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Original Research Article

Assessing the reporting quality of randomized-controlled clinical trials involving novel oral anticoagulants in patients with atrial fibrillation based on the CONSORT statement

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ABSTRACT

Background: Inadequate reporting of the published randomized controlled trials (RCTs) may restrict the generalizability of treatment effectiveness and tolerability of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation (AF). The main objective of this study was to assess the reporting quality of RCTs for efficacy and safety of NOACs vs. warfarin in patients with AF based on the consolidated standards of reporting trials (CONSORT) statement.
Methods: Pubmed was searched for relevant english-language RCTs. Eligible articles included pivotal RCTs and articles reporting results from sub-populations or post-hoc secondary analysis of the pivotal trials (non-pivotal trials). Eligible articles were assessed according to 37-item/sub-item checklist of CONSORT statement 2010. The assessment was overall and according to trial's type, NOAC treatment and impact factor (IF) of journals.
Results: Search identified 92 articles eligible for evaluation. Half of CONSORT items were reported by more than 90% of the articles and 25% of items were reported in all articles. The majority of pivotal studies (94%) answered >75% of CONSORT items, while only half of non-pivotal studies had similar compliance ($p<0.01$). NOACs showed similar pattern in reporting quality ($p>0.05$), while IF had a significant effect in quality ($p<0.01$).
Conclusions: RCTs for efficacy and safety of NOACs vs. warfarin in AF patients found to be well reported. Though, the quality of reporting is affected by type of trial and journals' IF.

Keywords: Atrial fibrillation, Novel oral anticoagulants, Stroke prevention, CONSORT statement, Quality of reporting, Randomized clinical trials

INTRODUCTION

Randomized controlled trials (RCTs), when properly designed, conducted and reported, are considered as a gold standard in clinical medicine and public health, for the evaluation of efficacy of new therapeutic or preventive interventions, as they minimize bias and provide the basis for valid statistical analysis.[1,2] However, they can also lead to biased results and misleading information if they lack methodological rigor.[1-3]

Clinicians depend at a great extent, on the reporting of methodological approaches of published RCTs, in order to determine the validity and reliability of all information

provided. Conclusions extracted, affect decision making, from patients' management to the formulation of treatment guidelines and national public health policies.[4,5] Consequently, there is a need for lucid information about trials' methodology and findings.[6,7] Unfortunately, attempted efforts frequently fail, because many reports omit critical methodological details.[2,8-10] For example, only 45% of trial reports indexed in PubMed in 2000 and 56% in 2006 defined primary end point, and only 27% in 2000 and 45% in 2006 reported a sample size calculation.[8-11]

The assessment of methodological quality of a trial is closely intertwined with the quality of reporting; that is, the extent to which a report provides information about the design, conduct, and analysis of the trial.[3] Hence, inadequate reporting often reflects faulty methods and a well-conducted but badly reported trial could be misclassified.[3,7] Furthermore, faulty reporting makes the interpretation of results complex and leads to biased conclusions.[12] Thus, authors must provide transparent information about RCTs, in order to enable readers to estimate unbiased the treatment effects.[4]

In response to the misleading evaluation of poorly reported RCTs and its consequences, an international group of scientists and journal editors developed the CONSORT (consolidated standards of reporting trials) Statement to improve the quality of reporting of RCTs. It was first published in 1996, last revised in 2010 and translated into 13 languages.[2,4,13] The 2010 CONSORT statement comprises a checklist of 25 items (37 items/sub-items) that should be included in reports of RCTs and a diagram for documenting the flow of participants through a trial. The CONSORT is not meant to be a quality judgement tool and should not be used to this direction, but rather as evidence based guide for proper reporting of RCTs.[4,14] To date, more than 600 biomedical journals worldwide have adopted the CONSORT statement.[15]

A number of review articles have assessed the quality of reporting of RCTs in several subspecialties of medicine so far.[1,10,16-18] However, no study has evaluated the reporting quality of RCTs focusing on the new therapeutic approaches in atrial fibrillation (AF), the most common arrhythmia in adults.[19] AF has been independently associated with a 2-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men. Recent studies show that 20-30% of all strokes are due to atrial fibrillation.[19-22] The most common anticoagulation treatment, so far, for the prevention of stroke in AF patients, has been considered warfarin and other vitamin K antagonists, reducing the risk of stroke by about two thirds.[23] However, their use is limited by the narrow therapeutic range, drug and food interactions, monitoring of international normalized ratio (INR), and risk of bleeding.[23] In the last fifteen years, research has been focused on assessing the efficacy and safety of non-vitamin K antagonist (Non-VKA) oral anticoagulants (NOACs) against warfarin in non-valvular AF patients.[24] The NOACs include products with marketing authorization (apixaban, edoxaban, dabigatran and rivaroxaban) and products without marketing authorization (ximelagatran, AZD0328, darexaban and betrixaban). So far, a number of large multi-centered RCTs have been conducted in this direction.[21] An assessment of the quality of these trials is mandatory to ensure the applicability of their findings in clinical practice and can be accomplished via a thorough reporting of their methodology, conduct, data analysis and results.[2]

