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Thrombophilia testing for prevention of recurrent venous thromboembolism (Review)

Cohn DM, Vansenne F, de Borgie CA, Middeldorp S

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Thrombophilia testing for prevention of recurrent venous thromboembolism.
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[Intervention Review]

Thrombophilia testing for prevention of recurrent venous thromboembolism

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ABSTRACT

Background

Tests for thrombophilia are being performed on a large scale in people after venous thromboembolism (VTE) even though the benefits of testing are still subject to debate. The most important benefit would be a reduction in the risk of recurrent VTE due to the use of additional prophylactic measures. This is an update of a review first published in 2009.

Objectives

The objective of this review was to assess the benefit of testing for thrombophilia after VTE in terms of risk reduction of recurrent VTE.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched May 21 2012) and CENTRAL (2012, Issue 5). The authors searched MEDLINE and EMBASE.

Selection criteria

Randomized controlled trials (RCTs) and controlled clinical trials (CCTs) that compared the rate of recurrent VTE in participants with VTE who were tested for thrombophilia with the rate in participants with VTE who were not tested were eligible.

Data collection and analysis

We planned to extract data from identified studies using data extraction forms.

Main results

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

Authors' conclusions

There are currently no randomized controlled trials or controlled clinical trials that have assessed the benefit(s) of testing for thrombophilia on the risk of recurrent VTE.

PLAIN LANGUAGE SUMMARY

Thrombophilia testing for the prevention of recurrent venous thromboembolism

Thrombophilia is the term used to describe an hereditary or acquired predisposition to thromboembolism (the formation of a venous clot), which manifests itself as either deep vein thrombosis (DVT) or pulmonary embolism (PE). The presence of thrombophilia can be tested and many people with venous thrombosis or pulmonary embolism nowadays have their blood tested for a deficiency in natural anticoagulants such as antithrombin, protein C, or protein S. However, the benefits of these costly tests are uncertain. The most important benefit would be a reduction in the risk of developing a new venous clot by taking preventative measures. To date no high quality trials have assessed this issue.

BACKGROUND

Thrombophilia is the term used to describe an hereditary or acquired pre-disposition to thromboembolism. Venous thromboembolism (VTE) manifests itself as either pulmonary embolism or deep vein thrombosis. The term thrombophilia was first referred to 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 (Egeberg 1965). Subsequently, in the 1980s, deficiencies of other natural anticoagulants, protein C and protein S, were found to increase the risk of VTE (Mannucci 1982; Schwarz 1984).

These deficiencies are rather uncommon, with a prevalence of less than 1% in the general population (Miletich 1987; Tait 1994; Tait 1995) and a prevalence of at most 5% among patients with thrombosis (Christiansen 2005). 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 (Bertina 1994) and the prothrombin G20210A mutation (Poort 1996). Also, elevated levels of factor VIII have been shown to be a risk factor for thrombosis (Koster 1995; Kraaijenhagen 2000). It has been found that (mild) hyperhomocysteinemia is also a risk factor for VTE (den Heijer 1996) but its clinical relevance seems small, especially since lowering the homocysteine level did not show a reduction in the recurrence of VTE (den Heijer 2007). As nowadays a thrombophilic defect can be demonstrated in at least 50% of people with VTE (Bauer 2001; Lane 1996), testing patients with a first VTE for thrombophilia has gained great interest. Potential advances of testing patients might be the opportunity to elucidate the cause of the thrombosis or to track unaffected family members. On the other hand, there are several potential disadvantages of testing for thrombophilia. The psychological consequences of testing people for thrombophilia might be considered as a drawback of testing. It is not inconceivable that a person's knowledge of being a carrier of a genetic risk factor might influence his or her well being. In addition, a positive test result for thrombophilia might cause problems with health or life insurance. The assessment of whether a person should be tested should mainly depend on the feasibility of reducing 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 we undertook a systematic literature search. We intended to perform a meta-analysis to assess the overall reduction in recurrent VTE after testing for thrombophilia.

