Reporting quality of randomized-controlled trials exploring the efficacy and safety of new anticoagulants in acute venous thromboembolism or pulmonary embolism, based on CONSORT statement

University Of Thessaly School Of Medicine

NTONTOY DIMITRA

Abstract

Purpose

The aim of this study is to assess the quality of reporting randomized controlled studies and investigated the efficacy and safety of new anticoagulants in acute venous thromboembolism or pulmonary embolism using a standard tool based on Consolidated Reporting Standards Tests (Consolidated Standards of Reporting Trials – CONSORT statement).

Methods

We searched Pubmed and the Cochrane Library until July 2015 for RCTs involving new anticoagulants in acute venous thromboembolism or pulmonary embolism. We used the Consolidated Standards of Reporting Trials (CONSORT) checklist for parallel RCTs revised in 2010 to assess the completeness of reporting of RCTs.

Results

Our search strategy identified 1197 studies, of which 6 met the inclusion criteria. From the six (6) RCTs, which were included in the analysis no-one mentioned the implementation of randomization in the title. All of them introduced random methods. Five studies were double-blinded and in those reported an estimation of sample size (83.34%). Five of them reported the statistical methods which used to compare groups for primary and secondary outcomes and methods for additional analyses (83.34%). All of them, reported, losses and exclusions after randomization. Only one study reported why the trial was stopped (16.67%). Three studies reported generalisability of the trial findings (50%) and two studies reported limitations or sources of potential bias of the trial (33.34%).

Conclusion

A well-designed RCT should use randomization and blinding. Endorsement of the CONSORT statement may optimize the reporting quality and enhance the validity of research.

Introduction

Venous thromboembolism, manifested as deep vein thrombosis or pulmonary embolism, is a common medical condition and is the third leading cause of cardiovascular mortality. [1-7] The mainstay of treatment has been initial use of parenteral anticoagulants followed by longer term use of oral vitamin K antagonists.[8] While the vitamin K antagonists are effective at preventing propagation and recurrence, they are also associated with an increased risk of bleeding and the need for laboratory monitoring.[9] In addition, they have potential for multiple drug-drug interactions, which are often clinically important because of their narrow therapeutic index. In the past decade two classes of novel oral anticoagulants have been developed: direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Factor Xa inhibitors prevent cleavage of prothrombin to thrombin, whereas the direct thrombin inhibitors prevent thrombin from cleaving fibrinogen.[10] Recent studies have evaluated the efficacy and safety of direct oral anticoagulants (with and without initial parenteral anticoagulant therapy) for the treatment of acute venous thromboembolism. Clinicians have many potential treatment options regarding management of acute venous thromboembolism and little guidance exists about which drug is most effective yet safe. Although individual studies have shown promising results, several therapies have been assessed in only a single trial, and direct comparisons are rarely available.

Randomized controlled trials (RCTs) are considered the best tool for establishing effectiveness due to minimization of bias in evaluating new treatment strategies [11,12,13]. RCTs represent a key research activity with the potential to improve the quality of health care and control costs through careful comparison of alternative treatments [14,15]. However, the recent flood of available information in biomedical journals during the last years has raised problems in a variety of areas, such as publication or selection bias and retraction of invalid literature [11,16,17].

An international group of scientists and editors developed and published in 1996, a common checklist for items to include in reports of RCTs, known as the Consolidated Standards of Reporting Trials (CONSORT) statement [13,18]. It was initially published in 1996 [19], then revised twice subsequently in 2001 and 2010.[20,21] 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 and a flow diagram. 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.

The aim of this study is to assess the quality of reporting randomized controlled studies and investigated the efficacy and safety of new anticoagulants in acute venous thromboembolism or pulmonary embolism using a standard tool based on Consolidated Reporting Standards Tests (Consolidated Standards of Reporting Trials – CONSORT statement).