The main objective of this study was to assess the reporting quality of RCTs that explore the efficacy and safety of NOACs vs warfarin in patients with AF, based on CONSORT checklist 2010.

METHODS

Search strategies and data sources

PubMed was systematically searched to identify RCTs that investigate the efficacy and safety of all NOACs vs warfarin in patients with AF, published till August 2016. The search criterion was the following term: "(apixaban OR edoxaban OR dabigatran OR rivaroxaban) vs warfarin AND atrial fibrillation, (new oral anticoagulants OR oral thrombin inhibitors OR oral factor Xa inhibitors) vs warfarin AND atrial fibrillation, as well as (ximelagatran OR darexaban OR betrixaban OR AZD08327) vs warfarin AND atrial fibrillation". Search was limited to the following criteria: "Randomized Controlled Trial" as the type of article, "English" language and inclusion of studies on "human" subjects. We intended to cover the whole spectrum of RCTs on new oral anticoagulants in AF, including NOACs not currently with marketing authorization.

Studies selection

Two investigators (AA and PM) independently screened all titles and abstracts of records retrieved from database searches. RCTs were eligible if they had randomly assigned participants to at least two treatment arms and if they had investigated the efficacy and safety of NOACs vs warfarin in patients with AF. We also included published articles reporting results from sub-populations of the pivotal RCTs or post-hoc secondary analysis of the primary data (non-pivotal trials).

Reviews, letters to editor, non-randomized trials, communications and conference abstracts were excluded. All references cited in the retrieved articles were also reviewed to identify additional published work not indexed by PubMed. Any discrepancies between the authors during data collection were resolved by discussion with a third author (EZ). Inter-rated agreement level between the reviewers was assessed using the Cohen's kappa statistic.

Data extraction and reporting assessment tool

All extracted eligible articles have been assessed for their quality of reporting using the revised CONSORT checklist, which includes a 25-item (37-item/sub-item) questionnaire.[2,25]

All items were investigated in terms of whether they were reported and not whether they were actually carried out during the trial. When an item was not reported in the right section of the article (title, abstract, methods, results, discussion) then it was considered as a negative response. Alternative responses (apart of yes or no) or unclear responses to each question were coded as negative responses. In a large number of non-pivotal studies, most items, regarding methodological approaches of the RCT, were not reported in detail, and instead, a reference of the study protocol or the pivotal was cited. If these items were not reported at all and only a reference of the pivotal study was cited, we coded them as negative. When specific items were not related to the trial or trial protocol (such as 3b, 6b, 7b, 11a, 11b, 12b, and 14b), then these items were not considered in the evaluation.