OBJECTIVES

To assess whether testing for thrombophilia is beneficial in terms of reducing the rate of recurrent VTE.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and controlled clinical trials (CCTs) that compared the rate of recurrent VTE in patients with existing VTE who were tested for thrombophilia with the rate in 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 intervention under investigation was testing for thrombophilia. Thrombophilia was defined as:

1. antithrombin deficiency;
2. protein C deficiency;
3. protein S deficiency;
4. factor V Leiden mutation;
5. factor II mutation (prothrombin mutation);
6. (mild) hyperhomocysteinemia;
7. persistently elevated levels of clotting factor VIII:c;
8. presence of antiphospholipid or anticardiolipin antibodies, or lupus anticoagulant.

Types of outcome measures

Primary outcomes

The primary outcome measure was recurrent VTE.

Secondary outcomes

Secondary outcome measures included:

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

Search methods for identification of studies

Electronic searches

2012 update searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched May 21 2012) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 5, part of *The Cochrane Library*, www.thecochranelibrary.com. See Appendix 1 for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

The authors re-ran the EMBASE and MEDLINE searches which are outlined in the text of the 2008 searches below.

2008 searches

The authors searched for potentially eligible articles in the MEDLINE, EMBASE and CENTRAL databases. In MEDLINE, a highly sensitive search filter was used for the identification of

RCTs or CCTs (Robinson 2002) that was obtained through the website of the Dutch Cochrane Centre: (http://www.cochrane.nl/index.html) (Appendix 2). As this search filter appeared to be superseded, we decided to apply the 'Cochrane highly sensitive search strategy' for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) published at: http://www.cochrane-handbook.org (Chapter 6.4.11 (search filter 6.4a). For EMBASE, we used the highly sensitive search filter described in the PVD Group's module in *The Cochrane Library* (Appendix 3).

The following search terms, structured as PI(C)O, were used as MeSH and EMTREE terms and as 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; hyperhomocysteinemia; 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 focusing on the association between thrombophilia and recurrent pregnancy loss and articles on hemophilia, respectively.

Searching other resources

We searched the reference sections of relevant papers for additional articles.

Data collection and analysis

Selection of trials

Two authors (DC and FV) independently screened the titles and abstracts and subsequently reviewed the text of articles that appeared to be eligible. 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 as randomized controlled trials. 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 (Higgins 2006). Only trials with adequate allocation of concealment were considered eligible. Quality of blinding was not applicable for this intervention.

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

We intended to perform a meta-analysis to assess the overall effect of testing for thrombophilia on recurrent VTE. Variance would have been calculated using the Peto odds ratio since this method was considered the most appropriate for dichotomous, sparse data without a large effect. Heterogeneity would have been calculated by the I^2 test and trials were considered heterogenic with $I^2 > 50\%$.

RESULTS

Description of studies

No studies were included in the review.

2012 update searches

The 2012 update searches of the PVD Group Specialised Register and CENTRAL revealed no relevant eligible trials.

The authors searches resulted in a total of 233 new citations in the EMBASE database, but none of these fulfilled the search criteria. In the MEDLINE database 196 new citations were identified, but again, none of these were relevant.

2008 searches

The 2008 searches 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 or focus (256); and an editorial or rebuttal (13). Of the 33 remaining articles we screened the abstracts. All these studies were excluded as: 11 were reviews; six were cohort studies; one was a case report; 13 focused on other outcome measures; and one was an editorial.

We identified one outline of an intervention trial (Nostradamus Study) that fulfilled the inclusion criteria (Cohn 2007a; Cohn 2007b). However, this trial (our trial) has recently been stopped early due to a low inclusion rate (Cohn 2008). 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, one was a case report, and 49 had a different outcome measure or focus. The abstracts of the remaining three articles were screened but had to be excluded as two articles were reviews and one had another focus. From a search of CENTRAL we identified 20 potential trials, of which 19 were not relevant. The remaining trial was the above mentioned Nostradamus Study (Cohn 2007a; Cohn 2007b).

Risk of bias in included studies

Not applicable since no studies were included in the review.

Effects of interventions

Not applicable since no studies were included in the review.

DISCUSSION

We did not identify any 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 (Cohn 2008).

AUTHORS' CONCLUSIONS

Implications for practice

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

Implications for research

Given the fact that tests for thrombophilia are being widely performed, even though the benefits have not yet been demonstrated, randomized controlled trials 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 and with a thrombophilic defect should receive a modified treatment (such as prolongation of anticoagulant therapy). The primary endpoint would be the composite outcome of recurrent VTE and bleeding.