Methods

Data sources and searches

A systematic search of the literature was conducted on Pubmed and the Cochrane Library. Each database was searched from its inception date to July 2015. References of included studies and narrative reviews were considered for additional potential studies. The retrieved articles were examined to eliminate potential duplicates or overlapping data. There were no language restrictions. The search string was: #1. (rivaroxaban) OR (apixaban) OR (edoxaban) #2. (dabigatran), #3. #2 OR #1 [(rivaroxaban) OR (apixaban) OR (edoxaban) OR(dabigatran)], #4. deep venous thrombosism OR deep vein thrombosism OR thrombophlebitis OR pulmonary embolism, #5. #3 AND #4 [(rivaroxaban) OR (apixaban) OR (edoxaban) OR (dabigatran) AND deep venous thrombosism OR deep vein thrombosism OR thrombophlebitis OR pulmonary embolism].

Study selection

Potentially relevant articles were reviewed in full to ensure that they satisfied 5 criteria: (1) the study prospectively enrolled patients who had objectively confirmed symptomatic acute venous thromboembolism (lower extremity deep vein thrombosis, pulmonary embolism, or both) and who had qualifying recurrent venous thromboembolism events that were symptomatic and objectively confirmed, (2) the intervention was treatment with a novel oral anticoagulants with or without initial treatment with heparin, (3) the comparison group was treatment with vitamin K antagonists always with initial treatment with heparin, (4) 1 or more of the primary or secondary outcomes were reported and (5) and it was a randomized controlled trial. Studies were excluded if (1) patients were randomized to placebo or observation, (2) patients were randomized to ximelagatran or idraparinux, (3) only patients with cancer-associated thrombosis were included and (4) study design was phase I or II.

Data extraction and quality assessment

We used the CONSORT statement for parallel RCTs revised in 2010 to assess the completeness of reporting of RCTs. The revised CONSORT checklist includes a 25-item-questionaire. The methodological items include the use of the term "randomized trial" in the title, location of data collection, predefined primary outcome, sample size estimation, method of randomization sequence generation, allocation concealment and implementation, who was blind and how blinding was achieved, publication of a participant flow diagram, period of recruitment, period of follow-up, as well as the attrition due to loss to follow-up, and intention-to-treat analysis. [25] All items were investigated in terms of whether they were reported, not whether they were actually carried out during the trial. The items that reported in the study were assessed as 'yes'. Otherwise, the item was rated as 'no'. For an item that contained multiple subitems, the reporting of the item was considered to be complete when at least one subitem was completely reported.

