ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«Μεθοδολογία Βιοϊατρικής Έρευνας,

Βιοστατιστική και Κλινική Βιοπληροφορική»

"Assess the reporting quality of randomized controlled trials exploring the efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation, based on CONSORT statement"

ΕΥΓΕΝΙΑ Δ. ΚΑΡΑΚΟΥ

ΧΗΜΙΚΟΣ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Επιβλέπων: Καθηγητής Ζιντζαράς Ηλίας

ΛΑΡΙΣΑ 2015

Τριμελής επιτροπή

1. Καθηγητής Ζιντζαράς Ηλίας (επιβλέπων)
2. Καθηγητής Στεφανίδης Ιωάννης
3. Καθηγητής Χατζηχριστοδούλου Χρήστος

Αφιερώνεται

στους γονείς μου

Contents

Abstract

Background: Randomized controlled trials (RCTs) are the 'gold standard' for assessing new interventions. The CONSORT statement designed to improve the quality of reporting RCTs. The novel oral anticoagulants (NOACs) appear to be a good alternative to traditional anticoagulation with warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation (AF). Despite the rapid increase in research in NOACs, little is known about the reporting quality of RCTs exploring the efficacy and safety of the NOACs versus warfarin in patients with AF.

Aim: We utilized the CONSORT 2010 statement to assess the reporting quality of published RCTs comparing the efficacy and safety of the NOACs versus warfarin in patients with AF.

Methods: A systematic literature search was performed for publications of RCTs comparing NOACs to warfarin in patients with AF. Papers were scored against the 25 items in the CONSORT 2010 checklist.

Results: Five articles were identified. The total quality scores on the CONSORT 2010 checklist ranged between 67.6% and 78.4%, with a mean score of 72.5%.

Conclusion: The overall reporting quality of published RCTs in this field was satisfactory. The adoption of the CONSORT statement seems to improve the quality of both the conduct and reporting of trials.

Introduction

The assessment of new drugs and treatments is extremely important to the clinician in the selection of best therapy.

Randomized controlled trials (RCTs), as the 'gold standard' of evidence based clinical practice, are generally considered to have the highest level of credibility in determining the efficacy of a new treatment.

Well-designed and properly conducted randomized controlled trials (RCTs) provide the most reliable evidence in health interventions. This, in turn, leads to improvement in the prevention or treatment of disease (1).

Many RCTs have been conducted with adequate methodological rigor to advance scientific knowledge. The ability to evaluate and disseminate this knowledge directly rests on the transparent and thorough reporting of trial methodology and findings.

In most cases the RCT report is the only source for clinicians, guideline developers, and other researchers to judge the validity and generalisability of the results, so the quality of reporting of trials is of inherent interest.

The lack of adequate reporting influences readers' interpretation of the evidence and makes it more difficult to replicate the results for future research and follow recommended treatment options (2, 3).

To alleviate this problem, guidelines have been created to assist researchers, peer reviewers, and journal editors in complete reporting of RCTs.

The Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org) is a minimum set of evidence-based recommendations designed to improve the quality of reporting RCTs. It was initially published in 1996 (4), then revised twice subsequently in 2001 and 2010 (5, 6).

The revisions were each accompanied by a detailed explanation and elaboration document for the purpose of enhancing the use, understanding, and dissemination of the statement (7, 8).

The CONSORT provides structured guidance to help researchers prepare reports of trial findings, facilitate complete and transparent reporting, and aid in critical appraisal and interpretation. The most current version of the statement includes a 25-item checklist (Picture 1, 2) and a flow diagram (Figure 2). The checklist provides standardized approaches to report the trial design, analysis, and interpretation, and the diagram gives instructions to display the progress of all participants throughout the trial.

Some journals require that manuscripts reporting the results of RCTs include the CONSORT flow diagram (Figure 2) showing the progress of patients throughout the trial, and that the CONSORT checklist (Picture 1, 2) also be completed and submitted with the manuscript. The Journal of the American Medical Association (JAMA), the Lancet and Annals of Internal Medicine all endorse the CONSORT statement. Even in those journals that require CONSORT compliance reporting on submitted trials, the published RCTs are not always 100% CONSORT-compliant.

Since the initial publication, the quality of clinical trial reporting has improved over the years in general (9, 10) and in many medical specialties (11-13). However, the

quality of reporting is far from satisfactory, and incompleteness and inaccurate reporting of trial results compounded with poor methodological rigor remain a serious concern (the authors may have used the correct methodology, but may not have explicitly reported all of the methodology used) (10, 14-16).

A number of publications have studied the quality of reports of RCTs in subspecialties of medicine (17-22).

Cardiology is a specialty in which a large volume of research is conducted annually.

Systematic evaluation on the reporting quality of RCTs exploring the efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation, based on the adherence to the CONSORT statement, has never been reported before.

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with increased morbidity and mortality. Patients with AF sustain an increased risk of arterial thromboembolism and stroke. Therefore, antithrombotic strategies using anticoagulant drugs and antiplatelet agents are recommended for patients with AF presenting with risk factors for stroke. Antithrombotic therapy is also associated with a risk of bleeding; therefore, the beneficial effects on stroke prevention should always be compared against a patient's risk of major bleeding.

Existing guidelines recommend anticoagulant therapy for patients at intermediate or high risk of stroke (23). Although standard adjusted dose vitamin K antagonist (VKA) (eg. warfarin) (24, 25) has been the cornerstone treatment (until 2009, warfarin and other vitamin K antagonists were the only class of oral anticoagulants available) for reducing the risk of stroke or systemic embolism (SE) in this population, it is associated with several drawbacks (narrow therapeutic range, drug and food interactions, regular monitoring, and risk of bleeding) which have prompted the development of novel (newer) oral anticoagulants (NOACs) such as direct thrombin

[Dabigatran (Pradaxa)] and factor Xa [eg. Apixaban (Eliquis), Edoxaban (Lixiana, Savaysa), Rivaroxaban (Xarelto)] inhibitors (Figure 1). Dabigatran etexilate is a prodrug that is rapidly converted to the active direct thrombin inhibitor dabigatran.