REFERENCES

References to studies excluded from this review

Nostradamus Study *{published data only}*

Cohn DM, Middeldorp S. A multicenter randomised clinical trial to evaluate the benefit of testing for thrombophilia following a first venous thromboembolism: the NOSTRADAMUS study. *Nederlands Tijdschrift Voor Geneeskunde* 2007;**151**(6):371-3.

* Cohn DM, Middeldorp S. Early termination of the multicentre randomised clinical trial to evaluate the benefit of testing for thrombophilia following a first venous thromboembolism: the NOSTRADAMUS study. *Nederlands Tijdschrift Voor Geneeskunde* 2008;**152**(38):2093-4.

Cohn DM, Middeldorp S. Necessity of screening for thrombophilia at diagnosis of venous thromboembolism: outline of the NOSTRADAMUS intervention trial. *Journal of Thrombosis and Haemostasis* 2007;**5 Suppl 2**:abstract no:P-M469.

Additional references

Bauer 2001

Bauer KA. The thrombophilias: well-defined risk factors with uncertain therapeutic implications. *Annals of Internal Medicine* 2001;**135**(5):367-73.

Bertina 1994

Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994;**369**(6475):64-7.

Christiansen 2005

Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA* 2005;**293**(19):2352-61.

Cohn 2007a

Cohn DM, Middeldorp S. A multicenter randomised clinical trial to evaluate the benefit of testing for thrombophilia following a first venous thromboembolism: the NOSTRADAMUS study. *Nederlands Tijdschrift Voor Geneeskunde* 2007;**151**(6):371-3.

Cohn 2007b

Cohn DM, Middeldorp S. Necessity of screening for thrombophilia at diagnosis of venous thromboembolism: outline of the NOSTRADAMUS intervention trial. *Journal of Thrombosis and Haemostasis* 2007;**5 Suppl 2**:abstract no:P-M469.

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den Heijer 1996

den Heijer M, Koster T, Blom HJ, Bos GM, Briet E, Reitsma PH, et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. *New England Journal of Medicine* 1996;**334**(12):759-62.

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Egeberg 1965

Egeberg O. Inherited antithrombin deficiency causing thrombophilia. *Thrombosis et Diathesis Haemorrhagica* 1965;**13**:516-30.

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Higgins JPT, Green S, editors. Assessment of study quality. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Section 6. www.cochrane.org/resources/handbook/hbook.htm (accessed 25 September 2007).

Koster 1995

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Kraaijenhagen 2000

Kraaijenhagen RA, in't Anker PS, Koopman MM, Reitsma PH, Prins MH, van den Ende A, et al. High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. *Thrombosis and Haemostasis* 2000;**83**(1):5-9.

Lane 1996

Lane DA, Mannucci PM, Bauer KA, Bertina RM, BochKov NP, Boulyjenkov V, et al. Inherited thrombophilia: Part 2. *Thrombosis and Haemostasis* 1996;**76**(6):824-34.

Mannucci 1982

Mannucci PM, Vigano S. Deficiencies of protein C, an inhibitor of blood coagulation. *Lancet* 1982;**2**(8296):463-7.

Miletich 1987

Miletich J, Sherman L, Broze G Jr. Absence of thrombosis in subjects with heterozygous protein C deficiency. *New England Journal of Medicine* 1987;**317**(16):991-6.

Poort 1996

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Robinson 2002

Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *International Journal of Epidemiology* 2002;**31**(1):150-3.

Schwarz 1984

Schwarz HP, Fischer M, Hopmeier P, Batard MA, Griffin JH. Plasma protein S deficiency in familial thrombotic disease. *Blood* 1984;**64**(6):1297-300.

Tait 1994

Tait RC, Walker ID, Perry DJ, Islam SI, Daly ME, McCall F, et al. Prevalence of antithrombin deficiency in the healthy population. *British Journal of Haematology* 1994;**87**(1):106-12.

Tait 1995

Tait RC, Walker ID, Reitsma PH, Islam SI, McCall F, Poort SR, et al. Prevalence of protein C deficiency in the healthy population. *Thrombosis and Haemostasis* 1995;**73**(1):87-93.