Results

Our search identified 1197 studies of interest, after removal of duplicates. Most studies were eliminated during screening as the indication for anticoagulation was not acute venous thromboembolism. After we reviewed 89 full text articles, six (6) studies with over 13.500 patients were suitable for data extraction and pooled analysis (figure 1). The trials evaluated two factor Xa inhibitors (rivaroxaban (two randomised controlled trials, n=4150), apixaban (one trial, n=2691) and edoxaban (one trial, n=4118)) and one direct thrombin inhibitors (dabigatran (two trials, n=2553)).[23,24,25,26,27,28]
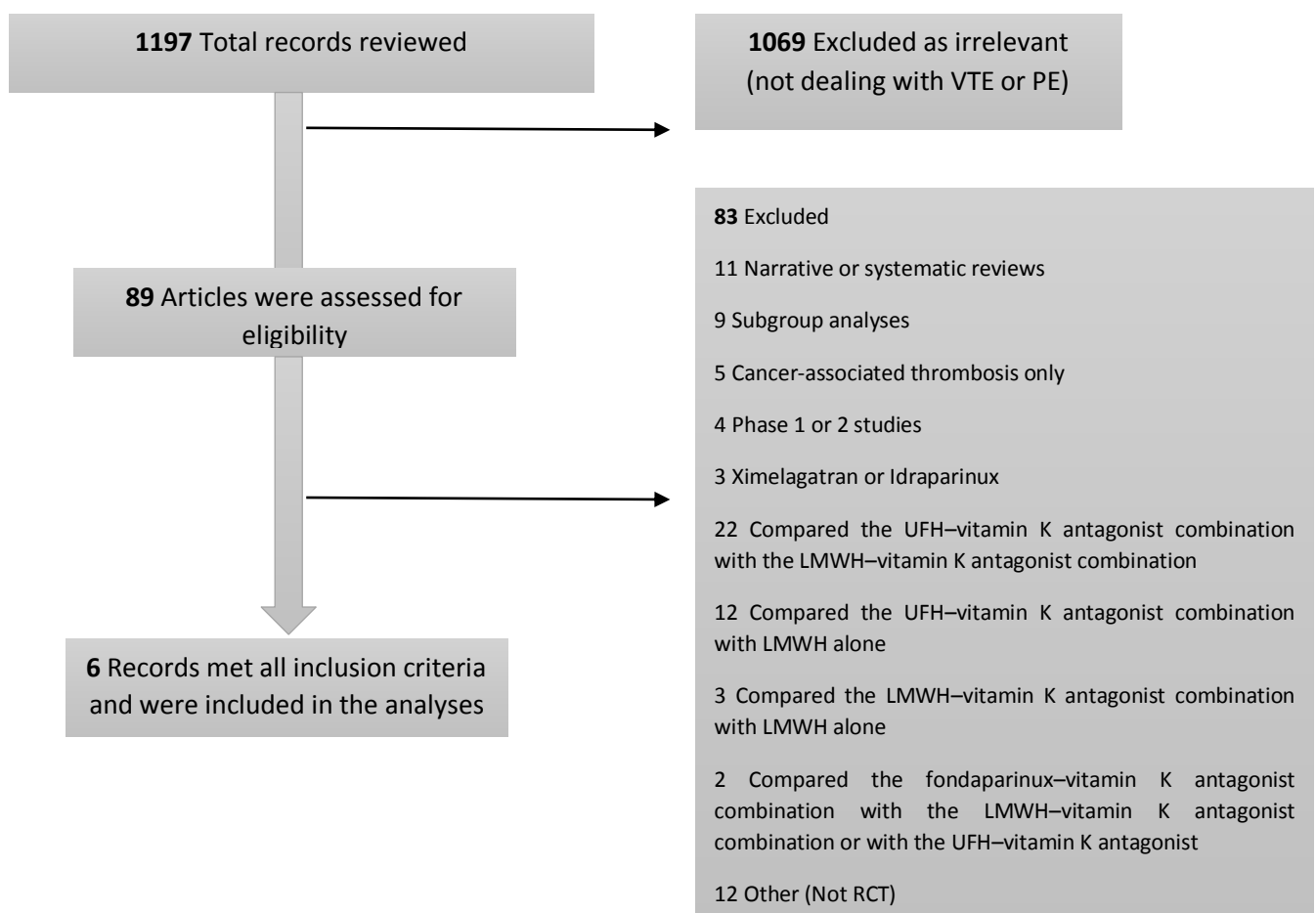
```
┌──────────────────────────────┐        ┌──────────────────────────────┐
│ 1197 Total records reviewed  │───────▶│ 1069 Excluded as irrelevant  │
│                              │        │ (not dealing with VTE or PE) │
└──────────────────────────────┘        └──────────────────────────────┘
              │
              ▼                          ┌──────────────────────────────────────┐
┌──────────────────────────────┐        │ 83 Excluded                            │
│ 89 Articles were assessed for │        │                                        │
│ eligibility                  │───────▶│ 11 Narrative or systematic reviews     │
└──────────────────────────────┘        │                                        │
              │                          │ 9 Subgroup analyses                    │
              ▼                          │                                        │
┌──────────────────────────────┐        │ 5 Cancer-associated thrombosis only    │
│ 6 Records met all inclusion   │        │                                        │
│ criteria and were included in │        │ 4 Phase 1 or 2 studies                 │
│ the analyses                 │        │ ...                                    │
└──────────────────────────────┘        └──────────────────────────────────────┘
```

- **1197** Total records reviewed
- **1069** Excluded as irrelevant (not dealing with VTE or PE)
- **89** Articles were assessed for eligibility
- **83** Excluded
  - 11 Narrative or systematic reviews
  - 9 Subgroup analyses
  - 5 Cancer-associated thrombosis only
  - 4 Phase 1 or 2 studies
  - 3 Ximelagatran or Idraparinux
  - 22 Compared the UFH–vitamin K antagonist combination with the LMWH–vitamin K antagonist combination
  - 12 Compared the UFH–vitamin K antagonist combination with LMWH alone
  - 3 Compared the LMWH–vitamin K antagonist combination with LMWH alone
  - 2 Compared the fondaparinux–vitamin K antagonist combination with the LMWH–vitamin K antagonist combination or with the UFH–vitamin K antagonist
  - 12 Other (Not RCT)
- **6** Records met all inclusion criteria and were included in the analyses