The novel oral anticoagulants (NOACs) appear to be a good alternative to traditional anticoagulation with vitamin K antagonists (VKAs). They have better oral bioavailability with less food and drug interactions. They do not require frequent INR monitoring and seem to be well tolerated in the long-term use.

Individually, the NOACs are at least as safe and effective as warfarin for prevention of stroke and systemic embolism in patients with AF (26-30).

The **aim** of this study was to assess the reporting quality of randomized controlled trials (RCTs) exploring the efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation, based on CONSORT statement.

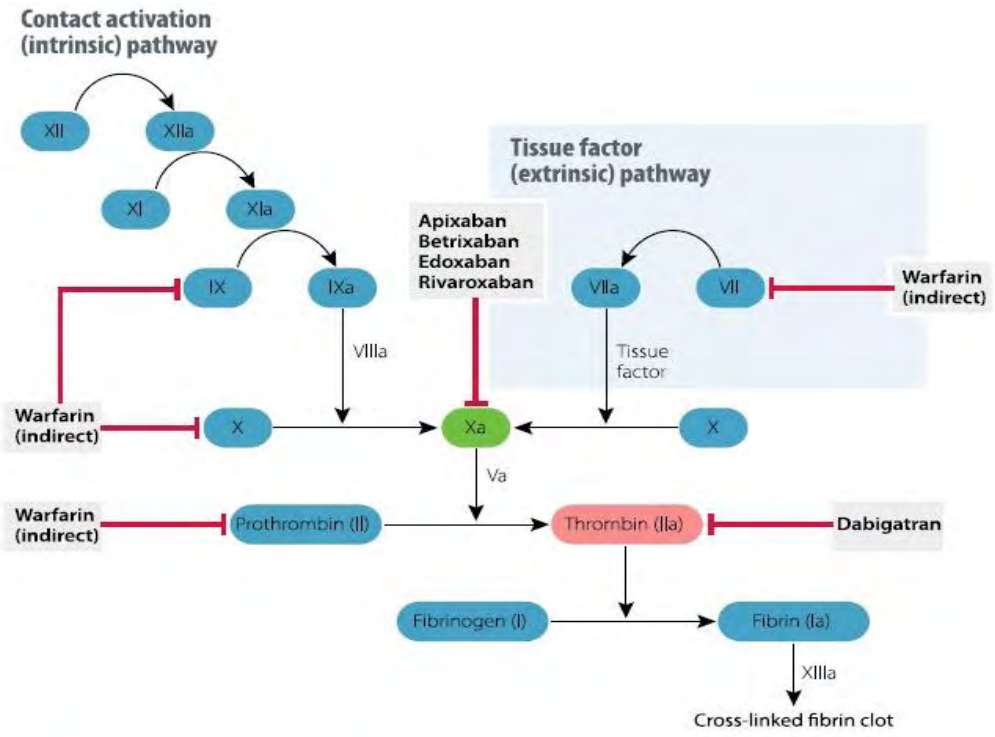


Figure 1. Nonvalvular atrial fibrillation.