Evaluation and statistical analysis

The evaluation of articles was conducted according to the 37-item/sub-item CONSORT checklist, which includes the reporting of the following sections: title and abstract, introduction, methods, results, discussion and other information. "Title and abstract" section refers to the identification of the randomised trial in the title (item 1a) and a structured summary of the whole trial, (item 1b) while "Introduction" section refers to the scientific background and explanation of rationale (item 2a) and specific objectives or hypotheses (item 2b). In addition, "Methods" section refers to the reporting of description of the trial design including allocation ratio (item 3a), important changes to methods after trial commencement with reasons (item 3b), eligibility criteria for the participants (item 4a), settings and locations where the data were collected (item 4b), interventions for each group with sufficient details to allow replication, including how and when they were actually administered (item 5), completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed (item 6a), any changes to trial outcomes after the trial commenced, with reasons (item 6b), how sample size was determined (item 7a), when applicable, explanation of any interim analyses and stopping guidelines (item 7b), as well as the method used to generate the random allocation sequence (item 8a), type of randomisation; details of any restriction(type 8b), the mechanism used to implement the random allocation sequence, describing any steps taken to conceal the sequence until interventions were assigned (item 9), who generated the random allocation sequence who enrolled participants, and who assigned participants to interventions (item 10), if done, who was blinded after assignment to interventions and how (item 11a), if relevant, description of the similarity of interventions (item 11b) and finally statistical methods used to compare groups for primary and secondary outcomes (item 12a) and methods for additional analyses, such as subgroup analyses and adjusted analyses (item 12b). Furthermore, the "Results" section refers to the numbers of participants who were randomly assigned in each group, received intended treatment, and were analysed for the primary outcome (item 13a), losses and exclusions after randomisation, together with reasons (item 13b), dates defining the periods of recruitment and follow-up (item 14a), why the trial ended or was stopped (item 14b), a table showing baseline demographic and clinical characteristics for each group (item 15), number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups (item 16), for each primary and secondary outcome, results for each group, and the estimated effect size and its precision (item 17a), for binary outcomes, presentation of both absolute and relative effect sizes is recommended (item 17b), results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory (item 18) and all important harms or unintended effects in each group (item 19). The "Discussion" and "Other information" sections refer to the trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses (item 20), generalisability of the trial findings (item 21), interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence (item 22), registration number and name of trial registry (item 23), where the full trial protocol can be accessed, if available (item 24) and sources of funding and other support, role of funders (item 25) (Table 1).

All Journals were searched and listed according to the ISI (Institute for Scientific Information) Impact Factor for 2015. Journals were also reviewed for their endorsement to the CONSORT Statement, which is usually clearly mentioned in Journal's instructions for authors on how to report clinical trials or there is a statement that the Journal adheres to the directives of International Committee of Medical Journal Editors that has also endorsed the CONSORT Statement 2010.

The articles were analyzed overall and according to the type of article (i.e. pivotal and non-pivotal (RCTs). The articles were also separated into 5 subgroups according to the NOAC treatment: apixaban, edoxaban, dabigatran, rivaroxaban, NOACs without marketing authorization. Finally, the articles were compared according to the IF of the journals: journals with IF above the median (high ranked) compared to those below the median (low ranked). Also, the articles were divided based on the percentage of compliance with the CONSORT statement items. [18,26] Comparisons between various subgroups were made by means of chi-square statistic.

Data extraction and article evaluation were made independently by two authors (AA and PM), who were

blinded for each other's ratings. The consistency between the two authors for assessment of all CONSORT items was determined using Cohen's kappa statistics. This method involves the degree of reviewers' agreement on whether an item was reported or not. For calculation of kappa, all items were considered together for each paper. Any discrepancies were resolved after discussion with author EZ. All variables are categorical and they are presented as numbers and frequencies. A result was considered significant at two-sided 0.05 level.

RESULTS

Eligible studies

A total of 422 potentially eligible references were identified (Figure 1), of which 4 were found to be duplicates. The remaining 418 unique citations were screened for eligibility and after screening, 8 citations that were not in English and another 318 citations that did not fulfill the inclusion criteria were excluded (16 referred just to the study protocol, 32 studies compared NOACs or warfarin with aspirin or heparin in AF patients, 74 articles referred to NOACs in venous thromboembolism and orthopedics, 120 pharmaco-dynamics studies, 46 studies referred to other heart disease, 15 articles were not RCTs, such as reviews, pooled analysis of many RCTs' results etc., 15 articles of secondary analysis did not focus on efficacy or safety of NOACs). Consequently, a total of 92 reports remained for analysis, requiring complete full-text evaluation. The inter-rater agreement level in article evaluation for eligibility was relatively high, with kappa=0.92 (0.88-0.96). The main discrepancy between the two raters concerned the eligibility of articles that were short reports. A full list of the 92 reports that were retrieved as full-text and included in final analysis is shown in Supplemental Table. The kappa score for inter-observer variability of CONSORT checklist scoring was k=0.86.

