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Thrombophilia ad dies vitae

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Chapter 3

Thrombophilia testing for prevention of recurrent venous thromboembolism

Cohn DM, Vansenne F, De Borgie CAJ, Middeldorp S. Thrombophilia testing for prevention of recurrent venous thromboembolism. Cochrane Database Syst Rev 2009;CD007069.

Abstract

Background

Tests for thrombophilia are being performed on a large scale in patients with venous thromboembolism (VTE), even though the benefits of testing are still subject of debate. The most important benefit would be reduction of the risk of recurrent VTE due to additional prophylactic measures.

Objective

To systematically review the available evidence for testing for thrombophilia after VTE, in terms of risk reduction of recurrent VTE.

Methods

We searched the Cochrane Peripheral Vascular Diseases (PVD) Group trials register (last searched 22 April 2008), MEDLINE, EMBASE, and the CENTRAL database (last searched 2008, Issue 2), and reference lists. Randomized controlled trials (RCTs) and Controlled clinical trials (CCTs) comparing the rate of recurrent VTE in patients with VTE who were tested for thrombophilia and patients with VTE who were not tested for thrombophilia were eligible. Data from identified studies was to be extracted and recorded on data extraction forms to allow pooling for meta-analysis.

Results

No studies were included because no RCTs or CCTs could be identified.

Conclusion

There are no trials that assessed the benefit(s) of testing for thrombophilia on the risk of recurrent VTE. RCTs are needed as tests for thrombophilia are being performed widely, even though the benefits have not been demonstrated yet.

Background

Thrombophilia is the term used to describe a hereditary or acquired pre-disposition to venous thromboembolism (VTE). VTE may manifest as either pulmonary embolism or deep vein thrombosis, or a combination of both. The term thrombophilia was first mentioned by Egeberg in 1965, when he described a Norwegian family with a high tendency to thrombosis due to a deficiency in the natural anticoagulant antithrombin.¹ Subsequently, in the 1980s, deficiencies of the other natural anticoagulants, protein C and protein S, were found to increase the risk of VTE.^{2,3}

These deficiencies are rather uncommon, with a prevalence of <1% in the general population⁴⁻⁶ and a prevalence of at most 5% among patients with thrombosis.⁷ During the last two decades, newer and more prevalent thrombophilic defects have been discovered, such as the factor V Leiden mutation which causes activated protein C resistance and the prothrombin G20210A mutation.^{8,9} Also, elevated levels of factor VIII have shown to be a risk factor for thrombosis.^{10,11} It has been found that (mild) hyperhomocysteinaemia is a risk factor for VTE¹², but its clinical relevance seems small, especially since lowering the homocysteine level did not show a reduction in recurrence of VTE.¹³ As nowadays a thrombophilic defect can be demonstrated in at least 50% of patients with a VTE^{14,15}, testing patients with a first VTE for thrombophilia, has gained in interest tremendously. Potential advances of testing patients might be the opportunity to elucidate the cause of the thrombosis in patients or to track unaffected family members. On the other hand, testing for thrombophilia has several potential disadvantages. The psychological consequences of testing patients for thrombophilia might be considered as a drawback of testing. It is not inconceivable that a patient's knowledge of being a carrier of a genetic risk factor might influence his/her well being. In addition, a positive test result for thrombophilia testing might cause problems with health or life insurance. The assessment whether a patient should be tested should mainly depend on the feasibility to reduce the risk of recurrent VTE (for example, by prolonging the duration of anticoagulant treatment). To assess whether testing for thrombophilia reduces the risk of recurrent VTE, a systematic literature search was undertaken. If possible, we aimed to perform a meta-analysis to assess the overall reduction in recurrent VTE after testing for thrombophilia.

Methods

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and controlled clinical trials (CCTs) comparing the rate of recurrent VTE in patients with existing VTE tested for thrombophilia and patients who were not tested for thrombophilia were considered eligible.