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

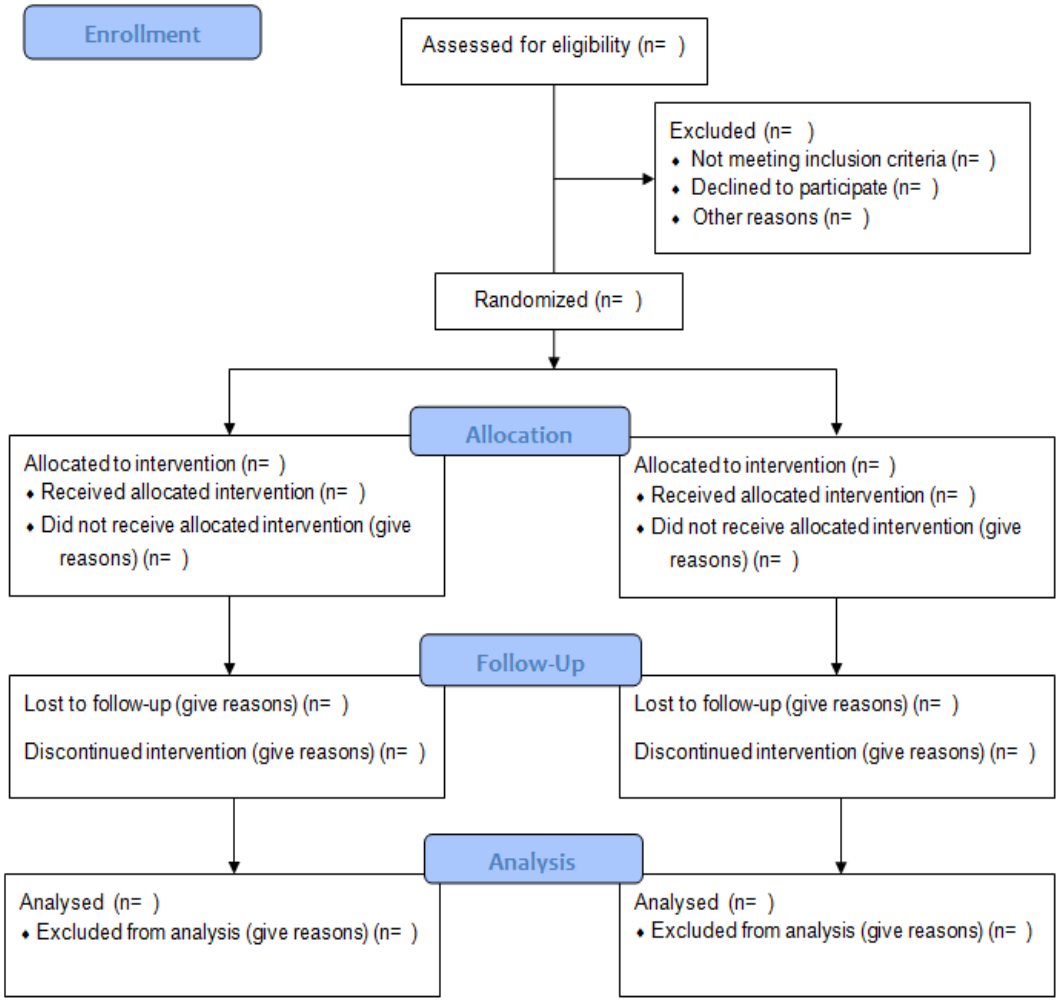
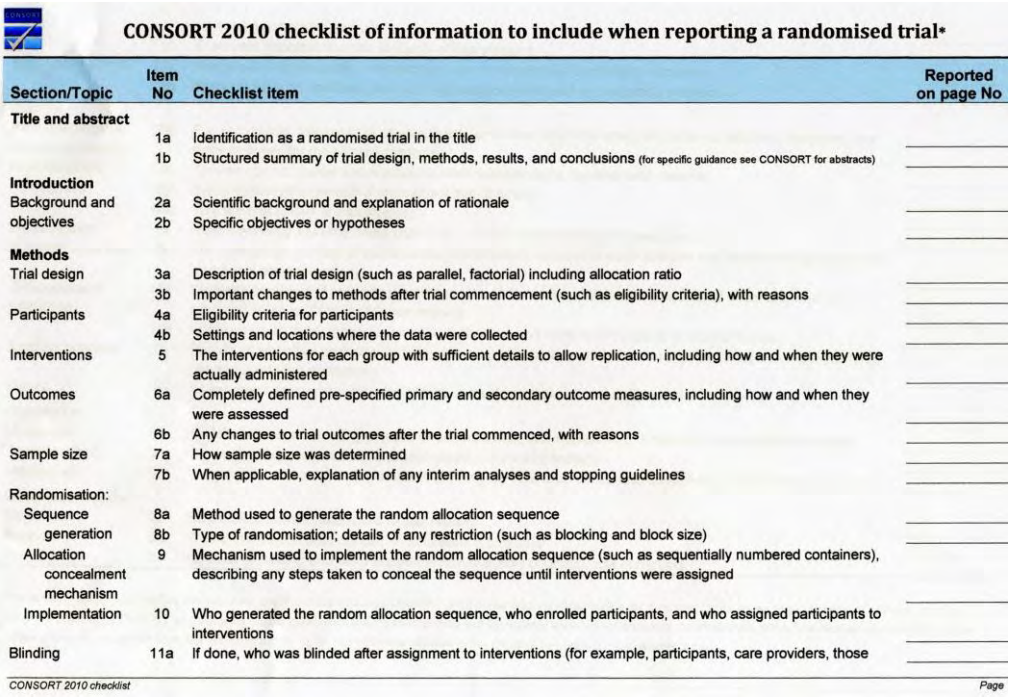


Figure 2. Flow diagram of the progress through the phases of a parallel randomised trial of two groups (enrolment, intervention allocation, follow-up, and data analysis) (http://www.consort-statement.org)

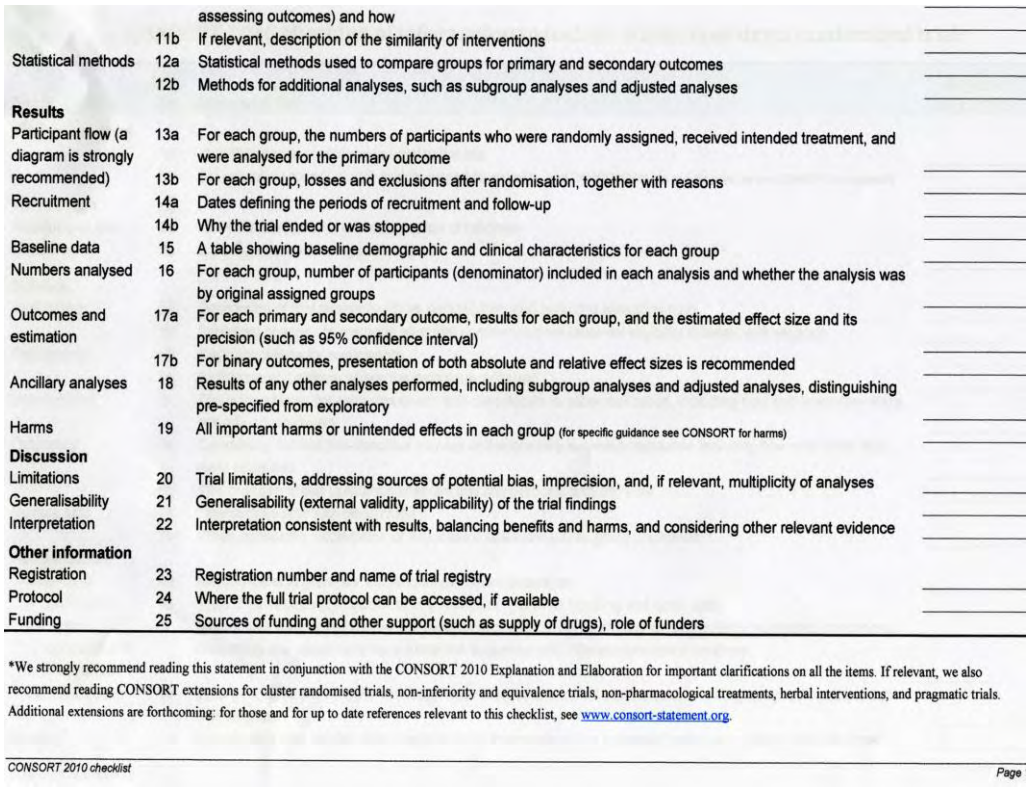


CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

CONSORT 2010 checklist Page

Picture 1. CONSORT 2010 checklist



		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSORT 2010 checklist Page

Picture 2. CONSORT 2010 checklist (continued)

Methods

Study Selection

We systematically searched the publications of RCTs comparing new oral anticoagulants (NOACs) to warfarin in patients with AF.