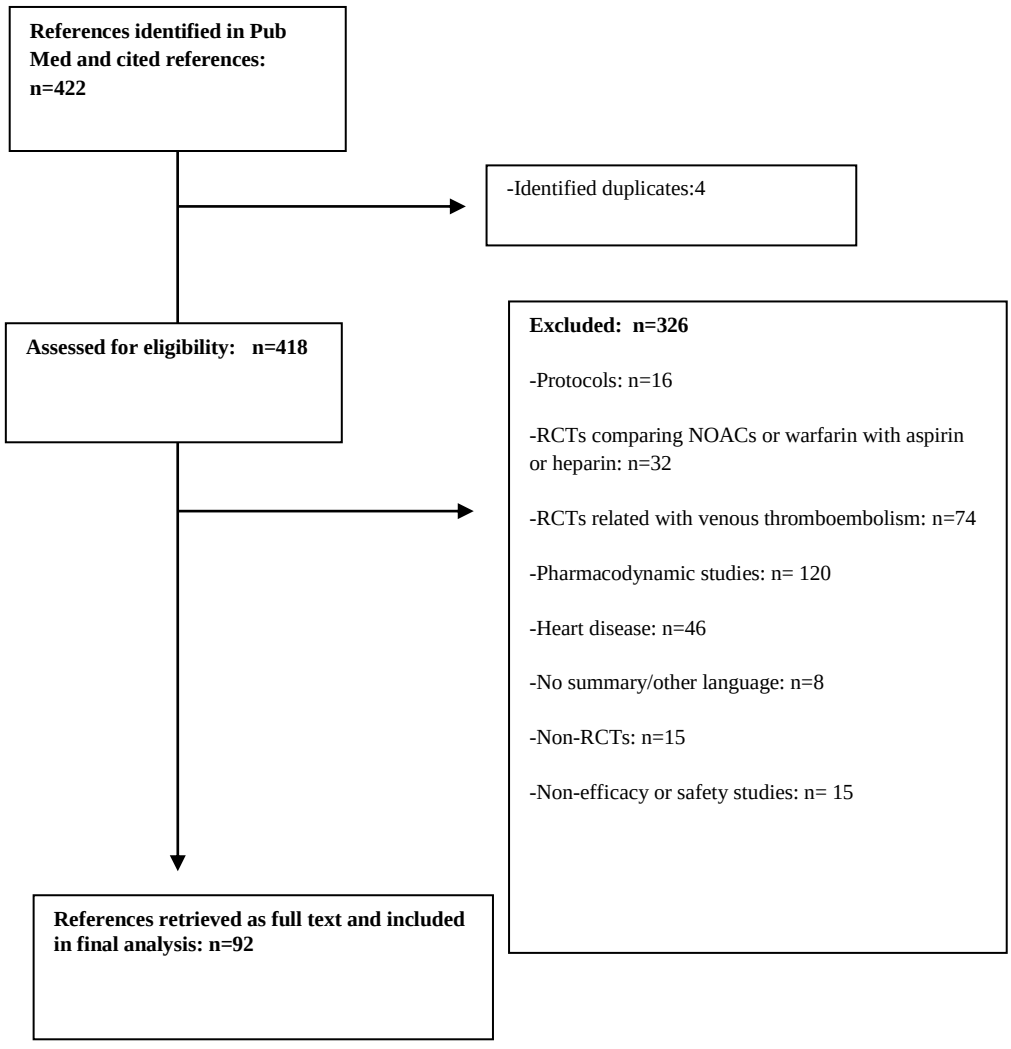

Figure 1: Flow diagram of citations through the retrieval and screening process.

The diagram shows the initial number of references that were screened for eligibility, the number of references that were excluded together with reasons and the final number of articles that deemed as eligible and were included for assessment.

Table 1: Reporting of CONSORT items and compliance differences between pivotal and non-pivotal trials.