Types of participants

Patients with VTE (either deep venous thrombosis or pulmonary embolism, or both).

Types of interventions

The investigated intervention was testing for thrombophilia. Thrombophilia was defined as:

- antithrombin deficiency;
- protein C deficiency;
- protein S deficiency;
- factor V Leiden mutation;
- factor II mutation (prothrombin mutation);
- (mild) hyperhomocysteinaemia;
- persistently elevated levels of clotting factor VIII:c;
- presence of antiphospholipid or anticardiolipin antibodies, or lupus anticoagulant.

Types of outcome measures

The primary outcome measure was recurrent VTE. Secondary outcome measures included:

- major bleeding;
- clinically relevant non-major bleeding
- quality of life

Search methods for identification of studies

The Cochrane Peripheral Vascular Diseases (PVD) Group searched their Trials Register (last searched 22 April 2008) and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (last searched 2008, Issue 2) for publications describing randomized controlled trials (RCTs) or controlled clinical trials (CCTs). The PVD Group's Trials Register was compiled from electronic searches of MEDLINE (1966 to date), EMBASE (1980 to date), and CINAHL (1982 to date), and through hand searching relevant journals. The full list of journals that have been hand searched, as well as the search strategies used are described in the 'Search strategies for the identification of studies' section within the editorial information about the Cochrane PVD Group in The Cochrane Library.

We searched for potentially eligible articles in the MEDLINE, EMBASE and CENTRAL databases. Highly sensitive search filters were used for the identification of RCTs or CCTs.

Table 1. Highly sensitive search filter for MEDLINE

MEDLINE highly sensitive search filter	
#1	randomized controlled trial [pt]
#2	controlled clinical trial [pt]
#3	randomized [tiab]
#4	placebo [tiab]
#5	drug therapy [sh]
#6	randomly [tiab]
#7	trial [tiab]
#8	groups [tiab]
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	humans [mh]
#11	#9 and #10

We used the "Cochrane Highly Sensitive Search Strategy: sensitivity-maximizing version (2008 revision)" filter, published at: <http://www.cochrane-handbook.org> (Chapter 6.4.11 (search filter 6.4a). for identifying randomized trials in MEDLINE (Table 1). For EMBASE, we used the highly sensitive search filter described in the Peripheral Vascular Diseases Group's module in *The Cochrane Library* (Table 2).

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Table 2. Highly sensitive search filter for EMBASE

EMBASE highly sensitive search filter	
1.	random\$.ti,ab.
2.	factorial\$.ti,ab.
3.	(crossover\$ or cross over\$ or cross-over\$).ti,ab.
4.	placebo\$.ti,ab.
5.	(doubl\$ adj blind\$).ti,ab.
6.	(singl\$ adj blind\$).ti,ab.
7.	assign\$.ti,ab.
8.	allocat\$.ti,ab.
9.	volunteer\$.ti,ab.
10.	CROSSOVER PROCEDURE/
11.	DOUBLE-BLIND PROCEDURE/
12.	RANDOMIZED CONTROLLED TRIAL/
13.	SINGLE-BLIND PROCEDURE/
14.	or/1-13
15.	exp ANIMAL/ or NONHUMAN/ or exp ANIMAL EXPERIMENT/
16.	exp HUMAN/
17.	16 and 15
18.	15 not 17
19.	14 not 18

The following search terms, structured as PI(C)O, were used as MeSH and EMTREE terms and free text:

Patients: thromboembolism; venous thrombosis; pulmonary embolism. Intervention: thrombophilia; prothrombin; protein C deficiency; protein S deficiency; antithrombin III deficiency; activated protein C resistance; factor VIII; lupus coagulation inhibitor; antibodies, antiphospholipid; antibodies, anticardiolipin; thrombophil*; hypercoagulabil*; at III; antithrombin; protein C; protein S; apc resistance; factor V; antiphospholipid antibody; anticardiolipin antibody; hyperhomocysteinaemia; homocyst*; hyperhomocyst*. The term "factor V/genetics" is only searched as a MeSH term. Comparison: no specific search terms. Outcome: recurrent VTE. The following words were searched in free text: relapse; recrudescence; recurr*.

