PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Shorter or longer anticoagulation to prevent recurrent venous thromboembolism: systematic review and meta-analysis - Protocol
AUTHORS	Lopes, Luciane; Eikelboom, John; Spencer, Frederick; Akl, Elie; Kearon, Clive; Neumann, Ignacio; Schulman, Sam; Bhatnaga, Neera; Guyatt, Gordon

VERSION 1 - REVIEW

REVIEWER	Sabine Eichinger Medical University of Vienna, Austria
REVIEW RETURNED	08-Jun-2014

GENERAL COMMENTS	Statistics are crucial for the trial so it may help if this is looked at one more time. This is an interesting analysis. My only concern is that we still will not get answers to the benefit or risks of indefinite anticoagulation. None of the study - particularly those with the new direct oral anticoagulants had observation times longer than 2-3 years. It is not exactly clear what the duration of anticoagulation in the long term treatment group actually will be. Is there an overlap with the other group in those who receive 9 months of anticoagulation?

REVIEWER	Couturaud Francis Department of internal medicine and chest diseases University Hospital of Brest
REVIEW RETURNED	09-Jun-2014

GENERAL COMMENTS	This is a well written and planned meta-analysis proposal focused on a important question. The authors have a major experience in this area. I have only minor comments. In general, one of the main limitation is that the metaanalysis is not done on individual data; therefore, information on subgroups will be limited (which is today an important challenge). I acknowledge that it is not the main purpose of the study but this should be mentioned in the discussion. Given the number of studies that were performed on novel oral anticoagulants, an indirect comparison VKA vs NOAC is warranted and will be feasible in this meta-analysis; maybe this is the authors mean in the “assessment of heterogeneity and subgroup analyses” (page 10) section, but it appears rather as a direct comparison than

	an indirect comparison: it remains unclear to me. I do not understand exclusion criteria (page 7, line 37): “pregnancy” as a high risk of recurrent VTE ? More than excluding studies that include patients with protein C or S deficiency, study of antiphospholipid syndrome should first be excluded ?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Reviewer Name Sabine Eichinger Institution and Country Medical
University of Vienna, Austria

Q1 - Statistics are crucial for the trial so it may help if this is looked at one more time.
R1 - We have looked carefully at the statistical plan. If the reviewer has specific suggestions we would be pleased to consider them.

Q2- This is an interesting analysis. My only concern is that we still will not get answers to the benefit or risks of indefinite anticoagulation. None of the study - particularly those with the new direct oral anticoagulants had observation times longer than 2-3 years.
R2 - The reviewer is correct that this is a limitation. However, the yearly events in the second and third year should provide a useful estimate of subsequent events. We have addressed this issue in the revised protocol as follows: Our study is likely to be limited by other aspects of study design and reporting of the primary studies. In particular, though we are interested in the impact of indefinite versus limited anticoagulation, studies will have limited follow-up, often 2 to 3 years. Both bleeding and event rates in the second and third years will, however, provide a useful estimate of what is liable to happen in subsequent years.

Q3 - It is not exactly clear what the duration of anticoagulation in the long term treatment group actually will be. Is there an overlap with the other group in those who receive 9 months of anticoagulation?
R3 - In the studies we have identified so far, the relevant duration of anticoagulation in the longer duration arm (that is, the period of follow-up while anticoagulated in the longer duration arm) has ranged from x to y.

Reviewer 2

Reviewer Name Couturaud Francis
Institution and Country Department of internal medicine and chest diseases
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Q1-This is a well written and planned meta-analysis proposal focused on a important question. The authors have a major experience in this area. I have only minor comments.
R1- Thank you!

Q2 - In general, one of the main limitation is that the meta-analysis is not done on individual data;

therefore, information on subgroups will be limited (which is today an important challenge). I acknowledge that it is not the main purpose of the study but this should be mentioned in the discussion.
R2 - The reviewer is correct. We have added the following sentence to the discussion: Another important limitation is that we will not have access to individual patient data and therefore subgroup analysis and inferences will be limited.

Q3 - Given the number of studies that were performed on novel oral anticoagulants, an indirect comparison VKA vs NOAC is warranted and will be feasible in this meta-analysis; maybe this is the authors mean in the “assessment of heterogeneity and subgroup analyses” (page 10) section, but it appears rather as a direct comparison than an indirect comparison: it remains unclear to me.
R3 - The issue at hand given the objective of this systematic review and meta-analysis is whether the impact of the longer versus the shorter arm effects differ in warfarin versus the NOACs (that is, whether anticoagulation of warfarin versus NOACs is an effect modifier of the relative effect of longer versus shorter anticoagulation). We believe this particular issue is best addressed with our current analysis plan which will use a test of interaction to look at the relative effect of shorter versus longer in the warfarin versus the NOAC studies.

Q4 - I do not understand exclusion criteria (page 7, line 37): “pregnancy” as a high risk of recurrent VTE ? More than excluding studies that include patients with protein C or S deficiency, study of antiphospholipid syndrome should first be excluded ?
R4 - On reflection, the exclusion of pregnancy was a little silly – pregnancy is not an indefinite state, and thus indefinite anticoagulation is not an option. We have deleted that exclusion. The reviewer makes a good point with respect to antiphospholipid antibody syndrome and we have substituted that for the pregnancy exclusion.