CONSORT section/topic	Item No	All trials n=92	Pivotal trials n=18	Non-pivotal trials n=74	P-value[¶]
Title and abstract					
	1a	19 (20.7)	8 (44.4)	11 (14.9)	0.005
	1b	87 (94.6)	15 (83.3)	72 (97.3)	0.019
Introduction					
Background and objectives	2a	91 (98.9)	18 (100)	73 (98.6)	0.620
	2b	92 (100)	18 (100)	74 (100)	-
Methods					
Trial design	3a	81 (88)	18 (100)	63 (85.1)	0.081
	3b	4 (4.3)	3 (16.6)	1 (1.4)	-
Participants	4a	86 (93.5)	18 (100)	68 (91.9)	0.210
	4b	46 (50)	16 (88.9)	30 (40.5)	0.001
Interventions	5	92 (100)	18 (100)	74 (100)	-
Outcomes	6a	89 (96.7)	18 (100)	71 (95.9)	0.385
	6b	N/A	N/A	N/A	-
Sample Size	7a	19 (20.7)	16 (88.9)	3 (4.1)	0.001
	7b	4 (4.3)	4 (22.2)	N/A	-
Randomisation					
Sequence generation	8a	21 (22.8)	10 (55.6)	11 (14.9)	0.001
	8b	53 (57.6)	16 (88.9)	37 (50)	0.003
Allocation concealment mechanism	9	5 (5.4)	4 (22.2)	1 (1.4)	0.001
Implementation	10	7 (7.6)	4 (22.2)	3 (4.1)	0.009
Blinding	11a	30 (32.6)	11 (61.1)	19 (25.7)	0.001
	11b	9 (9.8)	6 (33.3)	3 (4.1)	0.001
Statistical methods	12a	92 (100)	18 (100)	74 (100)	-
	12b	92 (100)	18 (100)	74 (100)	-
Results					
Participant flow	13a	90 (97.8)	18 (100)	72 (97.3)	0.480
	13b	84 (91.3)	18 (100)	66 (89.2)	0.140
Recruitment	14a	31 (33.7)	13 (72.2)	18 (24.3)	0.001
	14b	N/A	N/A	N/A	-
Baseline data	15	88 (95.7)	18 (100)	70 (94.6)	0.310
Numbers analysed	16	92 (100)	18 (100)	74 (100)	-
Outcomes and estimation	17a	92 (100)	18 (100)	74 (100)	-
	17b	90 (97.8)	17 (94.4)	73 (98.6)	0.270
Ancillary analyses	18	92 (100)	18 (100)	74 (100)	-
Harms	19	92 (100)	18 (100)	74 (100)	-
Discussion					
Limitations	20	81 (88)	11 (61.1)	70 (94.6)	0.001
Generalisability	21	85 (92.4)	16 (88.9)	69 (93.2)	0.532
Interpretation	22	92 (100)	18 (100)	74 (100)	
Other information					
Registration	23	53 (57.6)	12 (66.7)	41 (55.4)	0.386
Protocol	24	76 (82.6)	9 (50)	67 (90.5)	0.001
Funding	25	91 (98.9)	18 (100)	73 (98.6)	0.620

[¶]Pivotal vs. non-pivotal trials; N/A: Non Applicable.

Main results

The 92 eligible articles were published from inception until August 2016. All the articles were published after the introduction of the CONSORT statement. The articles were published in 25 different journals and 23 journals (92%) have endorsed the Consort statement. The articles were published in high-ranked journals (IF≥15, cutoff median value) and in lower ranked journals (IF<15). Among the studies, 18 (20%) were pivotal RCTs (8 phase III and 10 phase II) and 74 (80%) were non-pivotal RCTs. In addition, 18 articles investigated apixaban (20%), 12 edoxaban (13%), 22 dabigatran (24%), 31 rivaroxaban (34%) and 9 (10%) NOACs without marketing authorization (5 ximelagatran, 2 AZD0328, 1 darexaban and 1 betrixaban).

Table 1 shows the overall frequency of reporting of the 37 items/sub-items of the CONSORT statement. The overall reporting of CONSORT checklist items ranged from 4.3% to 100%. In detail, 19 out of 37 (51%) items/sub-items (1 in the title and abstract, 2 in the introduction, 5 in methods, 8 in the results, 2 in discussion and 1 in the other information section) were reported by 90% or more of the studies (Table 1). Nine out of 37 items (24%) were reported in all studies: items in background and objectives (item 2a), interventions (item 5), statistical methods (items 12a and 12b), numbers analysed (item 16), outcomes and estimation (item 17a), ancillary analyses (item 18), harms (item 19) and interpretation (item 22). Furthermore, 25 out of 37 (68%) items/sub-items (including the 19 items already mentioned above) were reported by 50% or more of the studies.

On the contrary, some items were reported only by a small proportion of articles. Ten CONSORT checklist items related with title (item 1a), sample size (item 7a), interim analyses (item 7b), randomization methods (items 8a, 9, 10), blinding (items 11a, 11b) and dates of recruitment (item 14a) were mentioned in less than 50% of the total articles. Five of these items (3b, 7b, 9, 10, 11b) were included in less than 10% of the reports.

Significant differences (p<0.05) between pivotal and non-pivotal trials were observed in reporting of items related with title (item 1a), participants (item 4b), sample size estimation (item 7a), randomization methods (items 8a, 8b, 9 and 10), blinding (items 11a and 11b), dates of recruitment (item 14a); the pivotal trials presented higher compliance. The non-pivotal trials shown significant (p<0.05) higher compliance for items in abstract (item 1b), limitations (item 20) and protocol (item 24).