References to other published versions of this review

Cohn 2009

Cohn D, Vansenne F, de Borgie C, Middeldorp S. Thrombophilia testing for prevention of recurrent venous thromboembolism. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD007069.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Nostradamus Study	Randomized controlled trial that was stopped early due to a low inclusion rate of 23 participants.

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor Thrombosis, this term only	1118
#2	MeSH descriptor Thromboembolism, this term only	954
#3	MeSH descriptor Venous Thromboembolism, this term only	208
#4	MeSH descriptor Venous Thrombosis explode all trees	2119
#5	(thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):ti,ab,kw	11119
#6	MeSH descriptor Pulmonary Embolism explode all trees	817
#7	(PE or DVT or VTE):ti,ab,kw	2098
#8	((vein* or ven*) near thromb*):ti,ab,kw	4682
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	12764
#10	MeSH descriptor Thrombophilia explode all trees	273
#11	MeSH descriptor Hyperhomocysteinemia explode all trees	184
#12	MeSH descriptor Factor V explode all trees	80

(Continued)

#13	MeSH descriptor Prothrombin explode all trees	335
#14	MeSH descriptor Blood Coagulation Factors, this term only	307
#15	MeSH descriptor Factor VIII explode all trees	249
#16	MeSH descriptor Antibodies, Antiphospholipid explode all trees	88
#17	MeSH descriptor Protein C explode all trees with qualifier: BL	0
#18	MeSH descriptor Protein C explode all trees	210
#19	MeSH descriptor Protein S explode all trees	58
#20	MeSH descriptor Factor V explode all trees	80
#21	thrombophilia	204
#22	(protein or APC) near3 resist*	293
#23	(protein near3 defici*)	178
#24	G20210A	29
#25	factor near2 (8 or VIII)	627
#26	factor near2 (II or 2)	1288
#27	factor near2 (5 or V)	429
#28	(antithrombin or anti-thrombin) near3 defic*	48
#29	leiden	1454
#30	hyperhomocyst* or hyper-homocyst*	410
#31	antiphospholipid or anti-phospholipid	186
#32	anticardiolipin or anti-cardiolipin	97
#33	lupus near3 anticoag*	63
#34	F5G1691A or FVR506Q or F2G20210A or "FV R506Q"	1
#35	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34)	5374
#36	(#9 AND #35)	564

Appendix 2. MEDLINE highly sensitive search filter

((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR "latin square" [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR

prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]).

As the above mentioned search strategy appeared to be superseded, we decided to apply the "Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision), published at: http://www.cochrane-handbook.org (Chapter 6.4.11 (search filter 6.4a)

#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

Appendix 3. 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

WHAT'S NEW

Date	Event	Description
20 November 2012	Review declared as stable	No new studies have been identified since 2009. This Cochrane review has been marked stable and will only be updated when new studies are identified.

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 1, 2009

Date	Event	Description
4 July 2012	New citation required but conclusions have not changed	Minor copy edits made. The review was assessed as up to date. Conclusions not changed.
4 July 2012	New search has been performed	Searches re-run, no new trials found. The review was assessed as up to date.
9 February 2009	Amended	Correction to placement of search strategy and spelling error.
6 May 2008	Amended	New MEDLINE highly sensitive search filter added.

CONTRIBUTIONS OF AUTHORS

DC and FV independently screened titles, assessed study quality, and extracted data. Both authors contributed to the text of the review.
CdB critically revised the manuscript for important intellectual content.
SM supervised the preparation of the systematic review in all of its phases.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Chief Scientist Office, Scottish Government Health Directorates, Scottish Government, UK.

  The PVD Group editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As the search filter for Pubmed described in the protocol appeared to be superseded, we decided to apply the 'Cochrane highly sensitive search strategy' for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) published at: http://www.cochrane-handbook.org (Higgins 2006) (Chapter 6.4.11 (search filter 6.4a).

INDEX TERMS

Medical Subject Headings (MeSH)

Secondary Prevention; Thrombophilia [complications] [*diagnosis]; Venous Thromboembolism [etiology] [*prevention & control]

MeSH check words

Humans