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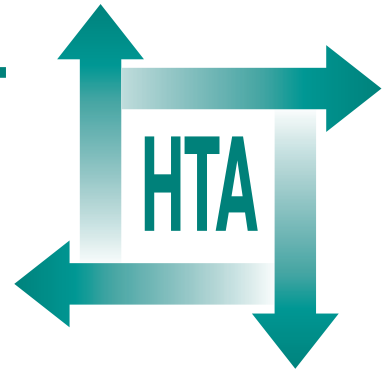

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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The research reported in this monograph was commissioned by the HTA Programme as project number 01/04/03. The contractual start date was in July 2002. The draft report began editorial review in March 2004 and was accepted for publication in September 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study

O Wu,[1] L Robertson,[1] S Twaddle,[2] GDO Lowe,[2,3] P Clark,[4] M Greaves,[5] ID Walker,[3] P Langhorne,[3] I Brenkel,[6] L Regan[7] and IA Greer[1*]

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Objectives: To assess the risk of clinical complications associated with thrombophilia in three high-risk patient groups: women using oral oestrogen preparations, women during pregnancy and patients undergoing major orthopaedic surgery. To assess the effectiveness of prophylactic treatments in preventing venous thromboembolism (VTE) and adverse pregnancy outcomes in women with thrombophilia during pregnancy and VTE in patients with thrombophilia, undergoing major orthopaedic surgery. To evaluate the relative cost-effectiveness of universal and selective VTE history-based screening for thrombophilia compared with no screening in the three high-risk patient groups.
Data sources: Electronic databases including MEDLINE, EMBASE, and four other major databases were searched up to June 2003.
Review methods: In order to assess the risk of clinical complications associated with thrombophilia, a systematic review of the literature on VTE and thrombophilia in women using oral oestrogen preparations and patients undergoing major orthopaedic surgery; and studies of VTE and adverse obstetric complications in women with thrombophilia during pregnancy was carried out. Meta-analysis was used to calculate pooled odds ratios (ORs) associated with individual clinical outcomes, stratified by thrombophilia type and were calculated for each patient group. To assess the effectiveness of prophylaxis, a systematic review was carried out on the use of prophylaxis in the prevention of VTE and pregnancy loss in pregnant women with thrombophilic defects and the use of thromboprophylaxis in the prevention of VTE in patients with thrombophilia undergoing major elective orthopaedic surgery. Relevant data were summarised according to the patient groups and stratified according to the types of prophylaxis. A narrative summary was provided; where appropriate, meta-analysis was conducted. An incremental cost-effectiveness analysis was then carried out, from the perspective of the NHS in the UK. A decision analytical model was developed to simulate the clinical consequences of four thrombophilia screening scenarios. Results from the meta-analyses, information from the literature and results of two Delphi studies of clinical management of VTE and adverse pregnancy complications were incorporated into the model. Only direct health service costs were measured and unit costs for all healthcare resources used were obtained from routinely collected data and the literature. Cost-effectiveness was expressed as incremental cost-effectiveness ratios (ICERs); an estimate of the cost per adverse clinical complication prevented, comparing screening with no screening, were calculated for each patient group.
Results: In the review of risk of clinical complications, 81 studies were included, nine for oral oestrogen

preparations, 72 for pregnancy and eight for orthopaedic surgery. For oral contraceptive use, significant associations of the risk of VTE were found in women with factor V Leiden (FVL); deficiencies of antithrombin, protein C, or protein S, elevated levels of factor VIIIc; and FVL and prothrombin G20210A. For hormone replacement therapy (HRT), a significant association was found in women with FVL. The highest risk in pregnancy was found for FVL and VTE, in particular, homozygous carriers of this mutation are 34 times more likely to develop VTE in pregnancy than non-carriers. Significant risks for individual thrombophilic defects were also established for early, recurrent and late pregnancy loss; preeclampsia; placental abruption; and intrauterine growth restriction. Significant associations were found between FVL and high factor VIIIc and postoperative VTE following elective hip or knee replacement surgery. Prothrombin G20210A was significantly associated with postoperative pulmonary embolism. However, antithrombin deficiency, MTHFR and hyperhomocysteinaemia were not associated with increased risk of postoperative VTE. In the review of the effectiveness of prophylaxis, based on available data from eight studies, low-dose aspirin and heparin was found to be the most effective in preventing pregnancy loss in thrombophilic women during pregnancy, while aspirin alone was the most effective in preventing minor bleeding. All the studies on thrombophilia and major elective orthopaedic surgery included in the review of risk complications were also used in the review of the effectiveness of thromboprophylaxis. However, there were insufficient data to determine the relative effectiveness of different thromboprophylaxis in preventing VTE in this patient group. For the cost-effectiveness analysis, of all the patient groups evaluated, universal screening of women prior to prescribing HRT was the most cost-effective (ICER £6824). In contrast, universal screening of women prior to prescribing combined oral contraceptives was the least cost-effective strategy (ICER £202,402). Selective thrombophilia screening based on previous personal and/or family history of VTE was more cost-effective than universal screening in all the patient groups evaluated.

Conclusions: Thrombophilia is associated with increased risks of VTE in women taking oral oestrogen preparations and patients undergoing major elective orthopaedic surgery, and of VTE and adverse pregnancy outcomes in women with thrombophilia during pregnancy. There is considerable difference in the magnitude of the risks among different patient groups with different thrombophilic defects. In women who are on combined oral contraceptives, the OR of VTE among those who are carriers of the FVL mutation was 15.62 (95% confidence interval 8.66 to 28.15). However, in view of the prevalence of thrombophilia and the low prevalence of VTE in non-users of combined oral contraceptives, the absolute risk remains low. Significant risks for VTE and adverse pregnancy outcomes have been established with individual thrombophilic defects. Thrombophilic defects including FVL, high plasma factor VIIIc levels and prothrombin G20210A are associated with the occurrence of postoperative VTE in elective hip or knee replacement therapy. These associations are observed in patients who were given preoperative thromboprophylaxis and are, therefore, of clinical significance. Universal thrombophilia screening in women prior to prescribing oral oestrogen preparations, in women during pregnancy and in patients undergoing major orthopaedic surgery is not supported by current evidence. The findings from this study show that selective screening based on prior VTE history is more cost-effective than universal screening. Large prospective studies should be undertaken to refine the risks and establish the associations of thrombophilias with VTE among hormone users and in patients undergoing orthopaedic surgery. The relative value of a thrombophilia screening programme to other healthcare programmes needs to be established.

Contents

List of abbreviations

APC	activated protein C
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CRD	Centre for Reviews and Dissemination
DARE	Database of Reviews of Effectiveness
DVT	deep vein thrombosis
ERA	Estrogen Replacement and Atherosclerosis
FVL	factor V Leiden
HERS	Heart and Estrogen/Progestin Replacement Study
ICER	incremental cost-effectiveness ratio
IUGR	intrauterine growth restriction
LMWH	low-molecular-weight heparin
MTHFR	methylene tetrahydrofolate reductase
OR	odds ratio
QALY	quality-adjusted life-year
UFH	unfractionated heparin
VTE	venous thromboembolism

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Thrombophilia is a recognised risk factor for venous thromboembolism (VTE). However, the optimal management is unclear in terms of the need for and effectiveness of antithrombotic interventions, especially in high-risk patient groups, including the use of oral oestrogen preparations, pregnancy and major orthopaedic surgery. Clinicians have come under pressure to initiate thrombophilia testing on an increasing number of patients and thrombophilia screening in selected patient groups has been suggested.

Objectives

The objectives of this study were as follows:

- To assess the risk of clinical complications associated with thrombophilia in three high-risk patient groups: (1) women who are prescribed oral oestrogen preparations, (2) pregnancy and the puerperium and (3) patients undergoing major orthopaedic surgery.
- To assess the effectiveness of prophylactic treatments in preventing VTE and adverse pregnancy outcomes in women with thrombophilia during pregnancy and VTE events in patients with thrombophilia, undergoing major orthopaedic surgery.
- To evaluate the relative cost-effectiveness of universal and selective VTE history-based screening for thrombophilia compared with no screening. Four screening scenarios were assessed: (1) testing women prior to prescribing combined oral contraceptives and restricting prescribing to those tested negative for thrombophilia; (2) testing women prior to prescribing hormone replacement therapy and restricting prescribing to those tested negative for thrombophilia; (3) testing women at the onset of pregnancy and prescribing prophylaxis to those tested positive for thrombophilia; and (4) testing all patients prior to major elective orthopaedic surgery and prescribing extended thromboprophylaxis to those tested positive for thrombophilia.

Methods

Risk of clinical complications

Systematic review and meta-analyses were conducted to establish the risk of clinical complications associated with thrombophilia in women who use oral oestrogen therapy, women who are pregnant and patients undergoing major orthopaedic surgery.

Data sources

All major electronic databases were searched by two independent reviewers: MEDLINE 1966 to June 2003, BIDS (EMBASE) 1980 to June 2003, the Cumulative Index to Nursing and Allied Health Literature print index (CINAHL) 1982 to June 2003, the Cochrane Database of Systematic Reviews 1998 to June 2003, Database of Reviews of Effectiveness (DARE) 1995 to June 2003 and Kings Fund, UK (last accessed June 2003). Relevant keywords related to thrombophilia, oral oestrogen, pregnancy and orthopaedic surgery were used to capture all potentially relevant studies. Only articles published in English were retrieved. This strategy was supplemented by using the Web of Science database to generate a list of articles that cited identified original studies. Handsearching of the abstracts of recent thrombosis conferences and the references of all studies meeting the reference criteria was also carried out.

Review methods

All prospective and retrospective studies of VTE events and thrombophilia in women taking oral oestrogen preparations and patients undergoing major orthopaedic surgery and studies of VTE events and adverse obstetric complications in women with thrombophilia during pregnancy were considered. Only relevant studies that reported categorical data relating to the presence and absence of thrombophilia were included. Data were extracted into prepiloted data extraction forms and the methodological quality of the studies was assessed based on a seven-criterion checklist. Odds ratios (ORs) associated with individual clinical outcomes, stratified by thrombophilia type, were calculated for each patient group. Meta-analysis was conducted based

on the random effects model. Testing of heterogeneity was carried out with the standard χ^2 test.