Table 2: Reporting of CONSORT items according to the type of study (p*<0.01).

Study type	(55-65) (%)	(65-75) (%)	(75-85) (%)	>85 (%)	Total
Pivotal studies	0	1 (5.5)	12 (66.7)	5 (27.3)	18 (100)
Non-pivotal studies	8 (10.8)	49 (66.2)	15 (20.3)	2 (2.7)	32 (100)
Total	8 (8.6)	50 (54.3)	27 (29.3)	7 (7.6)	92 (100)

*P statistic for comparison of reporting of CONSORT items (expressed as percentages in the first line of the table) between pivotal and non-pivotal studies.

Table 3: Reporting of CONSORT items and differences in compliance among articles regarding NOAC treatment.

Item No	Apixaban n=18 (%)	Edoxaban n=12 (%)	Dabigatran n=22 (%)	Rivaroxaban n=31 (%)	Rest NOACs[¥] n=9 (%)	P-value[¶]
1a	1 (5.6)	6 (50)	6 (27.3)	1 (3.2)	5 (55.6)	0.001
1b	17 (94.4)	11 (91.7)	20 (90.9)	31 (100)	8 (88.9)	0.539
2a	18 (100)	12 (100)	21 (95.5)	31 (100)	9 (100)	0.522
2b	18 (100)	12 (100)	22 (100)	31 (100)	9 (100)	-
3a	14 (77.8)	12 (100)	16 (72.7)	30 (96.8)	9 (100)	0.019
3b	N/A	1 (3.3)	3 (13.6)	N/A	N/A	-
4a	17 (94.4)	12 (100)	20 (90.9)	28 (90.3)	9 (100)	0.692
4b	10 (55.6)	3 (25)	12 (54.5)	14 (45.2)	7 (77.8)	0.167
5	18 (100)	12 (100)	22 (100)	31 (100)	9 (100)	-
6a	18 (100)	12 (100)	21 (95.5)	29 (93.5)	9 (100)	0.657
6b	N/A	N/A	N/A	N/A	N/A	-
7a	2 (11.1)	3 (25)	3 (13.6)	5 (16.1)	6 (66.7)	0.008
7b	1 (5.6)	N/A	1 (4.5)	N/A	2 (22.2)	-
8a	5 (27.8)	4 (33.3)	5 (22.7)	3 (9.7)	4 (44.4)	0.169
8b	7 (38.9)	7 (58.3)	3 (13.6)	27 (87.1)	9 (100)	0.001
9	1 (5.6)	0	0	1 (3.2)	3 (33.3)	0.003
10	0	3 (25)	0	2 (6.5)	2 (22.2)	0.024

11a	9 (50)	2 (16.7)	6 (27.3)	8 (25.8)	5 (55.6)	0.162
11b	2 (11.1)	1 (8.3)	2 (9.1)	3 (9.7)	1 (11.1)	0.990
12a	18 (100)	12 (100)	22 (100)	31 (100)	9 (100)	-
12b	18 (100)	12 (100)	22 (100)	31 (100)	9 (100)	-
13a	18 (100)	12 (100)	21 (95.5)	30 (96.8)	9 (100)	0.807
13b	18 (100)	5 (41.7)	22 (100)	30 (96.8)	9 (100)	0.001
14a	5 (27.8)	4 (33.3)	8 (36.4)	9 (29)	5 (55.6)	0.630
14b	N/A	N/A	N/A	N/A	N/A	
15	18 (100)	12 (100)	19 (86.4)	30 (96.8)	1.0 (9)	0.169
16	18 (100)	12 (100)	22 (100)	31 (100)	1.0 (9)	-
17a	18 (100)	12 (100)	22 (100)	31 (100)	1.0 (9)	-
17b	16 (88.9)	12 (100)	22 (100)	31 (100)	1.0 (9)	0.078
18	18 (100)	12 (100)	22 (100)	31 (100)	9 (100)	-
19	18 (100)	12 (100)	12 (54.5)	31 (100)	9 (100)	-
20	16 (88.9)	10 (83.3)	11 (50)	28 (90.3)	7 (77.8)	0.828
21	17 (94.4)	10 (83.3)	11 (50)	31 (100)	9 (100)	0.081
22	18 (100)	12 (100)	12 (54.5)	31 (100)	9 (100)	-
23	12 (57.6)	8 (66.7)	7 (31.8)	16 (51.6)	3 (33.3)	0.411
24	17 (82.6)	10 (83.3)	11 (50)	25 (80.6)	5 (55.6)	0.156
25	18 (100)	12 (100)	12 (54.5)	31 (100)	8 (88.9)	0.054

[¥]NOACs without marketing authorization; [¶]P-value for overall comparison between NOACs; N/A: Non applicable.

