors, country of origin, funding, name of the journal and its impact factor, settings, and trial design.

Data extraction

Data extraction was conducted independently by the first three authors of the study and discussed later. Any disagreements were resolved by discussion. All extracted data were reviewed by the two supervisors.

Table 1: Characteristics of the included studies

Characteristic	Number of studies
Country of origin	
Multinational	5 (55.6%)
Japan	3 (33.3%)
South Korea	1 (11.1%)
Year of publication	
2010 or before	3 (33.3%)
After 2010	6 (66.7%)
Funding	
NGO (non-governmental organization)	9 (100%)
Journal	
New England Journal of Medicine	4 (44.4%)
Circulation	3 (33.3%)
Thrombosis and Haemostasis	2 (22.2%)
Setting	
Multicentered	9 (100%)
Trial design	
Parallel	9 (100%)

Table 2: Completion score of adverse effect reporting in the use of direct oral anticoagulants against warfarin in the atrial fibrillation of each study

Study	Journal	Completion Score (%)
ENGAGE AF-TIMI 48 trial	The New England Journal of Medicine (NEJM)	13 (72%)
ROCKET AF trial	The New England Journal of Medicine (NEJM)	13 (72%)
J-ROCKET AF trial	Circulation Journal (Japan)	9 (50%)
ARISTOTLE trial	The New England Journal of Medicine (NEJM)	13 (72%)
J-ARISTOTLE trial	Circulation Journal (Japan)	9 (50%)
RE-LY trial	The New England Journal of Medicine (NEJM)	16 (89%)
Edoxaban-Asia trial	Journal of Thrombosis and Haemostasis	12 (67%)
Edoxaban-US/Europe trial	Journal of Thrombosis and Haemostasis	8 (44%)

Data were coded as values in the essence of completion of CONSORT items: (No) as 0, (Yes) as 1, (Not clear) as 2, (Not applicable) as 3, and (Yes but in a different section) as 4. After entering all the data in the Statistical Package for the Social Sciences (SPSS), we recoded (Not clear) to (No), because it would imply insufficient or ambiguous reporting, and both (Not applicable) and (Yes but in a different section) were recorded to (Yes), because they show that the intended item has been reported or was not relevant.

Ultimately, we transformed the data into a score of (Yes) and (No) from which we measured the rate of completion of the data extraction form as a percentage for each of the selected articles, wherein (Yes) means the authors of the study had reported the items and (No) means otherwise. The rate of completion means the number/frequency of "Yes" in our revised CONSORT checklist.

Statistical analysis

Descriptive analysis was employed to measure the rate and percentage of the completion of items in our revised CONSORT Statement of Harms. Data analysis was done using SPSS v.20 software (SPSS Inc., Chicago, IL, United States). Because of the low number of studies included, it deemed inappropriate to conduct any inferential analysis.

Results

We identified nine eligible trials including ARISTOTLE trial, ENGAGE AF-TIMI 48 trial, ROCKET AF trial, J-ROCKET AF trial, ARISTOTLE-J, RE-LY trial, Edoxaban-Asia, Edoxaban-US/Europe, and Edoxaban-Japan. All these trials were reviewed and included after a consensus between the authors [Appendix 1] [Figure 1]. All the studies were multicenter and were funded by a nongovernmental organization. The mean number of authors was 14.8 (the range was 3-32). Almost half of them were multinational studies and were published in the New England Journal of Medicine (NEJM). One study was done in 4 Asian countries (Singapore, Taiwan, Hong Kong, and South Korea) and was published in Thrombosis and Haemostasis. The median impact factor was 26.5 (range was 1.4-55.9).

Approximately half of the included studies reported statistical methods and adverse outcomes (55.6%). All of them had a complete reporting of eligibility criteria and baseline data [Appendix 3]. All studies from NEJM had a percentage of completion of 72.2% according to our revised CONSORT checklist.

The majority of included studies scored 50% or above the rate of completion with the exception of one study (Edoxaban-US/ Europe trial), scoring less than half of the total score (score of 8 out of 18) on our revised CONSORT checklist.

Discussion

Across all the studies, we found that four out of all nine studies were from the same journal, which had a high impact factor, and were multicentered with similar results, which can influence the findings of our study. In addition, they had a high rate of completion, so there might be a relationship between the journal or the country of origin (multinational or national) and the quality of adverse effects reporting.