The effectiveness of prophylaxis

Systematic review and meta-analyses were conducted to assess the effectiveness of prophylactic treatments in preventing VTE and adverse pregnancy outcomes in women with thrombophilia during pregnancy and VTE events in patients with thrombophilia, undergoing major orthopaedic surgery.

Data sources

All major electronic databases were searched by two independent reviewers: MEDLINE 1966 to June 2003, BIDS (EMBASE) 1980 to June 2003, the Cumulative Index to Nursing and Allied Health Literature print index (CINAHL) 1982 to June 2003, the Cochrane Database of Systematic Reviews 1998 to June 2003, Database of Reviews of Effectiveness (DARE) 1995 to June 2003 and Kings Fund, UK (last accessed June 2003). Relevant keywords related to thrombophilia pregnancy, and orthopaedic surgery were used to capture all potentially relevant studies. Only articles published in English were retrieved. This strategy was supplemented by using the Web of Science database to generate a list of articles that cited identified original studies. Handsearching of the abstracts of recent thrombosis conferences and the references of all studies meeting the reference criteria was also carried out.

Review methods

All prospective and retrospective studies containing data on the use of all types of prophylaxis in the prevention of VTE and pregnancy loss in women with thrombophilic defects who are pregnant and the use of thromboprophylaxis in the prevention of VTE in patients with thrombophilia undergoing major elective orthopaedic surgery were considered. Only relevant studies that reported categorical data relating to the presence and absence of thrombophilia, with the use of prophylaxis, were included. Data were extracted into prepiloted data extraction forms and the methodological quality of the studies was assessed based on a seven-criterion checklist. These were summarised according to the patient groups and stratified according to the types of prophylaxis. A narrative summary was provided; where appropriate, meta-analysis was conducted based on the random effects model. Testing of heterogeneity was carried out with the standard χ^2 test.

Cost-effectiveness analysis

An incremental cost-effectiveness analysis was conducted, from the perspective of the NHS in the UK, to determine the relative cost-effectiveness in universal and selective, history-based screening for thrombophilia in these patient groups. A decision analytical model was developed to simulate the clinical consequences of four thrombophilia screening scenarios: screening women prior to prescribing combined oral contraceptives, screening women prior to prescribing hormone replacement therapy, screening women at the onset of pregnancy (week six of gestation) and screening patients prior to major orthopaedic surgery. The probabilities of individual clinical events were derived from the meta-analyses and information from the literature. Healthcare resource use was determined by two Delphi studies of clinical management of VTE and adverse pregnancy complications. Only direct health service costs were measured and unit costs for all healthcare resources used were obtained from routinely collected data and the literature. Cost-effectiveness was expressed as incremental cost-effectiveness ratios (ICERs). The ICERs, which were presented as costs per adverse clinical complication prevented when comparing universal and selected screening with no screening, were calculated for each patient group.

Results

Risk of clinical complications

Of all the studies identified from the search, 201 related to oral oestrogen preparation, 234 to pregnancy and 149 to orthopaedic surgery. Overall, 81 studies were included in the review, nine for oral oestrogen preparations, 72 for pregnancy and eight for orthopaedic surgery. Reasons for exclusion included inappropriate study type (such as reviews, and editorials), inappropriate study population, no categorical measure of the presence or absence of thrombophilia and inappropriate clinical outcomes.

Oral oestrogen preparations

The highest risk of VTE in oral contraceptive users was observed in women with factor V Leiden (FVL), with an OR of 15.62 [95% confidence interval (CI) 8.66 to 28.15] calculated. Deficiencies of antithrombin (OR 12.60; 95% CI 1.37 to 115.79), protein C (OR 6.33; 95% CI 1.68 to 23.87) or protein S (OR 4.88; 95% CI 1.39 to 17.10) and elevated levels of factor VIIIc (OR 8.80) were also significantly associated with venous

thromboembolism in oral contraceptive use. For hormone replacement therapy, a significant association was found in women with FVL (OR 13.16; 95% CI 4.28 to 40.47).

Pregnancy

The highest risk in pregnancy was found for FVL and VTE. Results of the meta-analysis suggested that homozygous carriers of this mutation are 34 times more likely to develop VTE in pregnancy than non-carriers of the mutation. Significant risks for individual thrombophilic defects were also established for early pregnancy loss (ORs ranging from 2.49; 95% CI 1.24 to 5.00 observed with prothrombin G202010A to 6.25; 95% CI 1.37 to 28.42 observed with hyperhomocysteinaemia); recurrent pregnancy loss (ORs ranging from 1.91; 95% CI 1.01 to 3.61 observed with FVL to 2.70; 95% CI 1.37 to 5.35 observed with prothrombin G20210A); late pregnancy loss (ORs ranging from 2.06; 95% CI 1.10 to 3.86 observed with FVL to 20.09; 95% CI 3.70 to 109.15 observed with protein S deficiency); preeclampsia (ORs ranging from 1.32; 95% CI 1.05 to 1.66 observed with methylene tetrahydrofolate reductase (MTHFR) to 3.49; 95% CI 1.21 to 10.11 observed with hyperhomocysteinaemia); placental abruption (ORs ranging from 4.26; 95% CI 1.63 to 11.12 observed with hyperhomocysteinaemia to 7.71; 95% CI 3.01 to 19.76 observed with prothrombin G20210A) and intrauterine growth restriction (IUGR) (ORs ranging from 2.91; 95% CI 1.13 to 7.54 observed with prothrombin G20210A to 15.20; 95% CI 1.32 to 174.96 observed with homozygous FVL).

Orthopaedic surgery

Significant associations were found between FVL (OR 1.86; 95% CI 1.27 to 2.74) and high factor VIIIc (OR 1.65; 95% CI 1.06 to 2.58) and postoperative VTE following elective hip or knee replacement surgery. Prothrombin G20210A was significantly associated with postoperative pulmonary embolism (OR 9.14; 05% CI 2.27 to 36.89). However, antithrombin deficiency, MTHFR and hyperhomocysteinaemia were not associated with increased risk of postoperative venous thromboembolism.

The effectiveness of prophylaxis

Of all the studies identified from the search, eight studies evaluated the effectiveness of prophylactic interventions in pregnant women with thrombophilia. Low-dose aspirin and heparin was the most effective in preventing pregnancy loss in thrombophilic women during pregnancy (OR 1.62; 95% CI 0.51 to 5.10), whereas aspirin alone was the most effective in preventing minor bleeding (OR 1.68; 95% CI 0.38 to 7.39). However, there were insufficient data to demonstrate statistically significant associations.

All the studies on thrombophilia and major elective orthopaedic surgery included in the review of risk complications were also used in the review of the effectiveness of thromboprophylaxis. However, there were insufficient data to determine the relative effectiveness of different thromboprophylaxis in preventing VTE in this patient group.

Cost-effectiveness analysis

Based on a hypothetical model of 10,000 patients in each screening scenario, in the absence of thrombophilia screening, adverse clinical complications would be found in approximately seven women on combined oral contraceptives, 104 women on hormone replacement therapy, 2921 pregnant women and 1265 patients undergoing major orthopaedic surgery, at costs of £119,147, £1,185,428, £513,591 and £1,217,935, respectively.

When taking effectiveness of screening into account, universal screening of patients prior to prescribing hormone replacement therapy and restricting prescribing to those tested negative for thrombophilia would prevent 42 VTE events in this hypothetical population and was the most cost-effective screening strategy (ICER £6824). In contrast, screening women prior to prescribing combined oral contraceptives would only prevent three VTE events and was the least cost-effective strategy (ICER £200,402).

Irrespective of patient groups, selective screening based on the presence of previous personal or family history of VTE prevented fewer cases of adverse clinical complications but was more cost-effective than universal screening in all four screening scenarios.

Conclusions

Implications for healthcare

Thrombophilia is associated with increased risks of VTE in women taking oral oestrogen preparations and patients undergoing major elective orthopaedic surgery, and VTE and adverse pregnancy outcomes in pregnancy. There is considerable difference in the magnitude of the risks among different patient groups with different thrombophilic defects.

In women who are on combined oral contraceptives, the ORs of VTE among those who are carriers of the FVL mutation was 15.62. However, in view of the prevalence of thrombophilia and the low prevalence of VTE in non-users of combined oral contraceptives, the absolute risk remains low.

Significant risks for VTE and adverse pregnancy outcomes have been established with individual thrombophilic defects.

Thrombophilic defects including FVL, high plasma factor VIIIc levels and prothrombin G20210A are associated with the occurrence of postoperative VTE in elective hip or knee replacement therapy. These associations are observed in patients who were given preoperative thromboprophylaxis and are, therefore, of clinical significance.

Universal thrombophilia screening in women prior to prescribing oral oestrogen preparations, in women during pregnancy and in patients undergoing major orthopaedic surgery is not supported by the evidence. The findings from this study show that selective screening based on prior VTE history is more cost-effective than universal screening.

Recommendations for research

- Large prospective studies should be undertaken to refine the risks and establish the associations of thrombophilias with venous thromboembolism among hormone users and in patients undergoing orthopaedic surgery.
- The relative value of a thrombophilia screening programme to other healthcare programmes needs to be established.

Chapter 1
Background

Thrombophilia may be inherited or acquired or be the result of an interaction between inheritance and the environmental factors such as oestrogen use, obesity or other lifestyle factors.[1] To date, a limited number of genetic variants have been proven to be independent risk factors for thromboembolism (VTE). These include mutations in the genes encoding the natural anticoagulants antithrombin, protein C and protein S and the clotting factors fibrinogen, prothrombin and factor V. The most widely studied acquired thrombophilias are the antiphospholipid syndromes, characterised by persisting lupus inhibitor activity and/or elevated anticardiolipin levels in association with thrombotic problems or pregnancy morbidity. In some instances, for example elevated factor VIII, non-factor V Leiden (FVL) activated protein C (APC) resistance or elevated homocysteine levels, the changes are the result of interactions between genetic and environmental factors.