Figure 1: Flow Diagram of Study Selection

- Rivaroxaban

Two phase III studies were performed by the EINSTEIN investigators in a pair of open label non-inferiority studies. The EINSTEIN-DVT study enrolled 3449 patients with acute deep vein thrombosis and excluded patients with symptomatic pulmonary embolism.[24] The EINSTEIN-PE study recruited 4832 patients with acute symptomatic pulmonary embolism with or without symptomatic deep vein thrombosis. [23] The EINSTEIN investigators chose to load rivaroxaban at 15 mg twice a day for three weeks followed 20 mg once a day with standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist for 3, 6, or 12 months. The rivaroxaban patients typically received one to two doses of low molecular weight heparin before starting rivaroxaban, whereas the patients randomised to vitamin K antagonists received low molecular weight heparin concurrently for five days or more, until the target international normalised ratio (INR) was achieved.

- Apixaban

A randomized, double-blind study compared apixaban (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) with conventional therapy (subcutaneous enoxaparin, followed by warfarin) in 5395 patients with acute venous thromboembolism.[25]

- Dabigatran

The pivotal published study on dabigatran enrolled patients with acute venous thromboembolism who were initially given parenteral anticoagulation therapy for a median of 9 days.[27] This was a phase III non-inferiority, double blind, double dummy trial, which included sham monitoring of international normalised ratio (INR) and sham titration of vitamin K antagonists in the experimental group. Another randomized, double-blind, double-dummy trial of 2589 patients with acute VTE treated with low-molecular-weight or unfractionated heparin for 5 to 11 days, was designed to compare dabigatran 150 mg twice daily with warfarin, adjusted to maintain an international normalized ratio (INR) of 2.0 to 3.0 during 6 months, after initial parenteral anticoagulation.[28]

- Edoxaban

We found one published studies that looked at edoxaban. In this randomized, double-blind trial, investigators compared heparin (enoxaparin or unfractionated heparin) followed by edoxaban with heparin followed by warfarin with respect to efficacy and safety in patients with deep-vein thrombosis, pulmonary embolism, or both. Edoxaban (or placebo) was started after discontinuation of initial heparin. Edoxaban was administered at a dose of 60 mg orally once daily, taken with or without food, or at a dose of 30 mg once daily in patients with a creatinine clearance of 30 to 50 ml per minute or a body weight of 60 kg or less or in patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors. Warfarin (or placebo) was started concurrently with the study regimen of heparin, with adjustment of the dose to maintain the international normalized ratio (INR) between 2.0 and 3.0. Treatment with edoxaban or warfarin was to be continued for at least 3 months in all patients and for a maximum of 12 months. [26]