The restrictions "pregnancy loss" and "hemophilia" were applied to filter out articles focussing on the association between thrombophilia and recurrent pregnancy loss and articles on hemophilia.

Data collection and analysis

Selection of trials

Two authors (DC and FV) independently screened the titles, abstracts and subsequently review the text of articles that appeared to be eligible. We searched the reference sections of relevant papers for additional articles. The criteria for selection of trials were as specified in the above section 'Criteria for considering studies for this review'.

Quality of trials

Two authors (DC and FV) independently assessed the quality of the methods used in the trials based on methods of randomization. Disagreements were resolved by discussion. Only trials that explicitly affirmed a randomization process were considered eligible. We coded allocation of concealment as adequate (A), unclear (B), inadequate (C) or not used (D), as described in the Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Handbook). Only trials with adequate allocation of concealment were considered eligible. Quality of blinding in this case was not applicable.

Data extraction

Two authors (DC and FV) independently extracted data. Disagreements were resolved by discussion. We recorded the collected data on data extraction forms. If necessary, we contacted the trialists for additional data.

Statistical analysis

If possible, we aimed to perform a meta-analysis to assess the overall effect of testing for thrombophilia on recurrent VTE. Variance would be calculated using the Peto odds ratio, since this method was considered the most appropriate for dichotomous, sparse data without a large effect. Heterogeneity would be calculated by the I-square test and trials were considered heterogenic if I-square > 50%.

Results

The search through the Trial Register revealed no eligible trials. The above mentioned search strategies in MEDLINE and EMBASE yielded 556 and 123 hits, respectively. After screening for title we excluded 523 of the MEDLINE articles. Reasons for exclusion were: review article (95), cohort study (18); case report or case series (141), other outcome measure/other

focus (256) and editorial/rebuttal (13). Of the 33 remaining articles we screened the abstracts. All these studies were excluded, as 11 were reviews, 6 were cohort studies, 1 was a case report, 13 focused on other outcome measures and 1 was an editorial. We identified one outline of an intervention trial that fulfilled the inclusion criteria.^{16,17} However, this trial (our trial) has recently been stopped early due to a low inclusion rate.¹⁸ No conclusions can be drawn from the 23 patients that were included in this intervention trial before it was stopped. From EMBASE, 123 hits were identified, of which at least 47 overlapped with the search in the MEDLINE database. Of the remaining 76 hits, 22 were excluded because they were review articles, 1 was a case report, and 49 had a different outcome measure/other focus. The abstracts of the remaining 3 articles were screened but had to be excluded as 2 articles were reviews and 1 had another focus. From a search through CENTRAL we identified 20 potential trials, of which 19 were not relevant. The remaining trial was the above mentioned NOSTRADAMUS trial.^{16,17}

Discussion

We did not identify completed trials in which testing for thrombophilia was the intervention and recurrent VTE was the outcome measure. Most of the published studies on thrombophilia focused on the prevalence of various thrombophilic defects and lacked the appropriate design. The only trial that assessed the potential benefits and disadvantages of testing for thrombophilia was terminated early due to slow inclusion rates.¹⁸

Implications for practice

There is no information available from RCTs or CCTs on the benefits of thrombophilia testing to reduce the risk of recurrent VTE.

Implications for research

As tests for thrombophilia are being performed widely, even though the benefits have not been demonstrated yet, RCTs are needed. A useful design would be randomization between disclosure and no disclosure of the thrombophilia test results (for both treating physicians and participants). Those patients allocated to the "disclosure" group with a thrombophilic defect should receive a more intense treatment (such as prolongation of the anticoagulant therapy). The primary endpoint would be the composite of recurrent VTE and/or bleeding.

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