Population screening studies have shown that a reduction in antithrombin function may be evident in as many as one in 200–400 individuals.[2,3] Inherited deficiency of protein C has been estimated to occur in one in 300–500 of the population,[4,5] but to date the prevalence of protein S deficiency has not been established in a large-scale study of healthy individuals. Estimation of plasma levels of these factors is also dependent on age, sex,[6] lipid levels, oestrogen[7] and anticoagulant use. The FVL mutation occurs in 2–7% of Caucasian population[8] and the prothrombin G20210A mutation in around 2%.[9] The prevalence of high concentrations of factor VIIc and hyperhomocysteinaemia depend on the 'cut-off' applied. This also applies to the definition of abnormal APC resistance, occurring in the absence of FVL. Factor VIIIc concentrations exceeding 150 IU/dl have been reported in 11% of the general population and in 25% of subjects with venous thrombosis.[10] High levels of factor VIIIc may occur as part of an acute phase response and higher values are observed in subjects with non-FVL APC resistance[11] and in non-blood group O subjects.[12] Plasma homocysteine levels >18.5 mmol/l are found in 5–10% of European populations[12,13] and are associated with >2-fold increased risk of VTE. Hence, the overall prevalence of thrombophilic abnormalities is relatively high, in contrast to the adverse events that may be attributed to these conditions. This reflects the requirement for several thrombotic risk factors to be present for a clinical event to occur.[1] Acquired risk factors can often be identified in subjects presenting with VTE. Tissue trauma, including surgery, immobilisation, cancer, oestrogen use, pregnancy and the puerperium, are prominent participating factors. The attributable risk associated with each of these ranges from 4 to 18%.

Oral oestrogen use in women has been associated with increased risk of VTE. In premenopausal women, the risk of VTE has been shown to increase by about 2–6-fold during the use of combined oral contraceptives, and in peri- and postmenopausal women, 2–4-fold during the use of hormone replacement therapy.[14] In pregnancy and the puerperium, there is growing evidence that women with thrombophilia are at increased risk not only of pregnancy-related VTE, but also other vascular pregnancy complications, including fetal loss, preeclampsia and intrauterine growth restriction (IUGR).[15] One study reported that 65% of women with preeclampsia, IUGR, unexplained stillbirth or placental abruption had a form of heritable or acquired thrombophilia.[16] Patients undergoing major orthopaedic surgery have been recognised as high risk for developing postoperative VTE. However, few studies have investigated thrombophilia and VTE following major orthopaedic surgery. In particular, apparently conflicting results have been reported by studies examining the impact of VTE following APC resistance and/or the FVL mutation on the occurrence of VTE following hip and/or knee replacement.[17–20]

With the developing interest in the role of prothrombotic abnormalities in thrombosis risk, clinicians have come under pressure to initiate laboratory tests on an increasing number of patients. Performance of a comprehensive laboratory screen for thrombophilia has become commonplace in subjects presenting with deep vein thrombosis (DVT) or pulmonary embolism. Indeed, it is estimated that 25,000 tests for APC resistance/FVL are performed each year in the UK.[21] Despite the lack of evidence on the

beneficial value, thrombophilia screening has also been considered in clinical situations where patients are perceived to be at high risk of VTE. However, the clinical and economic value of screening these patient groups for thrombophilia is not clear.

Few studies in the literature have attempted to examine the cost-effectiveness of screening for some thrombophilias in different patient groups.[22–26] The cost of screening for thrombophilia in women prior to prescribing oral contraceptives has been shown to range from US$433 to detect one case of increased activated protein C resistance to US$7795 for protein S deficiency.[23] In another study, Creinin and colleagues[24] estimated that over 92,000 FVL carriers would need to be identified, at costs in excess of US$300 million, to prevent one VTE death attributable to the use of oral contraceptives.

A recent study evaluated the cost-effectiveness of FVL screening in a hypothetical female population who had prior venous thromboembolism events.[25] The study examined three hypothetical cohorts: (1) all patients receiving standard anticoagulation therapy for 6 months without testing, (2) testing and FVL-positive patients receiving 3 years of anticoagulant therapy and (3) testing and FVL-positive patients receiving life-long anticoagulant therapy. The study results showed that of the three scenarios evaluated, testing and treating FVL-positive patients with 3 years of anticoagulation was the preferred screening strategy. However, this was based on a very small margin of relative cost-effectiveness [$279.33 per quality-adjusted life-year (QALY) with testing followed by 3 years of treatment compared with $299.39 per QALY with no screening]; therefore, the authors concluded that screening for FVL is unlikely to be cost-effective.

Only one UK study has assessed the cost-effectiveness of thrombophilia screening and concluded that neither universal nor selective screening based on prior history of VTE was cost-effective in pregnancy.[22] Based on data from a prospective cohort (n = 967), this study reported an additional management cost of £7535 with selective screening and £13,281 with universal screening, compared with no screening for FVL to prevent one vascular event.

Thrombophilia as a whole constitutes an important health problem in terms of its overall prevalence and potential adverse effects. The optimal management is unclear in terms of the need for and effectiveness of antithrombotic interventions, the risks associated with such therapy and the potential to cause harm by restriction of other treatments, such as the combined oral contraceptive pill or hormone replacement therapy. As there is growing pressure on clinicians to perform thrombophilia screens, it is essential to provide an evidence base to guide management and future research priorities in this area.

Chapter 2

Aim of the review

The aims of this review were as follows:

1. To assess the risk of clinical complications associated with thrombophilia in three high-risk patient groups:
   (a) in women who were prescribed combined oral oestrogen preparations
   (b) in pregnancy and the puerperium and
   (c) in patients undergoing major elective orthopaedic surgery
   based on the hypothesis that patients in these groups, with congenital or acquired thrombophilia, are of increased risk of developing adverse clinical outcomes.
2. To assess the effectiveness of prophylactic treatments in various patients groups with thrombophilia:
   (a) in pregnancy and the puerperium and
   (b) in patients undergoing major orthopaedic surgery
   based on the hypothesis that the increased risk of thromboembolism in these patient groups may be reduced by prophylactic treatments.
3. To evaluate the relative cost-effectiveness of universal and selective VTE history-based screening for thrombophilia compared with no screening. Four screening scenarios were assessed:
   (a) testing women prior to prescribing combined oral contraceptives and restricting prescribing to those tested negative for thrombophilia
   (b) testing women prior to prescribing hormone replacement therapy and restricting prescribing to those tested negative for thrombophilia
   (c) testing women at the onset of pregnancy and prescribing prophylaxis to those tested positive for thrombophilia and
   (d) testing of all patients prior to major elective orthopaedic surgery and prescribing extended thromboprophylaxis to those tested positive for thrombophilia.

Chapter 3
Methods

Systematic reviews were conducted to assess the risk of clinical complications associated with thrombophilia and the effectiveness of prophylactic treatments in three high-risk patient groups. A cost-effectiveness analysis was carried out to evaluate the relative cost-effectiveness of universal and selective VTE history-based thrombophilia screening in these patient groups.

The risk of clinical complications

Searching

All major electronic databases were searched by two independent reviewers: MEDLINE 1966 to June 2003, BIDS (EMBASE) 1980 to June 2003, the Cumulative Index to Nursing and Allied Health Literature print index (CINAHL) 1982 to June 2003, the Cochrane Database of Systematic Reviews 1998 to June 2003, Database of Reviews of Effectiveness (DARE) 1995 to June 2003 and King's Fund, UK (last accessed June 2003). Relevant keywords related to thrombophilia (e.g. thrombophilia, hypercoagulable, factor V Leiden, prothrombin, protein C, protein S, antithrombin, methylenetetrahydrofolate reductase, antiphospholipid and anticardiolipin), oral oestrogen (e.g. hormones, oestrogen, progestin, medroxyprogesterone, SERMs, raloxifene, oral contraceptives and hormone replacement), pregnancy (e.g. pregnancy, puerperium and postpartum) and orthopaedic surgery (e.g. hip replacement, knee replacement, hip surgery, knee surgery, orthopaedic surgery, orthopaedic procedures and neck of femur) were used to capture all potentially relevant studies. Only articles published in English were retrieved. This strategy was supplemented by using the Web of Science database to generate a list of articles that cited identified original studies. Handsearching of the abstracts of recent thrombosis conferences (e.g. the British and International Societies of Thrombosis and Haemostasis, and the British and International Societies of Haematology) and the references of all studies meeting the reference criteria was also carried out.

Selection

Types of study

All prospective and retrospective primary studies of thrombophilia in women taking oral oestrogen preparations, women who were pregnant and patients undergoing major elective orthopaedic surgery were included in the review.

Types of participants

Patients with one or more identified thrombophilias from the following groups were included:

- women who were taking oral oestrogen preparations including combined oral contraceptives and hormone replacement therapy
- women who were pregnant or up to 6 weeks postpartum
- patients undergoing major elective orthopaedic surgery including new and revision procedures for total hip replacement, total knee replacement or fractured neck of femur repairs.

All patients with increased APC resistance in the absence of FVL were included as having acquired non-FVL APC resistance. The criteria for the diagnoses of deficiencies of antithrombin, protein C and protein S were activity levels below the lower limit of the normal range (cut-off at 95th percentile): 80% for antithrombin activity, 70% for protein C activity and 55% for protein S antigen level.[27] In the pregnancy group, for deficiencies of antithrombin, protein C and protein S, only cases where the diagnosis was made postpartum were included.

The measurements used to define positive anticardiolipin antibodies and lupus anticoagulants vary in the literature. The most commonly used definition of elevated anticardiolipins was levels of ≥20 GPL and MPL units for IgG and IgM antibodies, respectively. Lupus anticoagulants were considered positive if any of the following assays yielded a positive result: activated partial thromboplastin time, dilute Russell viper venom test and kaolin clotting time. Another form of diagnosing positive lupus anticoagulants was when

prolonged clotting times failed to correct when mixed 1:1 with standard plasma.

Types of outcomes

The major clinical outcomes assessed included:

- Measures of incidence of objectively diagnosed VTE events including DVT, pulmonary embolism and postphlebitic syndrome.
- For the pregnancy group only, adverse pregnancy outcomes including early pregnancy loss (spontaneous loss in the first or second trimester), late pregnancy loss (spontaneous loss in the third trimester), preeclampsia (diastolic blood pressure ≥90 mmHg plus proteinuria[28]), placental abruption, IUGR (birth weight below the tenth centile for gestational age) and postpartum haemorrhage [defined as 'minor' if blood loss was 500–1500 ml and 'major' if blood loss was >1500 ml after childbirth (Scottish Programme for Clinical Effectiveness in Reproductive Health, 1998, No. 149)].
- Mortality.

Various definitions of pregnancy loss were found in the literature, defined according to the timing of loss. For the purpose of this review, the first and second trimester losses were grouped together as early pregnancy loss and late fetal loss was defined as fetal demise at or after 24 weeks gestation'. Where possible, data were presented and analysed separately for recurrent first trimester and non-recurrent second trimester loss.