Table 4: Reporting of CONSORT items among articles of NOACs with market authorization (p*=0.99).

NOAC	(55-65) (%)	(65-75) (%)	(75-85) (%)	>85 (%)	Total (%)
Apixaban	3 (16.6)	8 (44.4)	6 (33.3)	1 (5.5)	18 (100)
Edoxaban	0	8 (66.7)	4 (33.3)	0	12 (100)
Dabigatran	5 (22.7)	10 (45.4)	6 (27.2)	1 (4.5)	22 (100)
Rivaroxaban	0	21 (67.7)	8 (25.8)	2 (6.4)	31 (100)

*P statistic for comparison of reporting of CONSORT items (expressed as percentages in the first line of the table) among articles of NOACs with market authorization.

Table 5: Reporting of CONSORT items and differences in compliance among articles published in high and low ranked journals according to median impact factor 2015.

Item No	IF≥15 n=47	IF<15 n=45	P-value[¶]
1a	12 (25.5)	7 (15.6)	0.237
1b	47 (100)	40 (88.9)	0.019
2a	47 (100)	44 (97.8)	0.304
2b	47 (100)	45 (100)	-
3a	42 (89.4)	39 (86.7)	0.690
3b	3 (6.4)	1 (2.2)	-
4a	46 (97.9)	40 (88.9)	0.081
4b	27 (57.4)	19 (42.2)	0.144
5	47 (100)	45 (100)	-
6a	47 (100)	42 (93.3)	0.072
6b	N/A	N/A	-
7a	10 (21.3)	9 (20)	0.880
7b	3 (6.4)	1 (2.2)	-
8a	16 (34)	5 (11.1)	0.009
8b	30 (63.8)	23 (51.1)	0.217
9	3 (6.4)	2 (4.4)	0.682
10	5 (10.6)	2 (4.4)	0.263
11a	19 (40.4)	11 (24.4)	0.074
11b	5 (10.6)	4 (8.9)	0.725

12a	47 (100)	45 (100)	-
12b	47 (100)	45 (100)	-
13a	46 (97.9)	44 (97.8)	0.975
13b	43 (91.5)	41 (91.1)	0.950
14a	17 (36.2)	14 (31.1)	0.608
14b	N/A	N/A	-
15	45 (95.7)	43 (95.6)	0.965
16	47 (100)	45 (100)	-
17a	47 (100)	45 (100)	-
17b	46 (97.9)	44 (97.8)	0.975
18	47 (100)	45 (100)	-
19	47 (100)	45 (100)	-
20	41 (87.2)	40 (88.9)	0.807
21	44 (93.6)	41 (91.1)	0.650
22	47 (100)	45 (100)	-
23	31 (66)	22 (48.9)	0.098
24	44 (93.6)	32 (71.1)	0.004
25	46 (97.9)	45 (100)	0.325

Brackets show percentage (%); ¶Articles published in journals with IF≥15 vs articles published in journals with IF<15 N/A: Non applicable.

Table 6: Reporting of CONSORT items among articles published in high and low ranked Journals **(P*<0.002)**.

IF	(55-65) (%)	(65- 75) (%)	(75-85) (%)	>85 (%)	Total (%)
IF≥15	3 (6.3)	22 (46.8)	16 (34)	6 (12.7)	47 (100)
IF<15	5 (11.1)	27 (60)	11 (24.4)	1 (2.2)	45 (100)
Total	8 (8.6)	50 (54.3)	27 (29.3)	7 (7.6)	92 (100)

Brackets show percentage (%); IF: Impact Factor; *P statistic for comparison of reporting of CONSORT items (expressed as percentages) among articles published in high and low ranked journals.

The majority of pivotal studies (94%) complied with >75% of the items, while about half of non-pivotal studies (53%) had similar compliance (p<0.01) (Table 2). In comparing the different NOACs, significant differences (p<0.05) were detected in eight reporting of items: Title (item 1a), trial design (item 3a), sample size (item 7a), sequence generation (item 8b), allocation concealment mechanism (item 9), implementation (item 10), participant flow (item 13b) and funding (item 25); the NOACs without marketing authorization presented a better compliance (Table 3). The four groups of NOAC articles with marketing authorization were not associated with the different levels of compliance (p=0.99) (Table 4).