A systematic literature search of MEDLINE (PubMed) and Cochrane databases from inception to July 2015 was performed.

The following were used as medical subject heading terms and/or keywords: “atrial fibrillation”, “warfarin”, “dabigatran”, “rivaroxaban”, “apixaban”, “edoxaban”.

Reference lists of all studies included in the present systematic review, were screened for potential additional eligible studies.

Studies were included if they met the following selection criteria: (1) they were phase III randomized controlled trials (RCTs) between NOACs and warfarin, (2) all the patients were randomized to warfarin (comparator) or to non-vitamin K antagonist oral anticoagulants (NOACs) (in our present study, we defined apixaban, dabigatran, edoxaban and rivaroxaban as NOACs), (3) the population of interest was patients with atrial fibrillation (AF), irrespective of cause (adults aged 18 years and older with nonvalvular AF-no criteria were enforced for gender), (4) to assess the long-term efficacy and safety of these agents, only RCTs with follow-up duration at least 1 year were included, (5) they were published in English language, (6) studies performed in humans. Except blinded, the open-label studies were also included because of the need of frequent INR monitoring for warfarin. For all the included studies, the primary efficacy endpoint was composite of stroke and systemic embolism. The secondary efficacy endpoints included ischemic stroke, hemorrhagic stroke, all-cause mortality, and myocardial infraction. For safety evaluation, the main endpoint was

major bleeding defined as fatal bleeding or bleeding in a critical site, and the secondary endpoint included gastrointestinal and intracranial bleeding. We only considered the studies approved or in development, so the studies for ximelagatran, which had been withdrawn (because of hepatoxicity) (31) and studies for darexaban, which is no longer in development (32) were excluded from our analysis.

Conference abstracts and presentations were also excluded, because their results may not be final and such publications undergo more limited peer review.

Data Extraction and Reporting Assessment Tool

As assessment tool for quality of reporting of randomized controlled trials (RCTs), we used the CONSORT checklist, revised in 2010, which includes a 25-item questionnaire (http://www.consort-statement.org). Papers were scored against the 25 items in the 2010 CONSORT statement (each item was given an equal weighting).

Each item was subdivided as outlined in the CONSORT statement: 12 items were divided into a and b parts giving a total of 37 points scored per paper. Hence, based on CONSORT reporting items, we developed a 37-items data extraction sheet (Table 2). We reviewed each article and determined whether the RCT paper reported on each of the 37 items of the revised CONSORT statement.

All items were investigated in terms of whether they were reported, not whether they were actually carried out during the trial. Each item was characterised as ‘yes’ if it was clearly and adequately reported in the trial or ‘no’ if it was partially reported, unclear, or not reported at all.

Each ‘yes’ answer received a score of 1 and each ‘no’ answer was scored as 0.

We conducted a descriptive statistical analysis of all evaluated articles. Data were analyzed using Microsoft Excel 2007 and SPSS software (version 19.0).

In order to assess adherence to CONSORT checklist items, we calculated the number and proportion of trial articles that clearly and adequately reported each of the 37 CONSORT items (proportion of each item = the number of articles that reported the item /total articles-for example, if 3 of 5 RCTs reported item 8a on the checklist, that item would score an overall compliance score of 60%) (Table 2) (Figure 4).

Although all items in the CONSORT checklist are considered important as to improve the quality of reports of RCTs, emphasis was placed on reporting of methodological items which are more specific to assess the methodological quality of RCTs, that is sample size, randomization (sequence generation, allocation concealment, implementation), blinding, performed statistical methods, description of baseline data, precision of estimated effect size and reporting of ITT analysis.

Explaining more specifically some methodological CONSORT criteria: i) randomization is the method used to generate the random allocation sequence, including details of any restriction (e.g. blocking, stratification) ii) allocation concealment is the method used to implement the random allocation sequence (e.g. numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned and iii) implementation of randomization answers the question of who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.

The number and percentage of articles reporting each applicable section on the CONSORT checklist was also calculated (proportion of each section =the sum of items percentage of each section/total items of each section) (Table 4).

The total quality of reporting score (the CONSORT score) of each trial article was calculated as a proportion of the ‘yes’ rated applicable items on the CONSORT checklist (possible range 0-37 points) (CONSORT score of each article = the number

of reported items/37 items-for example, a RCT reporting 20 of the 37 items on the checklist would score 54.1%) (Table 3), which was used to inform a global assessment of the quality of reporting.

Results

Our literature search identified a total of 917 articles.

After removing duplicates, we screened titles and abstracts and the full text of 68 publications was retrieved and evaluated for eligibility. Five trials (RE-LY, ARISTOTLE, ENGAGE AF-TIMI 48, ROCKET AF, J-ROCKET AF) that met our inclusion criteria were identified and included in the present study (Figure 3).