Validity assessment

An adapted version of a quality checklist recommended by the Centre for Reviews and Dissemination (CRD)[29] was used to assess the quality of all the studies. The CRD quality criteria for assessment of observational studies consist of three separate checklists for cohort studies, case–control studies and case series. For the purpose of this review, which was designed to summarise clinical evidence across various study types, a single checklist was designed for the ease of comparison between studies. Items consistent with the consensus statement of meta-analysis reporting of observational studies in epidemiology[30] were included. The adapted checklist assessed studies against the following methodological criteria: whether the study sample was representative of an inception cohort, whether the comparator group was selected appropriately, whether the outcome assessment was blind to exposure status, whether the groups were comparable on all important confounding factors and, where appropriate, adjustment for confounding was carried out, whether the length of follow-up was sufficient for outcomes to occur and whether loss to follow-up was described. Any disagreement relating to data extraction or quality assessment between the reviewers was resolved by discussion.

Data abstraction

Data from all the studies meeting the inclusion criteria were extracted into prepiloted data extraction forms (Appendix 1) independently by two reviewers (OW, LR). The data extraction process using the extraction forms was initially tested on five studies. The forms completed by the two reviewers were subsequently compared by one of the authors (ST) to ensure that the form was adequately designed and that all the relevant data were recorded by the two reviewers. Reviewers were not blinded to the names of study authors, institutions or publications.

Quantitative data synthesis

The results of the data extraction and quality assessment for each of the studies included in this review were presented in structured tables, grouped according to the patient groups of interest: women on oral oestrogen preparations, women who were pregnant and patients undergoing major elective orthopaedic surgery.

Each study included in the review was summarised according to its odds ratio (OR) associated with VTE and in the pregnancy group, the ORs associated with VTE and each adverse pregnancy outcome, stratified by individual thrombophilic defects, both alone and in combination. ORs >1 indicate an increased risk of VTE events, adverse pregnancy outcomes or mortality associated with hormone use, pregnancy or orthopaedic surgery and thrombophilia.

Where appropriate, meta-analysis was carried out and pooled ORs were calculated based on the random effect model,[31] which accounts for inter-study variations and provides a more conservative estimate of effect than the fixed-effect model. Potential sources of heterogeneity were investigated and assessed using standard the chi-squared (χ^2) test. In addition, the statistic I^2 was also used to investigate heterogeneity by examining the extent of inconsistency across the study results.[32] Sensitivity analysis was carried out to assess the robustness of the results of the meta-analysis.

Effectiveness of prophylaxis

Searching

All major electronic databases were searched by two independent reviewers: MEDLINE 1966 to June

2003, BIDS (EMBASE) 1980 to June 2003, the Cumulative Index to Nursing and Allied Health Literature print index (CINAHL) 1982 to June 2003, the Cochrane Database of Systematic Reviews 1998 to June 2003, Database of Reviews of Effectiveness (DARE) 1995 to June 2003 and Kings Fund, UK (last accessed June 2003). Relevant keywords related to thrombophilia (e.g. thrombophilia, hypercoagulable, factor V Leiden, prothrombin, protein C, protein S, antithrombin, methylenetetrahydrofolate reductase, antiphospholipid and anticardiolipin), pregnancy (e.g. pregnancy, puerperium and postpartum) and orthopaedic surgery (e.g. hip replacement, knee replacement, hip surgery, knee surgery, orthopaedic surgery, orthopaedic procedures and neck of femur), were used to capture all potentially relevant studies. Only articles published in English were retrieved. This strategy was supplemented by using the Web of Science database to generate a list of articles that cited identified original studies. Handsearching of the abstracts of recent thrombosis conferences (e.g. the British and International Societies of Thrombosis and Haemostasis, and the British and International Societies of Haematology) and the references of all studies meeting the reference criteria was also carried out.

Selection

Types of study

Owing to the limited literature available in the use of prophylaxis in patients with thrombophilia, all prospective and retrospective studies containing data on the use of all types of prophylaxis in the prevention of VTE and pregnancy loss in women with thrombophilic defects who are pregnant and the use of thromboprophylaxis in the prevention of VTE in patients with thrombophilia undergoing major elective orthopaedic surgery were included in the review.

Types of participants

Patients with one or more identified thrombophilias from the following groups were included:

- women who were pregnant or up to 6 weeks postpartum or
- patients undergoing major elective orthopaedic surgery, including new and revision procedures for total hip replacement, total knee replacement or fractured neck of femur repairs, who were given prophylaxis.

All patients with increased APC resistance in the absence of FVL were included as having acquired non-FVL APC resistance. The criteria for the diagnoses of deficiencies of antithrombin, protein C and protein S were activity levels below the lower limit of the normal range (cut-off at 95th percentile): 80% for antithrombin activity, 70% for protein C activity and 55% for protein S antigen level.[27] In the pregnancy group, for deficiencies of antithrombin, protein C and protein S, only cases where the diagnosis was made postpartum were included.

The measurements used to define positive anticardiolipin antibodies and lupus anticoagulants vary in the literature. The most commonly used definition of elevated anticardiolipins was levels of ≥20 GPL and MPL units for IgG and IgM antibodies, respectively. Lupus anticoagulants were considered positive if any of the following assays yielded a positive result: activated partial thromboplastin time, dilute Russell viper venom test and kaolin clotting time. Another form of diagnosing positive lupus anticoagulants was when prolonged clotting times failed to correct when mixed 1:1 with standard plasma.

Type of interventions

Prophylactic interventions assessed included:

1. antiplatelet
   (a) aspirin
2. anticoagulants
   (a) heparin
   (b) low-molecular-weight heparin (LMWH)
   (c) coumarin (e.g. warfarin)
   (d) pentasaccharides
3. dextran
4. thrombin inhibitors (e.g. hirudin)
5. plaquinil
6. mechanical devices
   (a) compression devices
   (b) foot pump
   (c) calf compression
   (d) graded compression stockings.

Types of outcomes

The major clinical outcomes assessed included:

- measures of incidence of objectively diagnosed VTE events including DVT, pulmonary embolism and postphlebitic syndrome
- for the pregnancy group, incidence of pregnancy loss
- adverse drug events including haemorrhage, serious wound complications, thrombocytopenia and osteoporotic fractures.

Validity assessment

An adapted version of a quality checklist recommended by the CRD[29] was used to assess the

quality of all the studies. For the purpose of this review, which was designed to summarise clinical evidence across various study types, a single checklist was designed for ease of comparison between studies. The adapted checklist assessed studies against the following methodological criteria: whether the study sample was representative of an inception cohort, whether the comparator group was selected appropriately, whether the outcome assessment was blind to exposure status, whether the groups were comparable on all important confounding factors and, where appropriate, adjustment for confounding was carried out, whether the length of follow-up was sufficient for outcomes to occur and whether loss to follow-up was described. Any disagreement relating to data extraction or quality assessment between the reviewers was resolved by discussion.

Data abstraction

Data from all the studies meeting the inclusion criteria were extracted into prepiloted data extraction forms (Appendix 1) independently by two reviewers (OW, LR). The forms completed by the two reviewers were subsequently compared by one of the authors (ST) to ensure that the form was adequately designed and that all the relevant data were recorded by the two reviewers. Reviewers were not blinded to the names of study authors, institutions or publications.

Quantitative data synthesis

Data relating to the effectiveness of various prophylaxis were extracted from the relevant studies and analysed independently. These were summarised according to the patient groups – pregnancy and orthopaedic surgery – and stratified according to the types of prophylaxis. A narrative summary was provided and, where appropriate, meta-analysis was conducted to calculate pooled ORs based on the random effect model.[31]

Cost-effectiveness analysis

Cost-effectiveness model

An incremental cost-effectiveness analysis was conducted, from the perspective of the NHS in the UK, to determine the relative cost-effectiveness in universal and selective screening based on a personal or family history of VTE compared with no screening for thrombophilia. Following consultation with clinicians, a probabilistic, decision analytical model was developed to analyse a range of possible clinical events associated with screening and no screening for thrombophilia, over a period of 12 months, in four high-risk patient groups (*Figure 1*).

Screening scenarios

It was assumed that thrombophilia screening comprised testing for FVL, prothrombin G20210A, deficiencies of antithrombin III, protein C and protein S, lupus anticoagulants and anticardiolipin antibodies. Four thrombophilia screening scenarios were evaluated:

1. Screening in women prior to prescribing combined oral contraceptives. Those tested positive would be perceived as at increased risk of VTE and would not be prescribed combined oral contraceptives, so avoiding the risk of VTE.
2. Screening in women prior to prescribing hormone replacement therapy. Those tested positive would be perceived as at increased risk of VTE and would not be prescribed hormone replacement therapy, so avoiding the risk of VTE.
3. Screening in women at the onset of pregnancy (week six of gestation). Those tested positive would be perceived as at increased risk of VTE and adverse pregnancy outcomes. These women would be prescribed prophylaxis to prevent VTE and early pregnancy loss.
4. Screening in patients prior to major orthopaedic surgery. Those tested positive would be perceived as at increased risk of VTE and would be given extended thromboprophylaxis to prevent VTE events.

In the universal screening model, all patients in each of the four groups would be tested from thrombophilia. However, in the selective screening model, only those with a previous personal and/or family history of VTE would be tested for thrombophilia.

