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Full Length Article

Extended anticoagulation and mortality in venous thromboembolism. A meta-analysis of six randomized trials

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A B S T R A C T

Data on all-cause mortality in patients with venous thromboembolism (VTE) and prolonged anticoagulation are inconclusive. The aim of this study was to compare the incidence of all-cause mortality in patients with VTE at intermediate risk of recurrence, i.e. without transient risk factors or cancer, exposed to shorter (at least three months) or longer anticoagulation.

We did a systematic revue and meta-analysis of randomized clinical trials searching MEDLINE and COCHRANE bibliographic databases. A random-effects model was used to pool study results. I2 testing was used to test for heterogeneity.

Six studies (5920 patients) entered in the final analysis. Mean course of anticoagulation was 7.5 months in the shorter and 18.6 months in the longer treatment arm. Prolonged anticoagulation was associated with a statistically significant reduction in all-cause mortality (RR 0.47, 95% CI 0.29 to 0.75; 0.8% vs 1.8%). Pulmonary embolism-related death was also lowered in the longer anticoagulation arm (RR 0.32, 95% CI 0.12 to 0.83; 0.2% vs 0.6%).

Longer compared with shorter anticoagulation significantly reduced all-cause mortality in patients with VTE at intermediate risk of recurrence.

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1. Introduction

Patients with venous thromboembolism (VTE), which encompasses deep vein thrombosis and pulmonary embolism, are usually treated with three to six months of anticoagulant therapy for their acute episode [1,2].

Beyond this period the management is based on the risk factors associated with the episode of VTE. Patients with transient risk factors have a low risk of recurrences and generally discontinue their treatment, while patients with cancer are usually treated indefinitely due to a high risk of recurrences.

In patients with VTE at intermediate risk of recurrences (mostly with unprovoked events), who have a risk of recurrences of about 30% at five years [3,4], the optimal duration of anticoagulation is matter of debate [5–7]. Several studies have consistently shown a reduction of about 90% of the recurrences with extended use of vitamin k antagonists (VKA) [8–10]. However, once the anticoagulant is discontinued, there is no difference in the subsequent rate of recurrences with three compared with six or twelve months of therapy [11]. Moreover, the

reduction of recurrences while on anticoagulants, come at the cost of an increase in major bleedings [7].

Current guidelines recommend extended anticoagulation (beyond three months) in patients with unprovoked VTE and low-to moderate risk of bleeding [12]. However inconsistencies in the duration of anticoagulation are reported in clinical practice [13–14].

Information on mortality in patients with different duration of treatment for VTE may affect the decision of the clinicians about continuing or not the anticoagulation. However, the studies designed to evaluate the efficacy and safety of the VKA in the prevention of recurrent VTE were not powered to assess this outcome. Previous meta-analyses did not report this result [15,16], or might have been underpowered to assess differences in mortality during treatment [17].

In the last years three direct oral anticoagulants (DOACs) (dabigatran, rivaroxaban and apixaban) have been evaluated in the secondary prevention of VTE, increasing the number of patients involved in the prophylaxis, and allowing for a more accurate determination of risks and benefits of the extended anticoagulation [18–20].

We therefore performed a meta-analysis of available data from randomized clinical trials (RCTs) on secondary prevention of VTE, with the aim to update the evaluation of the risk of all-cause mortality in patients with VTE at intermediate risk of recurrences treated for at least three months, compared with those treated for longer periods.

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2. Methods

2.1. Search strategy for identification of studies

A systematic review of the literature was performed. We sought relevant articles in the Medline data source and Cochrane Database of Systematic Review, from inception through May 2015. There were no language restrictions. The search was conducted using the terms "venous thromboembolism or pulmonary embolism or deep vein thrombosis or DVT or PE; warfarin or coumarin or heparin or low-molecular-weight heparin or anticoagulant(s) or anticoagulant treatment or anticoagulant therapy or duration of anticoagulant therapy or anticoagulation, or secondary prevention; rivaroxaban or apixaban or edoxaban or dabigatran" as both medical subject heading terms and text words. This was followed by a manual search of the reference list of the retrieved articles to identify additional studies.

2.2. Study selection

Two of the authors (CB, VM) independently reviewed all potentially relevant publications to determine whether an article met the inclusion/exclusion criteria. Disagreements were discussed at a team meeting where a final decision was reached. Studies were included in the meta-analysis if they met all the following criteria:

a) were RCTs;
b) randomized patients with VTE to a course of anticoagulants of at least three months or to a longer period;
c) included patients with clinical equipoise to continued anticoagulation, or a population with at least 70% of unprovoked events, or with recurrent (provoked or unprovoked) VTE;
d) showed the outcomes of interest, that is all-cause mortality, fatal pulmonary embolism, sudden unexplained death, and fatal bleeding;
e) presented the results at the end of the anticoagulation in the longer treatment arm, that is without additional follow-up.

We made this choice because the follow-up, although informative on the long term outcomes of the patients with shorter versus longer anticoagulation, might dilute potential benefits (or risks) of continued anticoagulation.

To avoid excluding studies with only a few months of unintended additional observation (for example due to drop-out of some patients), we considered the follow-up present if it lasted at least six months.