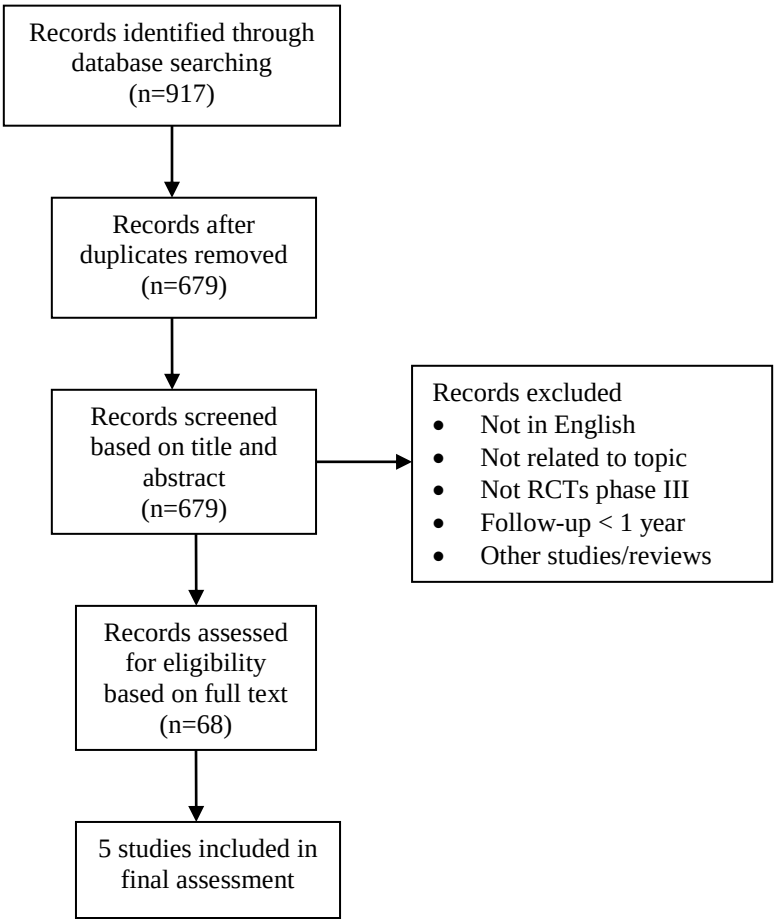


Figure 3. Flow chart of study selection process

The number of trials examining each drug were: one for apixaban (ARISTOTLE) (28), one for edoxaban (ENGAGE AF-TIMI 48) (29), one for dabigatran (RE-LY) (26) and two for rivaroxaban (ROCKET AF, J-ROCKET AF) (27, 30).

The 5 included randomized clinical trials assessed the relative efficacy and safety of a new oral anticoagulant, apixaban, dabigatran, rivaroxaban or edoxaban, compared to warfarin in patients with atrial fibrillation (AF).

They were each designed to determine if the study drug was noninferior to warfarin with respect to the composite end point of all stroke and systemic embolism.

These randomized clinical trials have a number of similar conclusions.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) was a randomized trial designed to compare two fixed doses of dabigatran, each administered in a blinded manner, with open-label use of warfarin [target international normalized ratio (INR), 2.0 to 3.0] in patients who had AF and were at increased risk for stroke (26). In this noninferiority trial, 18,113 patients were randomized. The median duration of the follow-up period was 2.0 years.

In conclusion, in patients with atrial fibrillation, dabigatran given at a dose of 110 mg twice daily was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg twice daily, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

In ARISTOTLE, 18,201 patients with nonvalvular AF were randomized to either apixaban 5 mg twice daily or to warfarin (28).

In conclusion, in patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

ROCKET AF compared a 20 mg/day dose of rivaroxaban to warfarin in 14,264 patients with nonvalvular AF (27).

In conclusion, in patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding.

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) was a randomized trial designed to compare two once-daily regimens of edoxaban with warfarin in 21,105 patients with moderate-to-high-risk AF (29).

In conclusion, both once-daily regimens of edoxaban were noninferior to warfarin for the prevention of stroke or systemic embolism.

J-ROCKET AF trial, compared the safety of a Japan-specific rivaroxaban dose with warfarin administered according to Japanese guidelines in Japanese patients with AF (30).

The main characteristics of the included trials are summarized in Table 1.

Reporting quality assessment of included trials was conducted using the CONSORT statement.

Table 2 shows the adherence of the selected RCTs to the CONSORT statement.

Table 1. Main characteristics of included randomized clinical trials

Trial	NOAC	Intervention	Patients	Follow-up period (median)	Trial design-double blind	CHADS2* score (mean)
RE-LY (26)	Dabigatran	Warfarin/ Dabigatran 150 mg Dabigatran 110 mg	18,113	2.0 years	No	2.1
ROCKET AF (27)	Rivaroxaban	Warfarin/ Rivaroxaban 20 mg	14,264	1.9 years	Yes	3.48
ARISTOTLE (28)	Apixaban	Warfarin/ Apixaban 5 mg	18,201	1.8 years	Yes	2.1
ENGAGE AF-TIMI 48 (29)	Edoxaban	Warfarin/Edoxaban 60 mg Edoxaban 30 mg	21,105	2.8 years	Yes	2.8
J-ROCKET AF (30)	Rivaroxaban	Warfarin/ Rivaroxaban 15 mg	1,280	1.3 years (mean)	Yes	3.27

* The CHADS2 score, an index of the risk of stroke in patients with atrial fibrillation, ranges from 1 to 6, with higher scores indicating a greater risk of stroke

Table 2. Reporting quality of 5 RCTs based on CONSORT 2010				
Section/Topic		**Item Number**	**Item description**	**Adherence [n (%)]**
Title and abstract		1a	Identification as a randomised trial in the title	0
		1b	Structured summary of trial design, methods, results, and conclusions	5 (100)
Introduction	Background and objectives	2a	Scientific background and explanation of rationale	5 (100)
		2b	Specific objectives or hypotheses	5 (100)
Methods	Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5 (100)
		3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	2 (40)
	Participants	4a	Eligibility criteria for participants	5 (100)
		4b	Settings and locations where the data were collected	2 (40)

	Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5 (100)
	Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5 (100)
		6b	Any changes to trial outcomes after the trial commenced, with reasons	0
	Sample size	7a	How sample size was determined	4 (80)
		7b	When applicable, explanation of any interim analyses and stopping guidelines	2 (40)
	Randomisation: Sequence	8a	Method used to generate the random allocation sequence	3 (60)
		8b	Type of randomisation; details of any restriction (such as	2 (40)

	generation		blocking and block size)	
	Randomisation: Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	0
	Randomisation: Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	0
	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5 (100)
		11b	If relevant, description of the similarity of interventions	4 (80)
	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5 (100)

		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	4 (80)
Results	Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	4 (80)
		13b	For each group, losses and exclusions after randomisation, together with reasons	5 (100)
	Recruitment	14a	Dates defining the periods of recruitment and follow-up	5 (100)
		14b	Why the trial ended or was stopped	0
	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5 (100)
	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	5 (100)

	Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	5 (100)
		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	0
	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	5 (100)
	Harms	19	All important harms or unintended effects in each group	5 (100)
Discussion	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	4 (80)
	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	5 (100)
	Interpretation	22	Interpretation consistent with results, balancing benefits	5 (100)

			and harms, and considering other relevant evidence	
Other information	Registration	23	Registration number and name of trial registry	5 (100)
	Protocol	24	Where the full trial protocol can be accessed, if available	3 (60)
	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	5 (100)

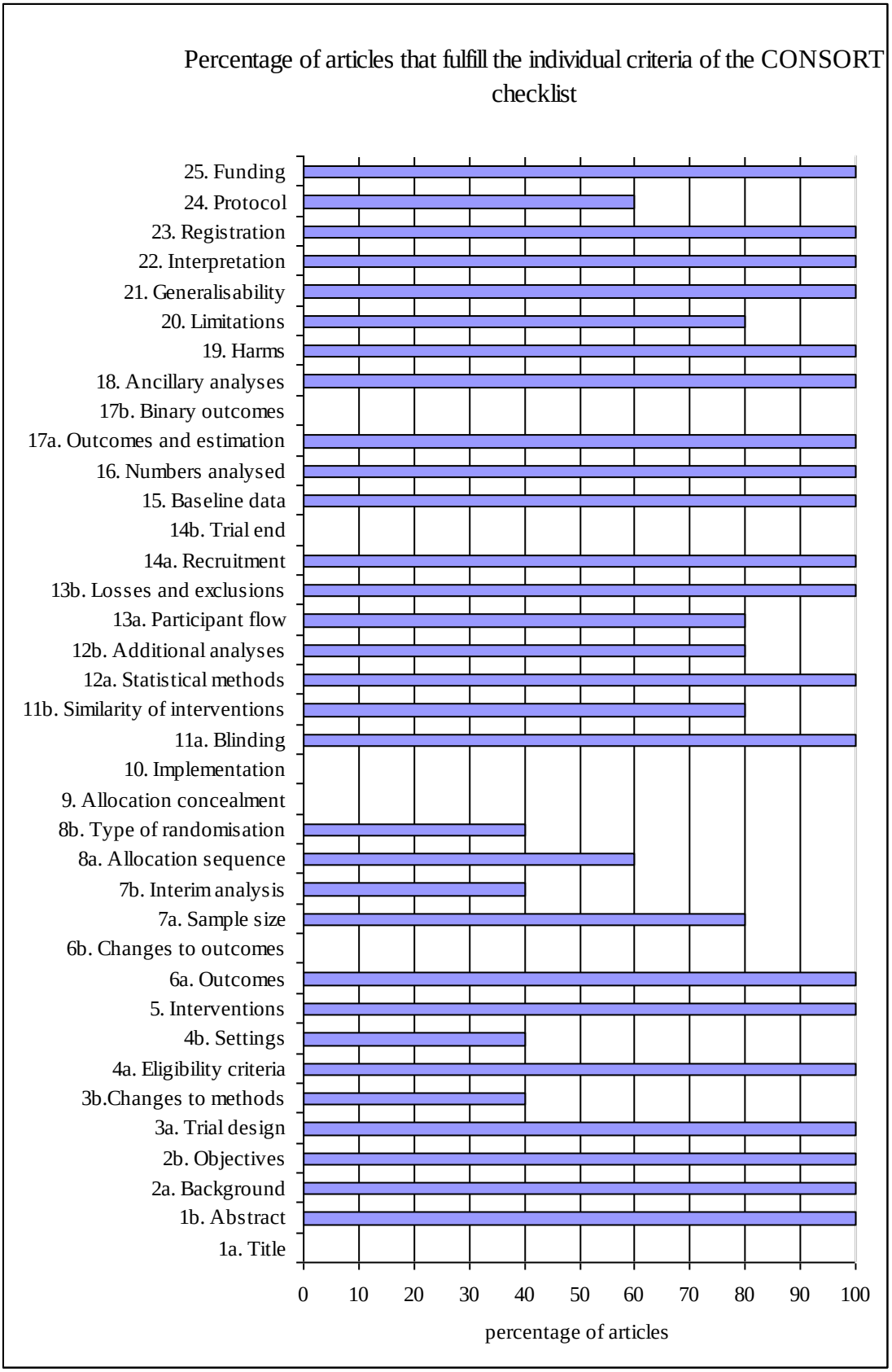


Figure 4. Percentage of articles that fulfill the individual criteria of the CONSORT checklist

The articles report on most of the items on the CONSORT 2010 statement, but none of the articles reported all 37 items (no paper scored fully on all items of the CONSORT 2010 guidelines). The total scores on the CONSORT 2010 checklist ranged from 25 to 29, with a mean score 26.8±1.79 of 37 items (the total scores on the CONSORT 2010 checklist ranged between 67.6% and 78.4%, with a mean score of 72.5% and standard deviation of 4.83%) (Table 3).

Consequently, the average adherence of the selected RCTs articles to the CONSORT statement was 72.5%.

Some methodological items from the checklist, including "randomization" (sequence generation), were poorly described, while we assessed most other items as adequately reported. Of all methodological items of the CONSORT statement, allocation concealment mechanism and randomization implementation were omitted in the selected studies.

Specifically, the following findings are summarized in Table 2:

None of all trial reports stated in the title of the report that the trial was randomized.

For the item relating to abstract content there was a high level of compliance (100%).

All RCTs reports introduced a scientific background and an explanation of rationale.

All articles reported hypothesis and objectives

Description of the trial design was reported by all the included studies.

Two trial reports mentioned important changes to methods after trial commencement.

All studies (100%) reported adequate information regarding the eligibility criteria for study participants.

Forty percent (2/5) of all trial reports provided the locations of the trial data collection.

There was 100% reporting of the details of the intended intervention in each group.

All trial reports (5/5) defined the primary and secondary outcome measures.

None of the trials reported any changes to trial outcomes after the trial commenced.