In the selective screening model, assumptions on the proportion of patients who would have had a prior personal and/or family history of VTE were made. Only data relating to the pregnancy group were found in the literature and were assumed to be 12%.[33] There is evidence in the literature that the risk of VTE is highly dependent on age.[34] The women in the pregnancy group should be of similar age to those in the combined oral contraceptives group. Therefore, the same proportion – 12% of those who had prior VTE history – was also applied to the combined oral contraceptives group. Through discussions with expertise in vascular medicine and orthopaedics

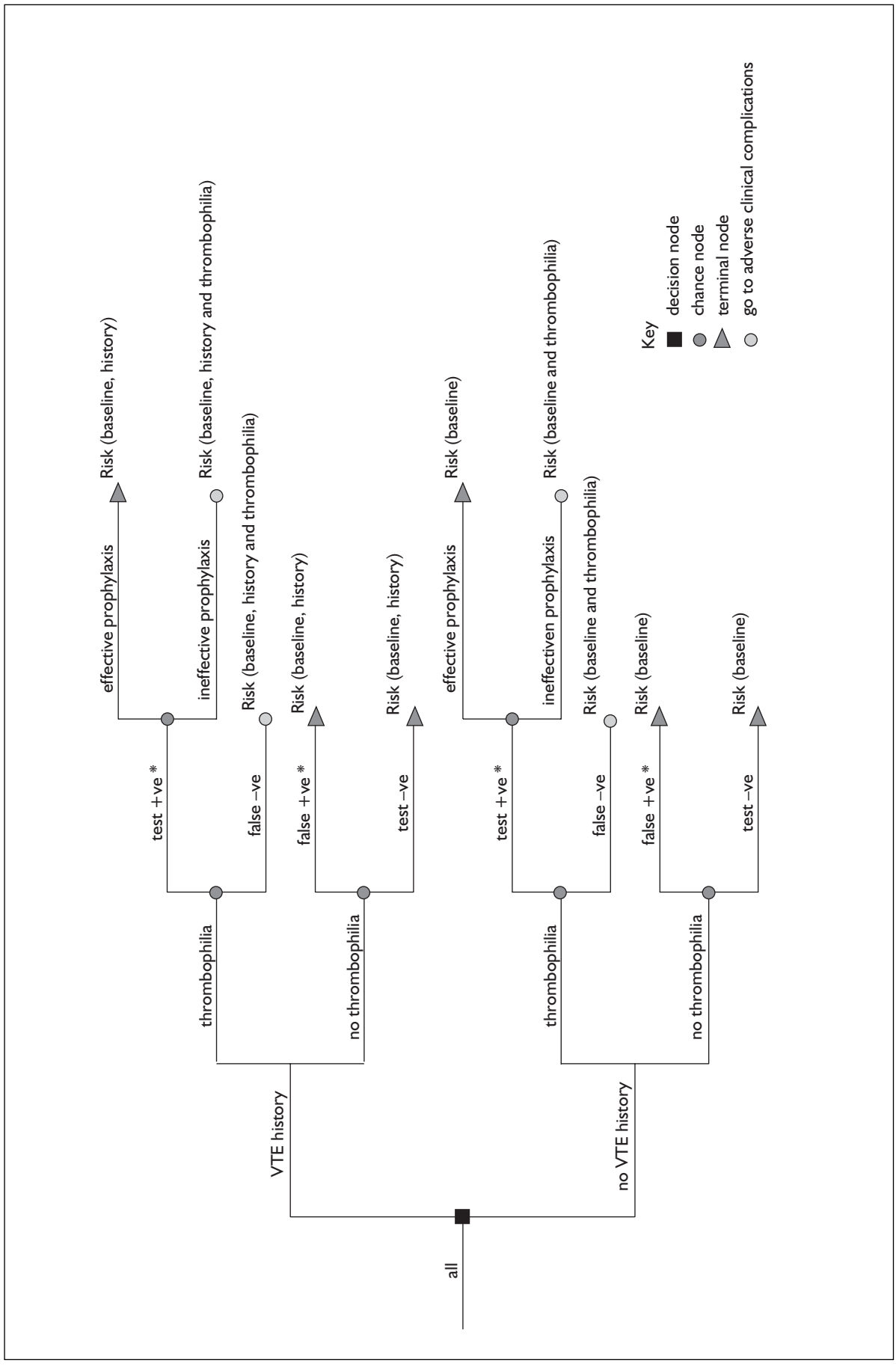

FIGURE 1 *Decision path showing the range of clinical alternatives and possible outcomes in thrombophilia screening*
** Those tested positive in the pregnancy and orthopaedic surgery group will be given thromboprophylaxis and extended thromboprophylaxis, respectively*

and taking into account the age factor, proportions of patients with prior VTE history in the hormone replacement therapy group and the orthopaedic surgery group were assumed to be 15 and 20%, respectively. These assumptions were tested in the sensitivity analysis.

Study cohort

This study consisted of four hypothetical cohorts of 10,000 individuals undergoing thrombophilia screening in different clinical scenarios. These include thrombophilia screening in women prior to prescribing oral oestrogen preparations such as combined oral contraceptives (n = 10,000) and oral hormone replacement therapy (n = 10,000), women at the onset of pregnancy (n = 10,000) and patients prior to major orthopaedic surgery (n = 10,000).

Delphi study

The clinical management strategy and healthcare resource use associated with all major adverse clinical complications were obtained from two Delphi studies. Two questionnaires requiring quantitative and qualitative answers regarding the clinical management of VTE in orthopaedic patients (Appendix 2), and VTE and pregnancy complications in women (Appendix 3) were designed and prepiloted among a small of group of consultants in orthopaedics and obstetrics. Following feedback from the pilot group, appropriate revisions were made to the questionnaires.

The two questionnaires regarding clinical management of VTE in orthopaedic patients and VTE and pregnancy complications were sent to all consultants of orthopaedics (n = 115) and obstetrics (n = 108) in Scotland by post and by email. Respondents were asked to indicate the routine diagnostic and treatment strategies used in patients with DVT, pulmonary embolism and various adverse pregnancy outcomes. In addition, they were also asked to estimate, if any, the average length of hospital stay associated with these clinical complications.

A two-round Delphi study was originally intended, where the results from the first round would be summarised and fed back to the respondents through a second questionnaire. However, the results from the first round of the study showed a high level of convergence among the responses, and average management strategies to the various clinical complications were indicated. Therefore, a second round was not conducted. There was divergence in the estimated length of hospital stay associated with various clinical complications, but owing to the nature of the modelling, an absolute agreed length of stay is not necessary and indeed unlikely in clinical practice. As a result, the mean length of stay was used in the basecase scenario, whereas the range obtained from the Delphi study was used in the sensitivity analysis.

Model inputs

Major clinical outcomes were defined as VTE including DVT and pulmonary embolism, and in the pregnancy arm of the model, adverse pregnancy outcomes including early pregnancy loss, late pregnancy loss, preeclampsia (defined as mild and severe), placental abruption and IUGR, were also incorporated in the model. The respective baseline probabilities and thrombophilia prevalences used in the model were based on published data (*Table 1*). The risks of VTE in thrombophilic patients during oral oestrogen therapy, during pregnancy and during major orthopaedic surgery were determined by the meta-analyses described in the previous sections. Similarly, the risks associated with individual pregnancy complications in thrombophilic patients who were pregnant were also calculated. The estimated ORs for VTE and adverse pregnancy complications associated with individual thrombophilic defects in each patient group were converted into probabilities, taking into account the background rate of events in patients with no additional risks.

Healthcare resource use associated with all clinical complications was obtained from the two Delphi studies and incorporated into the model.

Only direct health service costs were measured. The costs associated with thrombophilia screening and managing associated adverse clinical complications were calculated. The cost of thrombophilia screening consisted of the purchasing and processing cost of the diagnostic tests and staff time and the cost of prophylaxis and extended prophylaxis in the pregnancy and orthopaedics arm, respectively. The costs associated with managing adverse clinical complications included costs of all diagnostic investigations, hospitalisations, outpatient consultations, counselling and drug treatments.

Unit costs for all healthcare resources used were obtained from routinely collected data and the literature. These were combined with the quantity of resource use, which were determined by the results of the Delphi study reflecting expert

TABLE 1 *Probability of events in the model basecase (all values %)*

	No thrombophilia	FVL	Prothrombin G20210A	AT	PC	PS	LA	ACA
Thrombophilia prevalence		2.65[150,151]	2.00[134]	0.20[134]	0.30[134]	0.20[134]	3.00[134]	3.00[134]
VTE								
Combined oral contraceptives	0.03[14]	0.16	0.06	0.13	0.06	0.05	0.06[a]	0.02[a]
Hormone replacement therapy	0.48[152]	5.97	2.85	5.73	2.96	2.3	2.63[a]	1.05[a]
Pregnancy	0.10[153]	0.83	0.68	0.47	0.47	0.32	0.89[a]	0.89[a]
Orthopaedic surgery	6.05 DVT + 1.55 PE[35]	13.27	16.08	42.54	50.93[a]	40.01[a]	31.54[a]	15.32[a]
Adverse pregnancy outcomes:								
Early pregnancy loss	15.00[154]	21.91	30.53	13.44	28.78	38.52	34.39	37.50
Late pregnancy loss	0.50[155]	1.02	1.32	3.69	1.51	9.17	1.18	1.63
Mild preeclampsia	6.00[15]	13.00	13.95	19.98	24.74	15.3	8.47	14.84
Severe preeclampsia (of mild)	3.00 [b]							
Abruption	0.65[156]	2.98	4.80	0.70	3.73	1.36	2.05	0.92
IUGR	5.00[157]	7.90	13.28	9.09	22.29	6.68	49.51	15.25
Deep vein thrombosis (of VTE)	70.00[b]							
Pulmonary embolism (of VTE)	30.00[b]							
Sensitivity of tests	80.00[b]							
Specificity of tests	80.00[b]							
Effectiveness of prophylaxis	50.00[22,35]							

ACA, anticardiolipin antibodies; AT, antithrombin deficiency; FVL, factor V Leiden; LA, lupus anticoagulant; PC, protein C deficiency; PS, protein S deficiency. All probabilities were calculated from the odds ratios generated from the meta-analysis of this review unless otherwise indicated.

[a] Probabilities based on ORs of VTE in the general population: PC = 12.62;[152] PS = 8.11;[158] LA = 5.6;[159] ACA = 2.2.[159]

[b] Expert opinion from specialists in obstetrics, vascular medicine and haematology.

opinions, to obtain a net cost per patient associated with various major clinical complications (*Table 2*). All costs were calculated at 2002 values (UK £).

Cost-effectiveness analysis

Cost-effectiveness is measured as a ratio of cost to effectiveness. The effectiveness of screening was measured by the number of major clinical complications averted. An incremental cost-effectiveness ratio (ICER) is an estimate of the cost per unit of effectiveness of one strategy in preference to another. In this study, ICERs presented as net costs per major clinical complication averted, comparing universal and selective screening with no screening, were calculated for each individual patient group. ICERs are calculated by dividing the difference in cost (in this case, costs associated with screening and treating the major clinical complications that the particular strategy failed to prevent) by the difference in effectiveness (the number of major clinical complications prevented by the particular strategy) in the comparison groups.