Section/Topic	Item No	Checklist item	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6
Title and abstract								
	1a	Identification as a randomised trial in the title	No	No	No	No	No	No
	1b	Structured summary of trial design, methods, results, and conclusions	Yes	Yes	Yes	Yes	Yes	Yes
Introduction								
Background and objectives	2a	Scientific background and explanation of rationale	Yes	Yes	Yes	Yes	Yes	Yes
	2b	Specific objectives or hypotheses	No	Yes	No	Yes	Yes	Yes
Methods								
Trial design	3a	Description of trial design including allocation ratio	Yes	Yes	Yes	Yes	Yes	Yes
	3b	Important changes to methods after trial commencement, with reasons	No	No	No	No	No	Yes
Participants	4a	Eligibility criteria for participants	Yes	Yes	Yes	Yes	Yes	No
	4b	Settings and locations where the data were collected	Yes	No	Yes	Yes	Yes	Yes
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Yes	Yes	Yes	Yes	Yes	Yes
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Yes	Yes	Yes	Yes	Yes	Yes
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Yes	No	Yes	No	No	Yes
Sample size	7a	How sample size was determined	No	Yes	Yes	Yes	Yes	Yes
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Yes	Yes	No	Yes	No	No
Randomisation:								
Sequence generation	8a	Method used to generate the random allocation sequence	Yes	Yes	Yes	Yes	Yes	Yes
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Yes	Yes	Yes	Yes	Yes	Yes
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence, describing any steps taken to conceal the sequence until interventions were assigned	No	No	Yes	No	Yes	No
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Yes	No	Yes	Yes	No	No
Blinding	11a	If done, who was blinded after assignment to interventions and how	No	Yes	Yes	Yes	Yes	Yes
	11b	If relevant, description of the similarity of interventions	Yes	No	No	Yes	Yes	Yes
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Yes	No	Yes	Yes	Yes	Yes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Yes	Yes	Yes	Yes	No	Yes
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	Yes	Yes	Yes	Yes	Yes	Yes
	13b	For each group, losses and exclusions after randomisation, together with reasons	Yes	Yes	Yes	Yes	Yes	Yes
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Yes	Yes	Yes	Yes	Yes	Yes
	14b	Why the trial ended or was stopped	No	No	No	No	No	No
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Yes	Yes	Yes	Yes	Yes	Yes

Numbers analysed	16	For each group, number of participants included in each analysis and whether the analysis was by original assigned groups	Yes	Yes	Yes	Yes	Yes	Yes
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision	Yes	Yes	Yes	Yes	Yes	Yes
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	No	No	No	No	No	No
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Yes	Yes	Yes	Yes	No	Yes
Harms	19	All important harms or unintended effects in each group	No	Yes	Yes	Yes	Yes	Yes
Discussion								
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Yes	Yes	Yes	No	Yes	No
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	No	Yes	Yes	Yes	No	No
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Yes	Yes	Yes	Yes	Yes	Yes
Other information								
Registration	23	Registration number and name of trial registry	Yes	Yes	Yes	Yes	Yes	Yes
Protocol	24	Where the full trial protocol can be accessed, if available	Yes	Yes	Yes	Yes	No	No
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Yes	Yes	Yes	Yes	Yes	Yes

Table 2: Proportion of reporting of 25 data items in a total of 6 randomized clinical trials in acute venous thromboembolism or pulmonary embolism. (Study 1: Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism, Study 2: Oral Rivaroxaban for Symptomatic Venous Thromboembolism, Study 3: Oral Apixaban for the Treatment of Acute Venous Thromboembolism, Study 4: Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism, Study 5: Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism, Study 6: Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis)

Section/Topic	Item No	Checklist item	Number of reported RCTs [n (%)]
Title and abstract			
	1a	Identification as a randomised trial in the title	0
	1b	Structured summary of trial design, methods, results, and conclusions	6/6
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6/6
	2b	Specific objectives or hypotheses	4/6 (66.67%)
Methods			
Trial design	3a	Description of trial design including allocation ratio	6/6
	3b	Important changes to methods after trial commencement, with reasons	1/6 (16.67%)
Participants	4a	Eligibility criteria for participants	5/6 (83.34%)
	4b	Settings and locations where the data were collected	5/6 (83.34%)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6/6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6/6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	3/6 (50%)
Sample size	7a	How sample size was determined	6/6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	3/6 (50%)
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6/6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6/6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence, describing any steps taken to conceal the sequence until interventions were assigned	3/6 (50%)
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3/6 (50%)
Blinding	11a	If done, who was blinded after assignment to interventions and how	5/6 (83.34%)
	11b	If relevant, description of the similarity of interventions	4/6 (66.67%)
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5/6 (83.34%)
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	5/6 (83.34%)
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	6/6
	13b	For each group, losses and exclusions after randomisation, together with reasons	6/6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6/6
	14b	Why the trial ended or was stopped	0
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	6/6
Numbers analysed	16	For each group, number of participants included in each analysis and whether the analysis was by original assigned groups	6/6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision	6/6
	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	5/6 (83.34%)
Harms	19	All important harms or unintended effects in each group	5/6 (83.34%)
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	4/6 (66.67%)
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	3/6 (50%)
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	6/6
Other information			
Registration	23	Registration number and name of trial registry	6/6
Protocol	24	Where the full trial protocol can be accessed, if available	4/6 (66.67%)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	6/6