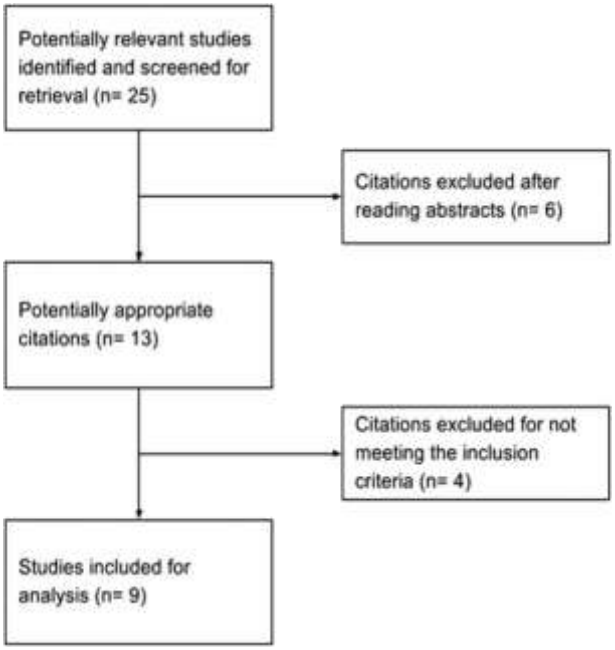

Figure 1: Selection of articles

There was an apparent lack of reporting statistical methods related to adverse outcomes in the majority of included studies which could be related to the country of origin or the journal's own regulations of reporting the data. Reporting of eligibility criteria, settings, and location, interventions, recruitment, and baseline data were very clear and well defined in the majority of included studies.

Because of the lack of previous studies in this field, it was difficult to directly compare the findings of our study for credibility. However, despite a Chinese article, which assessed the quality of RCTs on Wenxin granule for the treatment of AF and found that no included RCT reported the allocation concealment, our study showed that this item was mentioned in the studies we included.[12] This appears true because the majority of the included studies came from

highly cited and respected journals such as NEJM. Regarding the sample size, the same Chinese study did not find any RCT that reported the estimation of the sample size, whereas, in our study, we found that this was well reported (77.8%).

The Chinese article found that only one study used blinding, but we found nearly half of the included studies (55.6%) reported this item. Half of the included studies (55.6%) reported the loss of participants due to harm that was consistent with the findings of the Chinese study, which reported 59%. They found only six studies (9.1%) that mentioned the method of generating the random sequence, however, we found that less than half of the included studies (44.4%) reported this item. For the inclusion and exclusion criteria, we found that all the included studies (100%) had reported this item.

clearly, whereas in the Chinese study, only 19 studies (28.8%) had reported the inclusion criteria. They found that six studies (9.1%) had reported the follow-up record while in our study, (77.8%) had reported this item. Finally, our study found that only half of the included studies (44.4%) described the adverse effects in the RCT, whereas in the Chinese study, the majority of studies (77.3%) mentioned the adverse effects.

The major limitation of our study was the specificity of the topic because we found a limited number of articles that met our inclusion criteria and no other similar studies were available to compare our findings. A broader scope of studies can be considered in the future to analyze the data by inferential analysis and compare the findings with other similar studies.

The current quality of adverse effect reporting for DOACs against warfarin in AF clinical trials is appropriate but can be improved by following the CONSORT extension of Harm guide to provide a more consistent and optimized approach to report adverse effects.

Conclusion

There is an adequate reporting of adverse effects in the use of DOAC against warfarin in AF clinical trials. However, this reporting seems to be dependent on the type of journal the study is published in. It might be early to draw any conclusion because of the very limited number of studies included. Nevertheless, this study validates the importance of the wider implementation of the CONSORT Statement of Harms in medical journals.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix 1

Included research articles

(1) Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine 369(22):2093–104 doi:10.1056/NEJMoa1310907

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(9) Yamashita T, Koretsune Y, Yasaka M, Inoue H, Kawai Y, Yamaguchi T, et al. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. Circulation Journal 2012;76(8):1840–7 doi:10.1253/circj.CJ-11-1140

Appendix 2

Excluded research articles

(1) Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. The Lancet 2008;372(9632):31–9 doi:10.1016/S0140-6736(08)60880-6.

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APPENDIX 3

Quality of adverse effect reporting rating using items from the CONSORT statement

Standard CONSORT checklist: paper section and topic	Standard CONSORT checklist: item number	Descriptor	Frequency of completion ("Yes")
Methods			
Participants	1a	Eligibility criteria for participants	100%
	1b	Settings and locations where the data were collected	77.8%
Intervention	2	The interventions for each group with sufficient details to allow replication	88.9%
Objectives	3	Specific objective or hypotheses	55.6%
Outcomes	4	List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs. unexpected events, a reference to standardized and validated definitions, and description of new definitions) Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, the intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent)	88.9%
Sample size	5a	How the sample size was determined	77.8%
	5b	When applicable, explanation of any interim analyses and stopping guidelines	33.3%
Randomization			
Sequence generation	6a	The method used to generate the random allocation	88.9%
	6b	Type of randomization; details of any restriction (such as blocking and block size)	77.8%
Allocation concealment	7	The mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until intervention was assigned	44.4%
Blinding (masking)	8	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	55.6%
Statistical methods	9	Describe plans for presenting and analyzing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses)	44.4%
Results			
Participant flow	10	Describe for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment	55.6%
Recruitment	11	Dates defining the periods of recruitments and follow-up	77.8%
Baseline data	12	A table showing baseline demographic and clinical characteristics for each group	100%
Numbers analyzed	13	Provide the denominators for analyses on harms	33.3%
Outcomes and estimation	14	Present the absolute risk per arm and per adverse event type, grade, and seriousness, and present appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent	11.1%
Adverse events	15	Describe any subgroup analyses and exploratory analyses for harms	44.4%