Sensitivity analysis

For the purpose of modelling, several key assumptions were made. It was assumed that individuals in the pregnancy and orthopaedic groups would be given thromboprophylaxis if tested positive for thrombophilia. These prophylactic therapies were assumed to be 50% effective.[22,35] The sensitivity and specificity of the thrombophilia were assumed to be 80% in the model basecase.

Univariate sensitivity analysis was carried out to test the sensitivity of these major assumptions made. In addition, the impact of varying unit costs data and model input probabilities was also assessed. The unit costs data were inflated and reduced by 20% and the extreme values of the 95% confidence intervals (CIs) associated with the calculated ORs were used to test the robustness of the basecase analysis.

Scenario analysis was also conducted to test other assumptions made in the model. The most commonly prescribed combined oral contraceptive (Microgynon 30) and hormone replacement therapy (Premique), based on national prescribing data in Scotland, were selected for the respective screening arms. This was tested using the second most commonly prescribed oral oestrogen preparations (Cilest and Premarin, respectively) in the sensitivity analysis.

In the case of hormone replacement therapy, evidence suggested that transdermal preparations do not incur similar risks to oral preparations. Therefore, scenario analysis was also carried out to investigate the cost-effectiveness of prescribing transdermal preparations to women who were tested positive for thrombophilia.

TABLE 2 *Resource use and unit costs*

	Average resource use	Unit costs (2002 UK £)	Sources of unit costs
Thrombophilia screen[a]			
Testing for FVL, prothrombin G20210A, antithrombin deficiencies, protein C deficiencies, protein S deficiencies, lupus anticoagulants and anticardiolipin antibodies		59.97	Clinical Services Division, Laboratory Directorate, North Glasgow University Hospitals NHS Trust
Thromboprophylaxis			
Pregnancy			
LMWH (enoxaparin 40 mg)	322	4.52	BNF
Warfarin 3 mg	1.19	1.11	BNF
Low-dose aspirin (75 mg)	4.5	3.03	BNF
Compression stocking class 3	1	8.92	BNF
Monitoring INR	3	19.69	Ref. 160
Orthopaedic surgery (extended prophylaxis)			
LMWH (enoxaparin 40 mg)	36	4.52	BNF
Low-dose aspirin (75 mg)	18	3.03	BNF
Compression stocking class 3	1	11.76	BNF
Outpatient clinic	5	27.00	Ref. 161

continued

TABLE 2 *Resource use and unit costs (cont'd)*

	Average resource use	Unit costs (2002 UK £)	Sources of unit costs
Management of DVT			
Ultrasound	1	25.40	Ref. 160
LMWH (enoxaparin 100 mg)	7	7.19	BNF
Warfarin 3 mg	8.4	1.11	BNF
Warfarin 5 mg	0.1	1.21	BNF
Monitor INR	24	4.90	BNF
Compression stocking class 3	1	11.76	BNF
Outpatient clinic	12	27.00	Ref. 161
Management of pulmonary embolism			
Lung perfusion and ventilation scan	1	138.06	Ref. 160
LMWH (enoxaparin 100 mg)	7	7.19	BNF
Warfarin 3 mg	8.4	1.11	BNF
Warfarin 5 mg	0.1	1.21	BNF
Monitor INR	24	4.90	Ref. 160
Compression stocking class 3	1	11.76	BNF
Inpatient stay	7	185.80	Ref. 161
Outpatient clinic	12	27.00	Ref. 161
Routine pregnancy			Ref. 161, NHS hospital trust cost
Antenatal clinic visits	10	19.69	
Routine delivery	1	194.81	
Inpatient stay	3	329.62	
Postnatal midwife visits	10	53.00	
Management of DVT in pregnancy			
Ultrasound	1	25.40	BNF, Refs 160, 161
LMWH (enoxaparin 80 mg)	10	5.81	
Compression stocking class 2	1	8.92	
Inpatient stay	5	185.80	
Management of pulmonary embolism in pregnancy			
Lung perfusion and ventilation scan	1	138.06	BNF, Refs 160,161
LMWH (enoxaparin 80 mg)	10	5.81	
Compression stocking class 2	1	8.92	
Inpatient stay	7	185.80	
Management of first/second trimester loss			
Ultrasound	1	19.69	BNF, Ref. 160, NHS hospital trusts costs
Oxytocin (syntocinon 5 units)	1	1.23	
Counselling	1	26.00	
Management of late pregnancy loss			
Mifepristone (Mifegyne 200 mg × 3)	2	41.83	BNF, NHS hospital trusts cost
Counselling	1	26.00	
Management of mild preeclampsia			
Antenatal clinic visits	18	19.69	Ref. 161
Management of severe preeclampsia			
Antihypertensive (methyldopa 250 mg)	6.3	0.60	BNF, Ref.161
Anticonvulsant [magnesium sulfate 2 ml (1 g) ampule]	24	2.85	
Inpatient stay (ICU)	1	1130.37	
Inpatient stay	3	329.62	
Postnatal consultant visits	1	19.69	
Management of placental abruption			Ref. 161
Inpatient stay	2	329.62	Ref. 161
Management of intra-uterine growth restriction			
Antenatal clinic visits	31	19.69	

continued

TABLE 2 *Resource use and unit costs (cont'd)*

	Average resource use	Unit costs (2002 UK £)	Sources of unit costs
Combined oral contraceptives			
Microgynon 30[b]	12	0.94	BNF
Cilest[c]	2	12.84	BNF
Hormone replacement therapy			
Premique[d]	4	27.14	BNF
Premarin[e]	4	9.72	BNF
Transdermal hormone replacement therapy			
Estraderm TTS[f]	4	16.83	BNF
Evorel Conti Patches[g]	4	38.70	BNF

INR, international normalised ratio.

[a] One test per person screened; in addition, those tested positive would receive a repeat test to confirm results. The most commonly prescribed combined oral contraceptive[b], hormone replacement therapy[d] and transdermal hormone replacement therapy[f] in Scotland 2003 (Information and Statistics Division). The second most commonly prescribed combined oral contraceptives[c], hormone replacement therapy[e] and transdermal hormone replacement therapy[g] in Scotland 2003 (Information and Statistics Division).

Chapter 4
Results

Risk of clinical complications

Oral oestrogen preparations

Of 201 studies identified from the searches, only nine met the inclusion criteria (*Figure 2*). Studies that were retrieved for detailed evaluation but subsequently excluded are listed in Appendix 4.

Combined oral contraceptives

Six case–control studies and one retrospective cohort study on combined oral contraceptives met the inclusion criteria for the review (*Table 3*).

Venous thromboembolism events observed in 1127 combined oral contraceptive users were compared with 1767 non-users. The methodological qualities of the studies were relatively consistent (*Table 3*). The major limitation common to most studies was the failure to measure or adjust for confounding factors. Only one study described blinded assessment of outcomes.

The results of the meta-analysis (*Figure 3*) showed strong associations between the use of oral contraceptives and thrombophilia (alone and in

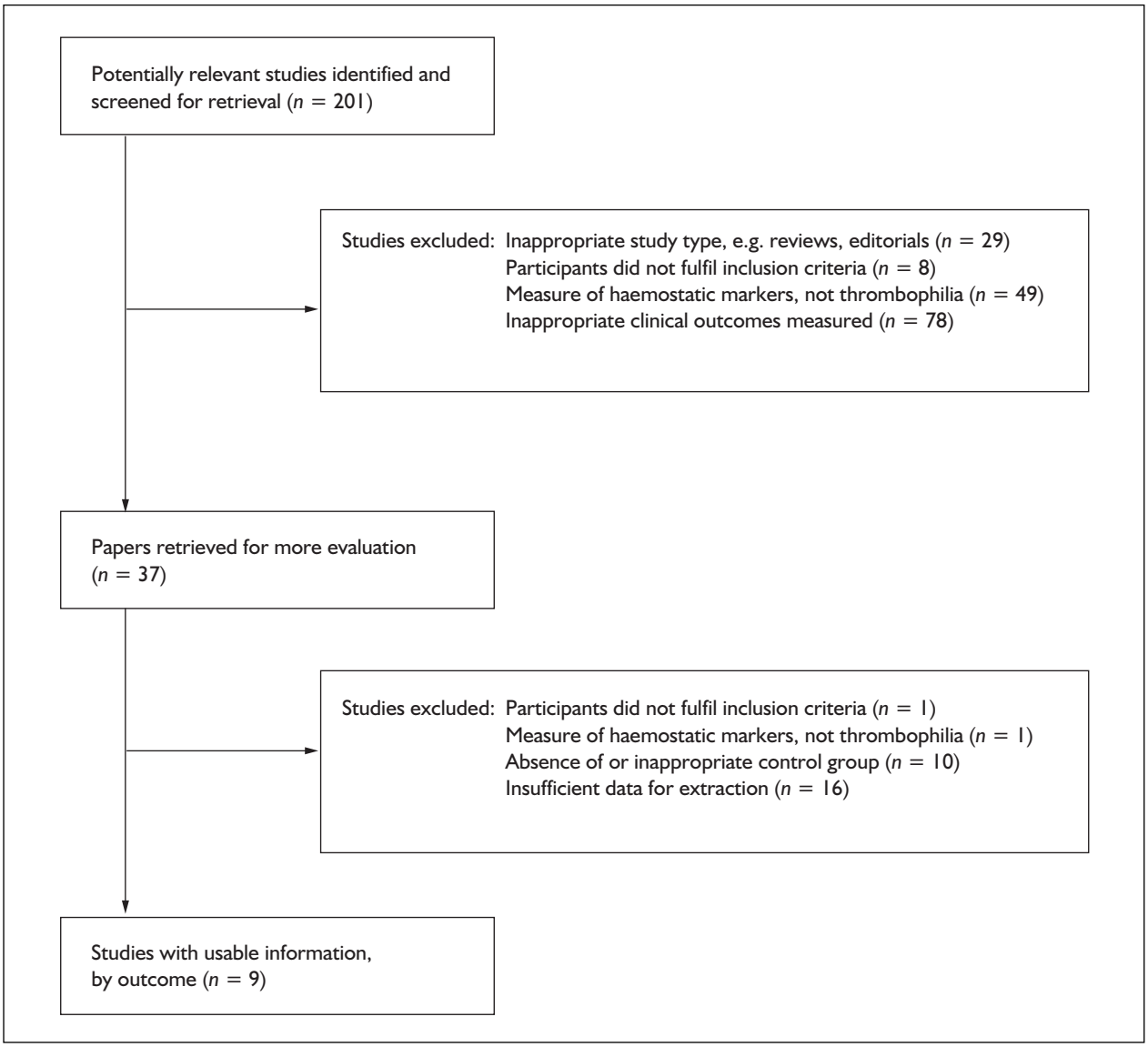

FIGURE 2 *'Trial flow' – selection of studies for systematic review on oral oestrogen preparations*