80% of trial papers (4/5) stated that an estimation of sample size had been done.

Two studies reported that interim analyses had been applied.

The method used to generate the random allocation sequence in the RCTs was reported from three papers (60%): Randomization was performed with the use of a central, 24-hour, computerized, automated voice-response system (ROCKET AF); Randomization was performed with the use of a central, 24-hour, interactive, computerized response system (ENGAGE-TIMI 48); all trial participants were randomly assigned to receive one of two doses of dabigatran, or to receive warfarin, by means of a central, interactive, automated telephone system (RE-LY).

Only two studies (40%) reported the type of randomization.

While all of these studies were reported as RCTs, none of the articles described the allocation concealment mechanism and the personnel who implemented the randomization process, i.e. none of the trial reports provided information on who generated the random allocation sequence, administered the intervention and/or assigned the intervention groups.

All articles reported whether there was any blinding.

In addition to reporting who was blinded, 80% (4/5) of the trial reports provided information on how blinding was achieved.

All RCTs articles reported statistical methods.

Four studies (80%) reported the methods for additional analyses (such as subgroup analyses and adjusted analyses).

A participant flow diagram through each stage of the study was given in 80% (4/5) of the trial reports.

All trial reports provided information on any loss and exclusion after randomization, for each study group.

All trial reports (5/5) supported information on the time of the recruitment period and the follow-up period.

All trial reports used a table to show baseline demographic and clinical characteristics for each group.

All trial reports (100%) stated any information about "intention-to-treat" analysis.

All trial reports (100%) stated the estimates of the precision of estimated effect size (i.e. presentation of 95% confidence intervals).

All trial articles included reporting of the use of ancillary analyses.

All trial reports mentioned adverse or unintended effects in each group.

Four trial reports analyzed the trial limitations and all balanced the benefits and harms of the results.

Generalizability of the trial findings, was reported by 100% of the included trials.

Registration numbers or names of trial registries were reported by all studies.

(The first U.S. federal law requiring trial registration was established in 1997 and the registry of ClinicalTrials.gov was released by the National Institutes of Health in 2000).

Of all articles reviewed, 60% (3/5) reported where the full trial protocol could be accessed.

The details of the funding sources were provided in all trial reports (all the trials were fully funded by industry).

Table 3 presents an overall quality score for each trial as a global assessment of the quality of reporting.

Table 3. The total scores on the CONSORT 2010 checklist by year of publication and study name

Study name	Journal name	Publication year	CONSORT 2010 statement score[*] [$]
RE-LY	The New England Journal of Medicine (NEJM.org)	2009	25 (67.6%)
ROCKET AF	The New England Journal of Medicine	2011	27 (73.0%)
ARISTOTLE	The New England Journal of Medicine	2011	28 (75.7%)
J-ROCKET AF	Circulation Journal	2012	25 (67.6%)
ENGAGE AF-TIMI 48	The New England Journal of Medicine	2013	29 (78.4%)

[*] The score for each article was calculated as the total points scored for this article divided by the number of applicable items. For example, the RE-LY trial article, that fulfilled 25 items from the CONSORT 2010 checklist out of applicable 37 items, received a score of 67.6%.

[$] The higher the percentage, the more adequately authors reported their trial.

These articles were published in the post-CONSORT period, after 1996 and were retrieved from the journals:

The New England Journal of Medicine (impact factor: 55.873) and the Circulation Journal (impact factor: 14.430) which require the CONSORT checklist and flow diagram to accompany any reports of RCTs-have endorsed the CONSORT statement.

Table 4 summarizes the average reporting percentage for each section of the CONSORT checklist of the included trials. The reporting percentage for the 'title and abstract' section was 50%, for the 'introduction' section 100%, for the 'methods' section 62%, for the 'results' section 78%, for the 'discussion' section 94% and for the 'other information' section 86%.

Table 4. The average reporting percentage for each section of the CONSORT checklist of the included trials

Section	**Number (n)***	**Percentage (%)*$**
Title and abstract	2.5	50
Introduction	5.0	100
Methods	3.1	62
Results	3.9	78
Discussion	4.7	94
Other information	4.3	86

* The number and percentage of articles reporting each applicable section on the CONSORT checklist

$ percentage of each section = the sum of items percentage of each section/total items of each section

Conclusions

The researchers have the most thorough understanding of the trial, so it is important for them to give a complete description of the trial process and a deep analysis of outcomes.

A well-designed and well-reported RCT should meet all of the criteria of the CONSORT statement. With adequate reporting, readers will understand what was actually done, rather than assume what was done.

The CONSORT items do not actually assess the quality of the methodology of an RCT, but rather assess the reporting of key items that are crucial in determining the validity and quality of the RCT. The CONSORT checklist was developed as a guideline, not as an actual scale for assessing methodology of an RCT.

In the present study, we assessed the quality of reporting of randomized controlled trials that compared the efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation. The results showed that the overall reporting quality of published RCTs was moderate to high.

These articles reported satisfactorily on many important items (i.e. outcome measures, participant criteria, participant flow, sample size calculation, intention-to-treat analysis and precision of measurement), making it easy for any reader to determine the quality and validity of results without needing to make various assumptions.

Compliance was poorest for items relating to randomization: although the studies had a high score failed to report on the implementation of randomization and allocation concealment mechanism.

Good randomization protocols aim to produce treatment groups that are comparable and have an equal distribution of both known and unknown confounders. Achieving patient randomization suitable for a clinical trial is a complex issue. The fact that all

items relating to the reporting of randomization (items 8a, 8b, 9, and 10) were poorly adhered to, highlights the need for further education regarding this aspect of trial description.

There is no evidence that the failure to mention methodological details equates to the lack of methodological knowledge or skills: a method of a trial that is not reported does not mean actually that it has not been performed. The reporting of methodological aspects of RCTs does not necessarily reflect the conduct of the trial.

The responsibility for reporting lies not only with the authors.

Peer reviewers and editors are at fault for not insisting on complete description of the studies as dictated by the CONSORT statement.