Table 3:Reporting quality of 6 RCTs based on CONSORT 2010

CONSORT 2010 adherence

From the six (6) RCTs, which were included in the analysis no-one mentioned the implementation of randomization in the title. However, all of them introduced random methods. Of them, four used a voice-response system with stratification, one used a computer generated randomization scheme with variable block sizes and one used an interactive Web-based system. Five studies were double-blinded and in those reported an estimation of sample size. Only one study reported important changes to methods after trial commencement, with reasons. In which were reported that the protocol stated as hierarchically equal safety outcomes major bleeding, major or clinically relevant nonmajor bleeding, and any bleeding but was not planned for independent central adjudication of acute coronary syndromes, so this decision was revised by the steering committee and performed at the end of the trial, after database locked.

Five of them reported the statistical methods which used to compare groups for primary and secondary outcomes and methods for additional analyses. All of them reported, losses and exclusions after randomization, together with reasons and included a table showing the baseline demographic and clinical characteristics for each group. Three studies reported generalisability of the trial findings and two studies reported limitations or sources of potential bias of the trial. No one study reported why the trial was stopped. All of the included studies reported sources of funding and the registration number. Four studies mentioned, where the full protocol was available. Only one trial did not report the eligibility criteria for participants, however report that they are described in another study, and gives us the referral.

CONCLUSION

We prepared this study to assess the quality of reporting randomized controlled studies and investigated the efficacy and safety of new anticoagulants in acute venous thromboembolism or pulmonary embolism. In our search we decided to exclude the direct thrombin inhibitor ximelagatran which was withdrawn from the market in 2006 because of concerns over hepatotoxicity. We also exclude idraparinux because is oldest than the other four anticoagulants that we include in our alanysis.

We searched on Pubmed and the Cochrane Library up to July 2015. Our search strategy identified 1197 studies, of which 6 met the inclusion criteria. We evaluated the quality of reporting using the CONSORT Statement checklists.

A well-designed RCT should use randomization and blinding. Widely acceptable methods should be used to generate a random allocation sequence and an allocation concealment mechanism should be used. All of the studies which were included in the analysis introduced random methods but only three of them reported the mechanism used to implement the random allocation sequence. Five studies were double-blinded and reported the methods of statistical analysis.

In general, the studies included in the analysis meet most of the requirements of a good randomized trial. However, the design of RCTs, the methods of statistical analysis, and other parts of the study should be improved and the reporting of RCTs should follow the CONSORT 2010.

References

1. Cohen AT[1], Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, Greer IA, Heit JA, Hutchinson JL, Kakkar AK, Mottier D, Oger E, Samama MM, Spannagl M; VTE Impact Assessment Group in Europe (VITAE).
Venous thromboembolism (VTE) in Europe : the number of VTE events and associated morbidity and mortality.
Thromb Haemost.2007;98:756-764.

2. Ageno W[1], Prandoni P, Romualdi E, Ghirarduzzi A, Dentali F, Pesavento R, Crowther M, Venco A.
The metabolic syndrome and the risk of venous thrombosis: a case-control study.
J Thromb Haemost. 2006;4:1914-1918.

3. Heit JA[1].
The epidemiology of venous thromboembolism in the community: implications for prevention and management.
 J Thromb Thrombolysis.2006;21:23-29.

4. White RH[1].
The epidemiology of venous thromboembolism.
Circulation. 2003;107:I4-I8.

5. Prins MH[1], Marchiori A.
Risk of recurrent venous thromboembolism—expanding the frontier.
Thromb Haemost.2002;87:1-3.

6. Silverstein MD[1], Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd.
Trends in the incidence of deep vein thrombosis and pulmonary embolism: a25-yearpopulation-basedstudy.
Arch Intern Med. 1998;158:585-593.

7. Anderson FA Jr[1], Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE.
A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT Study.
ArchInternMed.1991;151: 933-938.

8. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al.
Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Dec;142:1698-1704.

9. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G, et al.
Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.
Chest 2012;141:e44-88S.

10. Weitz JI[1].
New oral anticoagulants: a view from the laboratory.
Am J Hematol 2012;S1:S133-136.

11. Djulbegovic B[1], Loughran TP Jr, Hornung CA, Kloecker G, Efthimiadis EN, Hadley TJ, Englert J, Hoskins M, Goldsmith GH.
The Quality of Medical Evidence in Hematology-Oncology.
Am J Med. 1999;106:198–205. doi: 10.1016/S0002-9343(98)00391-X.

12. Moher D, Jadad AR, Tugwell P.
    Assessing the quality of randomized controlled trials. Current issues and future directions.
    Int J Technol Assess Health Care. 1996;12:195–208. doi: 10.1017/S0266462300009570.

13. Altman DG.
    Better reporting of randomised controlled trials: the CONSORT statement.
    BMJ. 1996;313:570–571

14. 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. doi: 10.1016/j.annepidem.2009.03.018.

15. Papathanasiou AA, Zintzaras E.
    Assessing the Quality of Reporting of Observational Studies in Cancer.
    Ann Epidemiol. 2009

16. Pfeifer M, Snodgrass GL.
    The continued use of retracted invalid scientific literature.
    JAMA. 1990;263:1420–1423. doi: 10.1001/jama.263.10.1420.

17. Olkin I[1].
    Meta-analysis: reconciling the results of independent studies.
    Stat Med. 1995;14:457–472. doi: 10.1002/sim.4780140507.

18. Junker C, Egger M, Schneider M, Zellweger T, Antes G.
    The CONSORT statement.
    JAMA. 1996;276:1876–1877. doi: 10.1001/jama.276.23.1876.

19. Begg C[1], Cho M, Eastwood S, Horton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz KF, Simel D, Stroup DF.
    Improving the quality of reporting of randomized controlled trials. The CONSORT statement.
    JAMA. 1996 Aug 28;276:637-639.

20. Moher D[1], Schulz KF, Altman DG; CONSORT Group.
    The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials.
    Clin Oral Investig. 2003 Mar;7:2-7. Epub 2003 Jan 31.

21. Schulz KF[1], Altman DG, Moher D; CONSORT Group.
    CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.
    J Clin Epidemiol. 2010 Aug;63:834-840. doi: 10.1016/j.jclinepi.2010.02.005. Epub 2010 Mar 25.

22. Lu J[1], Gary KW[2], Copolillo A[2], Ward J[3], Niemeier JP[4], Lapane KL[5].
    Randomized Controlled Trials in Adult Traumatic Brain Injury: A Review of Compliance to CONSORT Statement.
    Arch Phys Med Rehabil. 2015 Apr;96:702-714. doi: 10.1016/j.apmr.2014.10.026. Epub 2014 Dec 9.

23. EINSTEIN–PE Investigators, Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A,Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A.
    Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism.
    N Engl J Med. 2012 Apr 5;366:1287-1297. doi: 10.1056/NEJMoa1113572. Epub 2012 Mar 26.

24. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S.
Oral Rivaroxaban for Symptomatic Venous Thromboembolism.
N Engl J Med. 2010 Dec 23;363:2499-2510. doi: 10.1056/NEJMoa1007903. Epub 2010 Dec 3.

25. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators.
Oral Apixaban for the Treatment of Acute Venous Thromboembolism.
N Engl J Med. 2013 Aug 29;369:799-808. doi: 10.1056/NEJMoa1302507. Epub 2013 Jul 1.

26. Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M,Verhamme P, Wells P.
Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism.
N Engl J Med. 2013 Oct 10;369:1406-1415. doi: 10.1056/NEJMoa1306638. Epub 2013 Aug 31.

27. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group.
Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism.
N Engl J Med. 2009 Dec 10;361:2342-2352. doi: 10.1056/NEJMoa0906598.

28. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C; RE-COVER II TrialInvestigators.
Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis.
Circulation. 2014 Feb 18;129:764-772. doi: 10.1161/CIRCULATIONAHA.113.004450. Epub 2013 Dec 16.