TABLE 3 *Study characteristics of studies on thrombophilia and oral contraceptive use included in the review*

Source and type of study	Participants	Hormones	Thrombophilia	Outcome measures	Results	Quality criteria[a]
Andersen *et al.* (1998); Denmark[38] Case–control study	Cases (n = 67) – women with spontaneous DVT or PE identified from discharge records Controls (n = 134) – blood donors from the same region, age-matched (2:1)	Oral contraceptives – classified into third-generation and other (i.e. first- and second-generation and progestogen-only pill) OC Information on OC use (3 months prior to admission for cases) was obtained from hospital records, telephone interviews and self-administered questionnaires	FVL, AT, PC, PS	VTE events Thrombotic events were confirmed at diagnosis by phlebography, ultrasound, perfusion lung scan echocardiography or when the event led to treatment with heparin or anticoagulants	The risk of VTE in the presence of heritable thrombophilia (including FVL, AT, PC and PS) was similar for both third-generation OC users and users of other OC (OR 52.5; 95% CI 3.7 to 738.1 and OR 63.3; 95% CI 6.2 to 648.4, respectively)	1 = Yes 2 = Yes 3 = NS 4 = No 5 = Yes 6 = Yes 7 = Yes
Bloemenkamp *et al.* (1999); The Netherlands[42] Case–control study	Cases (n = 155) – premenopausal women with confirmed first DVT identified from the records of anticoagulation clinics Controls (n = 169) – friends and acquaintances, or partners of other patients at the clinic, with no history of DVT, matched for age	Oral contraceptives – classified into non-current OC use and current OC use Information on OC use (1 month prior to event for cases) was obtained from personal interviews	High FVIII (≥150 IU/dl)	DVT First episode of proven DVT diagnosed by established objective methods	Both OC use and high FVIII levels were shown to be associated with increased DVT risk (OR 3.8, 95% CI 2.4 to 6.0 and OR 4.0, 95% CI 2.0 to 8.0). The presence of both factors had an additive effect, resulted in OR 10.3 (95% CI 3.7 to 28.9)	1 = Yes 2 = Yes 3 = Yes 4 = NS 5 = Yes 6 = Yes 7 = NA
Legnani *et al.* (2002); Italy[41] Case–control study	Cases (n = 301) – women who had at least one venous thromboembolism event during reproductive age Controls (n = 650) – healthy women of reproductive age from the same geographical area	Oral contraceptives – classified according to the type of progestin into second- and third-generation Information on OC use was obtained from personal interviews	AT, PC, PS, APCR, FVL, prothrombin G20210A	VTE events Objectively confirmed DVT (confirmed by compression ultrasonography or venography) of the lower limb, with and without PE (confirmed by ventilation perfusion lung scan)	A strong interaction between OC use and the presence of either FVL (OR 41.0, 95% CI 13.5 to 125) or prothrombin G20210A (OR 58.6, 95% CI 12.8 to 276) mutations was observed. The risk of VTE in OC users who had both mutations was significantly increased (OR 86.5, 95% CI 10.0 to 747)	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = Yes 7 = NA

continued

TABLE 3 *Study characteristics of studies on thrombophilia and oral contraceptive use included in the review (cont'd)*

Source and type of study	Participants	Hormones	Thrombophilia	Outcome measures	Results	Quality criteria[a]
Martinelli *et al.* (1999); Italy[39] Case–control study	Cases (n = 148) – women with first objectively documented DVT Control (n = 277) – healthy women who were friends or partners of referred patients in the same 3-year study period	Oral contraceptives – classified into first-, second- and third-generation Information on OC use at the time of thrombosis, i.e. until 2 weeks or less before the thrombotic event (cases) or time of sampling (controls) was recorded	Thrombophilia screen: prothrombin G20210A, FVL, antiphospholipid syndrome, AT, PC, PS, LA and anticardiolipin antibodies	DVT First, objectively documented episode of DVT of the lower extremities	The most prevalent circumstantial risk factor in patients and the only one observed in controls was OC use, conferred a 6-fold increased risk of thrombosis. The risk increased to OR 16.3 (95% CI 3.4 to 79.1) and OR 20.0 (95% CI 4.2 to 94.3) in OC users with prothrombin G20210A and FVL, respectively, indicating a multiplicative interaction between the genetic risk factors and OC use	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = Yes 6 = Yes 7 = Yes
Santamaria *et al.* (2001); Spain[36] Retrospective cohort study	Cohort (n = 325) – women from 97 families with at least two family members identified as carriers of one or more thrombophilic factors (AT, PC, PS, FVL, prothrombin G20210A)	Oral contraceptives – first-, second- and third-generation Information was obtained by questionnaires filled out during an appointment or by a telephone interview	AT, PC, PS, FVL, prothrombin G20210A	VTE events DVT with or without PE. Standard objective diagnostic procedures were used for all symptomatic women	The risk of VTE in prothrombin carriers using OC was three-fold higher (95% CI 1.3 to 6.8) than that in non-carriers. Carriers of FVL taking OC showed OR 1.4 (95% CI 0.6 to 3.3)	1 = Yes 2 = Yes 3 = NS 4 = No 5 = Yes 6 = Yes 7 = NA
Spannagl *et al.* (2000); Germany[40] Case–control study	Cases (n = 80) – women with DVT or PE Controls (n = 406) – women randomly sampled by computer form the population-based BATER study database. Up to six controls were randomly matched per case, by age group	Oral contraceptives – current use and no use (never or past use) at the time of event or interview Information on OC use was obtained by self-administered questionnaires	FVL	VTE events VTE diagnosed if clinical signs were present and confirmed by imaging tests and/or treated with anticoagulants	Matched, adjusted OR for idiopathic VTE in women without and with FVL who used OC were 4.1 (95% CI 2.1 to 7.8) and 10.2 (95% CI 1.2 to 88.4), respectively. The adjusted OR for FVL carrier was 2.0 (95% CI 1.0 to 4.4). The OR for women with FVL and OR versus no FVL and no OC was 10.2 (95% CI 3.8 to 27.6)	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = Yes 6 = Yes 7 = NA

continued

TABLE 3 *Study characteristics of studies on thrombophilia and oral contraceptive use included in the review (cont'd)*

Source and type of study	Participants	Hormones	Thrombophilia	Outcome measures	Results	Quality criteria[a]
Vandenbroucke *et al*. (1994); The Netherlands[37] Population-based case–control study	Cases (n = 155) – premenopausal women with confirmed first DVT identified from the records of anticoagulation clinics Controls (n = 169) – friends and acquaintances, or partners of other patients at the clinic, with no history of DVT, matched for age	Oral contraceptives – classified into non-current and current OC use Information on OC use (1 month prior to event for cases) was obtained from personal interviews	FVL	DVT First episode of proven DVT diagnosed by established objective methods	The risk of thrombosis among OC users was increased four-fold (RR 3.8, 95% CI 2.5 to 6.0). The risk of thrombosis among FVL carriers was increased eight-fold (RR 7.9, 95% CI 3.2 to 19.4). Compared with non-OC users not carrying the mutation, the risk of thrombosis among those with both risk factors was increased more than 30-fold (RR 34.7, 95% CI 7.8 to 154)	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = Yes 6 = Yes 7 = NA

APCR, activated protein C resistance; AT, antithrombin deficiency; DVT – deep vein thrombosis; FVL, factor V Leiden; LA, lupus anticoagulant; OC, oral contraceptive; OR, odds ratio; PC, protein C deficiency; PE, pulmonary embolism; PS, protein S deficiency; RR, relative risk; VTE, venous thromboembolism.

[a] Quality criteria: 1 = representative inception cohort; 2 = comparator group reliability ascertained; 3 = blinded assessment of outcomes; 4 = confounding factors comparable; 5 = adjust for confounding; 6 = appropriate follow-up; 7 = description of drop-outs; NA, not applicable; NS, not stated.