Since we planned a study-level meta-analysis, we accepted studies that included some patients with cancer or low risk of recurrence such as patients with transient risk factors for VTE, provided a substantial proportion (at least 70%) of patients included had an unprovoked VTE.

Trials on DOACs in which patients were randomized to the drug or placebo, were also eligible, provided the randomization had been preceded by at least three months of anticoagulation.

We excluded trials that focused on particular subgroups of patients, such those with abnormal d-dimer [10] or residual vein thrombosis [21, 22], or that evaluated only patients with transient risk factors for VTE [23], or compared less than three months of anticoagulation with longer periods [24,25]. We also excluded one study on Ximelagatran [26] because the drug is no more available.

The main outcome of interest was all-cause mortality. We also sought data about pulmonary embolism-related mortality. For this purpose we considered fatal pulmonary embolism (as adjudicated in each study) and sudden unexplained deaths, as pulmonary embolism-related mortality. Finally, we collected information on fatal, intracranial (ICH), major and non-major bleeding (as defined in each study).

2.3. Data extraction

For each study the following data were sought: mean age and gender; number of participants in each treatment arm; proportion of unprovoked VTE; duration, type, and intensity of anticoagulation; incidence of all-cause mortality; deaths due to pulmonary embolism and sudden unexplained death; fatal bleedings and ICH; major and non-major bleedings.

2.4. Assessment of study quality

Two of the authors (CB, VM) independently reviewed the studies included in the meta-analysis to appraise their quality. The risk of bias was
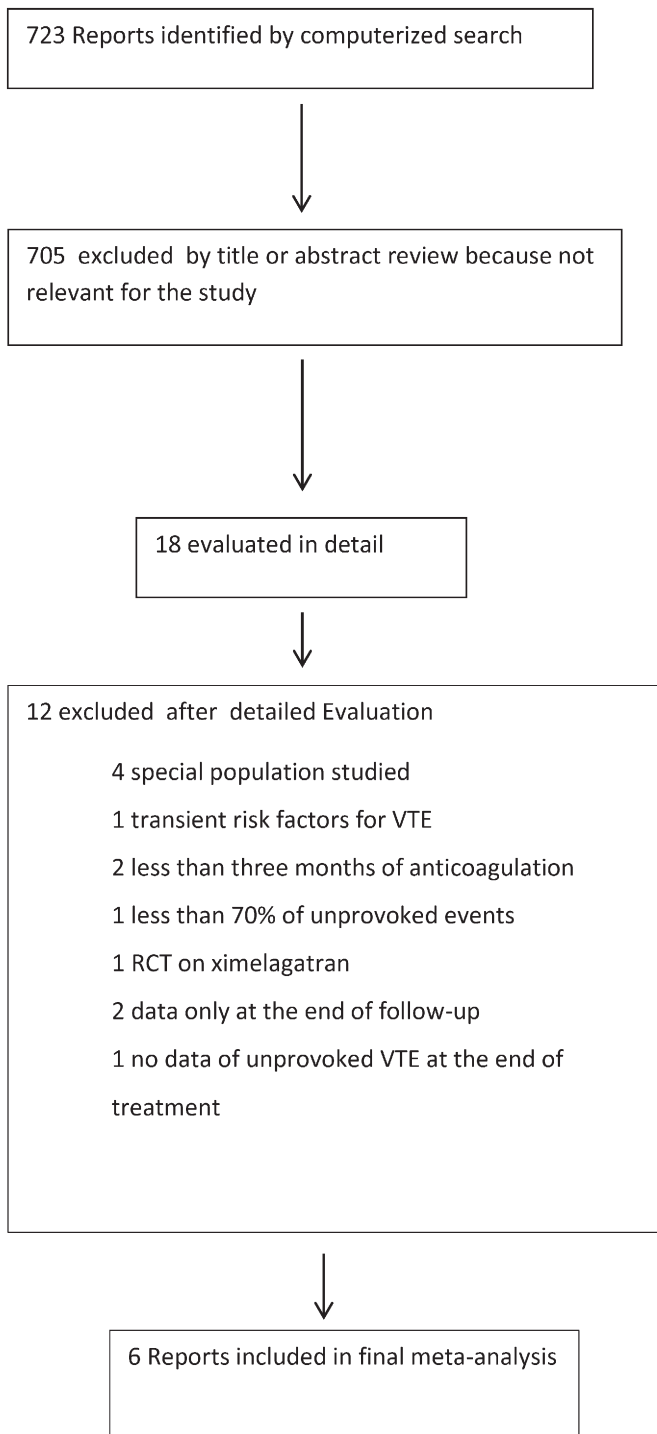
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723 Reports identified by computerized search

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705 excluded by title or abstract review because not relevant for the study

↓

18 evaluated in detail

↓

12 excluded after detailed Evaluation

4 special population studied

1 transient risk factors for VTE

2 less than three months of anticoagulation

1 less than 70% of unprovoked events

1 RCT on ximelagatran

2 data only at the end of follow-up

1 no data of unprovoked VTE at the end of treatment

↓

6 Reports included in final meta-analysis

Fig. 1. Flow diagram of study selection.