Half of the articles (n=47, 5%) were published in journals considered as high-ranked. Significant differences (p<0.05) between high-ranked vs. low-ranked journals were detected in three items (Table 5): 1b-structured summary of trial design, methods, results, and conclusions and, 8a-method used to generate the random allocation sequence and 24-protocol. The IF was associated with the different levels of compliance (p<0.05) (Table 6).

In high-ranked journals, almost half of the articles (n=18, 46.7%) complied with more than 75% of the items. Only, 27% (n=13) of articles published in low-ranked journals reported more than 75% of the items.

DISCUSSION

The present study investigated the reporting quality of RCTs that compare the efficacy and safety of NOACs vs. warfarin in patients with AF based on the CONSORT statement. Almost all evaluated trials (92%) have been published in peer reviewed journals that have endorsed the CONSORT statement; these trials have been conducted and reported by cooperating groups of scientists, anticipating a high reporting quality. Indeed, 94% of the pivotal studies complied with >75% of CONSORT items. Also, there was not significant difference in reporting quality among the four NOACs with marketing authorization (apixaban, dabigatran, edoxaban, rivaroxaban). On the other hand, significant difference was spotted between articles published in high–ranked and lower-ranked journals. This can be easily explained since high-ranked journals demand the good compliance to CONSORT items in order to publish an RCT.

Although the actual quality of trial design and implementation is not necessarily correlated with the reporting quality, the reporting quality may be used as a

surrogate of the actual quality. However, it is possible that a trial with a biased design may be considered of high quality when it is well reported; whereas, a well-designed trial with poor reporting quality may be neglected. In addition, a poorly reported RCT could be misleading; though, it was designed and executed appropriately.[7,11,27]

In the area of cardiovascular diseases, very few evaluations of reporting quality based on the CONSORT statement exist. In a systematic review regarding the reporting quality of 33 RCTs in heart failure with preserved ejection fraction,[28] a low quality was shown and a significant correlation between CONSORT score and journals' impact factor was found. In another study for hypertension again the reporting quality of articles in harms was poor.[27]

This study indicates that pivotal RCTs complied with a satisfactory percentage of CONSORT items. Thus, the information provided in methods and results of the articles may allow the physicians to evaluate better the efficacy and safety of the NOACs in patients with AF and direct them in treating their patients appropriately. The findings of the present study, in conjunction with the results of three relevant meta-analyses, may lead to the conclusion that the NOACs could be administered efficiently and with safety to AF patients with specific characteristics.[29-31] However, significant efforts should be made by authors and journals, for a further enhancement of compliance with the CONSORT items, allowing the physicians to have a more clear and precise picture of all aspects (study design, methodology, analysis) of RCTs. Also, the accurate assessment of RCTs' quality may assist in deriving unbiased estimates of the treatments' effect which will be useful in every day patients' care.

The present study has some limitations: the research has been restricted in PubMed, which is the most common used database in medicine and did not extent to other databases. In addition, only articles published in English were considered, which may lead to language bias. However, this risk is limited since only 8.6% of the articles, captured by our search strategy, were published in other languages. In the analysis, only the reported material in the articles of the non-pivotal trials was evaluated. In particular, when an article is using just a reference for describing the methods and results, then the relevant items were considered as non-reported. This might be the reason for the poor reporting quality of the non-pivotal trials. The revised CONSORT 2010 checklist was applied to all trials, despite some were published before its introduction. The analysis included phase III and II RCTs and non-pivotal trials which may lead to heterogeneity in the data. However, this could be also a strength, since the adherence to CONSORT statement was investigated in a wide spectrum of studies. Lastly, the evaluation process was independently performed by two reviewers and a substantial degree of agreement for most items was achieved, lending internal validity to our results.

In conclusion, this study indicated the high quality of reporting of pivotal RCTs that examined the efficacy and safety of NOACs vs. warfarin in AF patients. However, the compliance of the non-pivotal trials is considered inadequate and more efforts should be made in order to increase their reporting quality. In addition, it has been shown that RCTs published in high-ranked journals adhered significantly higher to CONSORT than those published in lower-ranked ones. Furthermore, NOACs showed similar pattern in reporting quality. Finally, trials investigating the efficacy and safety of the NOACs vs warfarin found to be well reported; thus, it might be assumed that they were appropriately designed and conducted and so, their results could be generalized in clinical practice.

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