The findings of the present study suggest that many investigators engaging in RCTs in Cardiology are familiar with the CONSORT statement and understand of how to properly design and execute an RCT.

The study showed that journals such as the New England Journal of Medicine and the Circulation Journal, that have adopted the CONSORT checklist, have improved levels of compliance in their trial reports. There is good evidence in the literature that the adoption of CONSORT statement improves the quality of both the conduct and reporting of trials in journals that have taken the decision to make it a requirement for submission acceptance.

Although all papers scored highly, a maximum score of 29 (78.4%) was achieved, no papers successfully met all criteria laid out in the 2010 CONSORT statement. This suggests that there is still room for improvement when publishing trials in cardiology. Trial groups, authors, journals, and funding bodies should work collaboratively to improve the quality of trial reporting.

Journal editors, reviewers and authors should be encouraged to adhere to the CONSORT statement when reporting on RCTs and/or reviewing the reports of RCTs, in order to ensure high-quality trials.

Researchers also need to design research with full understanding of the CONSORT reporting guidelines and full consideration of items whose reporting quality is low.

In conclusion, the reporting of randomized controlled trials that compared the efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation in the last decade has been more than adequate, and better in general than in many other fields. It seems that funding agencies, investigators, and journals have developed a cohesive strategy to implement the reporting standards laid down in the 2010 CONSORT statement.

During a period of rapid transition in the healthcare delivery system and especially during a period of new pharmaceutical and genetic discoveries, higher quality reports are likely to improve RCT interpretation, minimize biased conclusions, and ultimately facilitate decision-making about treatment effectiveness.

The knowledge gained from this study should be viewed as an opportunity for improved adherence and increased awareness of the CONSORT statement.

References

1. Altman DG, Moher D, Schulz KF. Improving the reporting of randomised trials: the CONSORT statement and beyond. Stat Med 2012;31:2985-97.
2. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Obstet Gynecol 2009;114:1341-5.
3. Laine C, Goodman SN, Griswold ME, Sox HC. Reproducible research: moving toward research the public can really trust. Ann Intern Med 2007;146:450-3.
4. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. the CONSORT statement. JAMA 1996;276:637-9.
5. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001;357:1191-4.
6. Schulz KF, Altman DG, Moher D CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Med 2010;8:18.
7. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. Ann Intern Med 2001;134:663-94.
8. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869.
9. Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. Lancet 2005;365:1159-62.
10. Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. BMJ 2010;340:c723.
11. Ladd BO, McCrady BS, Manuel JK, Campbell W. Improving the quality of reporting alcohol outcome studies: effects of the CONSORT statement. Addict Behav 2010;35:660-6.
12. Areia M, Soares M, Dinis-Ribeiro M. Quality reporting of endoscopic diagnostic studies in gastrointestinal journals: where do we stand on the use of the STARD and CONSORT statements? Endoscopy 2010;42:138-47.

13. Ziogas DC, Zintzaras E. Analysis of the quality of reporting of randomized controlled trials in acute and chronic myeloid leukemia, and myelodysplastic syndromes as governed by the CONSORT statement. Ann Epidemiol 2009;19:494-500.
14. Smith BA, Lee HJ, Lee JH, et al. Quality of reporting randomized controlled trials (RCTs) in the nursing literature: application of the consolidated standards of reporting trials (CONSORT). Nurs Outlook 2008;56:31-7.
15. Kane RL, Wang J, Garrard J. Reporting in randomized clinical trials improved after adoption of the CONSORT statement. J Clin Epidemiol 2007;60:241-9.
16. Sut N, Senocak M, Uysal O, Koksalan H. Assessing the quality of randomized controlled trials from two leading cancer journals using the CONSORT statement. Hematol Oncol Stem Cell Ther 2008;1:38-43.
17. Lai TY, Wong VW, Lam RF, Cheng AC, Lam DS, Leung GM. Quality of reporting of key methodological items of randomized controlled trials in clinical ophthalmic journals. Ophthalmic Epidemiol. 2007;14:390–398.
18. Agha R, Cooper D, Muir G. The reporting quality of randomised controlled trials in surgery: a systematic review. Int J Surg. 2007;5: 413–422.
19. Hill CL, Buchbinder R, Osborne R. Quality of reporting of randomized clinical trials in abstracts of the 2005 annual meeting of the American College of Rheumatology. J Rheumatol. 2007;34:2476–2480.
20. Farrokhyar F, Chu R, Whitlock R, Thabane L. A systematic review of the quality of publications reporting coronary artery bypass grafting trials. Can J Surg. 2007;50:266–277.
21. Soares H, Daniels S, Kumar A, Clarke M, Scott C, Swann S, et al. Bad reporting does not mean bad methods for randomised trials: observational study of randomised controlled trials performed by the Radiation Therapy Oncology Group. BMJ. 2004;328:22–24.
22. Mills E, Loke YK, Wu P, Montori VM, Perri D, Moher D, Guyatt G. Determining the reporting quality of RCTs in clinical pharmacology. Br J Clin Pharmacol. 2004;58:61–65.
23. Kirchhof P, Curtis AB, Skanes AC, et al. Atrial fibrillation guidelines across the Atlantic: a comparison of the current recommendations of the European Society of Cardiology / European Heart Rhythm Association / European Association of

Cardiothoracic Surgeons, the American College of Cardiology Fou. Eur Heart J 2013;34:1471–4.

24. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131:492-501.
25. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.
26. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
27. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
28. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.
29. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104.
30. Hori M, Matsumoto M, Tanahashi N, et al; J-ROCKET AF study investigators. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation. Circ J. 2012;76:2104–2111.
31. Keisu M, Andersson TB. Drug-induced liver injury in humans: the case of ximelagatran. Handb Exp Pharmacol. 2010;196:407–418.
32. Apostolakis S, Lip GY. Novel oral anticoagulants: focus on the direct factor Xa inhibitor darexaban. Expert Opin Investig Drugs. 2012;21:1057–1064.