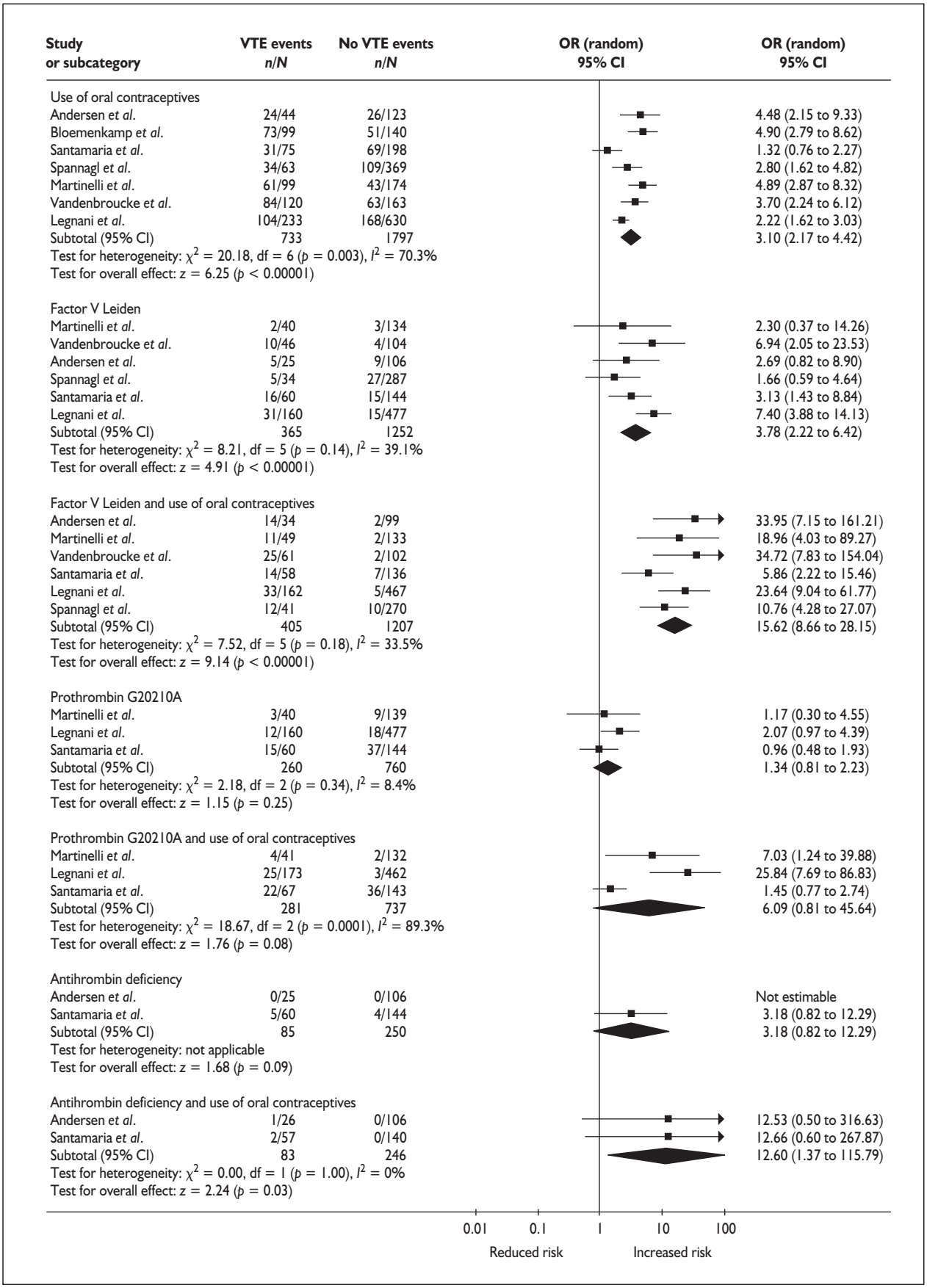

FIGURE 3 *Odds ratios for selected thrombophilias and the risk of VTE in oral contraceptives use and no oral contraceptives use*

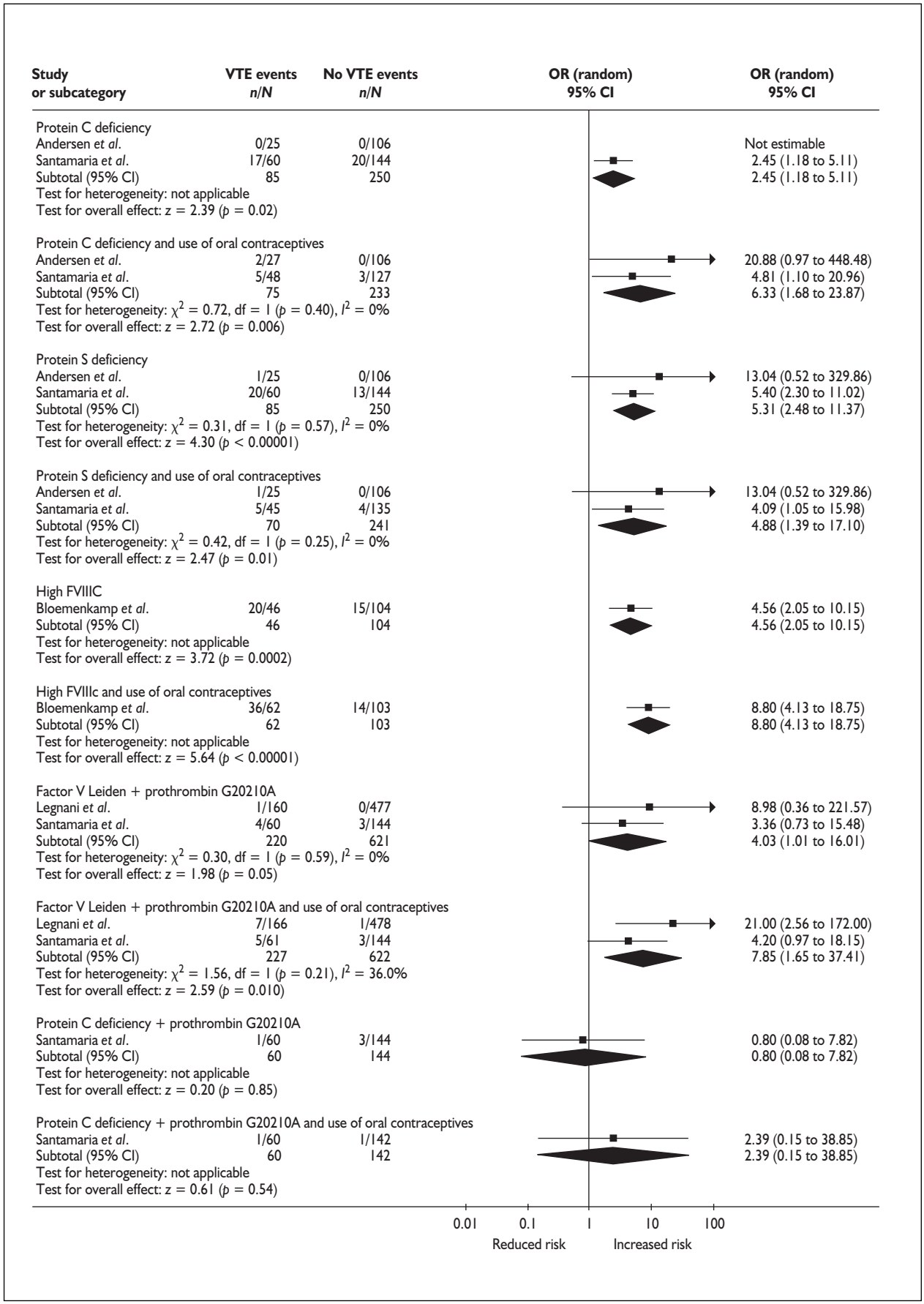

FIGURE 3 *(cont'd)*

combination), and venous thromboembolism. The ORs for oral contraceptive use and the risk of VTE ranged between 1.32 and 4.90. Although all the studies showed an increase in risk, the results from one study did not show statistical significance.[36] Overall, the odds of developing VTE among oral contraceptive users were almost three times greater than those of non-users (OR 3.10; 95% CI 2.17 to 4.42). However, significant (p = 0.00) and important (I^2 = 70.30%) heterogeneity was present among the studies.

The risk associated with thrombophilia and VTE in this study population was also calculated (*Figure 3*). Positive associations between FVL and VTE were reported in six studies and a pooled OR of 3.78 (95% CI 2.22 to 6.42) was observed.[36–41] Although no significant heterogeneity was detected (p = 0.14), the inconsistency among the study results was moderately large (I^2 = 39.10%). The odds of developing VTE in those with protein S deficiency were approximately five times (OR 5.31; 95% CI 2.48 to 11.37) those of subjects without the deficiency. This finding was based on data from two studies.[36,38] No evidence of heterogeneity (p = 0.57) and inconsistency in the OR estimates (I^2 = 0.00%) was detected between the two studies. Significant increases in risk of VTE were also reported with protein C deficiency (OR 2.45; 95% CI 1.18 to 5.11) and elevated levels of factor VIIIc (OR 4.56; 95%CI 2.05 to 10.15) in individual studies.[36,42] Non-significant increases in risks associated with the combined defects of FVL and prothrombin G20210A were reported in two studies.[36,41] However, meta-analysis gave a statistically significant pooled OR (OR 4.03; 95% CI 1.01 to 16.01). These studies showed no evidence of heterogeneity (p = 0.59) and inconsistency of results (I^2 = 0.00%). The prothrombin G20210A mutation and antithrombin deficiency were described in three[36,39,41] and two studies,[36,38] respectively. Although increased risks were observed with prothrombin G20210A (OR 1.34; 95% CI 0.81 to 2.23) and antithrombin deficiency (OR 3.18; 95% CI 0.82 to 12.29), the ORs were not statistically significant. No association was observed with the combined defect of prothrombin G20210A and protein C deficiency (OR 0.80; 95% CI 0.08 to 7.82). However, data were available from only one study.[36]

A supra-additive effect was for the risk of VTE observed between the use of oral contraceptives and thrombophilias. The odds of developing VTE in those who had both risk factors were substantially amplified compared with either of the risk factors considered alone. The most significant increased risk was observed with FVL and use of oral contraceptives (OR 15.62; 95% CI 8.66 to 28.15), five times that observed with either risk factor in isolation. Although no significant heterogeneity was detected (p = 0.18), a moderate inconsistency among the results was observed (I^2 = 33.50%). Similar, but less pronounced, effects were also observed in oral contraceptive users who had deficiencies of antithrombin or protein C. The combination of risk factors resulted in odds four (OR 12.60; 95% CI 1.37 to 115.79) and two times (OR 6.33; 95% CI 1.68 to 23.87) those observed with either risk factor in isolation, respectively. Test for heterogeneity was non-significant (p = 1.00 and 0.40, respectively) and no inconsistencies among the results were detected (I^2 = 0.00% in both cases). Meta-analysis of two studies[36,41] showed that the use of oral contraceptives doubled the risk of those with combined thrombophilic defects of FVL and prothrombin G20210A but no oral contraceptive use (OR 7.85; 95% CI 1.65 to 37.51). No significant heterogeneity (p = 0.21) but moderate inconsistency (I^2 = 36.00%) were detected among the results. One study reported a significant association between elevated levels of factor VIIIc in combination with oral contraceptive use and venous thromboembolism (OR 8.8; 95% CI 4.13 to 18.75).[42] No significant association was observed with prothrombin G20210A (OR 6.09; 95% CI 0.81 to 45.64) or with combined defects on prothrombin G20210A and protein C (OR 2.39; 95% CI 0.15 to 38.85) with oral contraceptive use. A pooled OR of 4.88 (95% CI 1.39 to 17.10) was observed with protein S deficiency and the use of oral contraceptives. However, this was lower than the risk observed with protein S deficiency in isolation (OR 5.31; 95% CI 2.48 to 11.37).

Sensitivity analysis was carried out to explore the heterogeneity and inconsistencies of the results of the studies included in the meta-analysis. All the analyses were repeated using a fixed-effect model; however, there was little change in the results. The effect of study type was also investigated by restricting the analysis to case–control studies and excluding the cohort study[36] in the analysis. This resulted in a modest increase in the estimated risk, and the inconsistency among the results reported in the individual studies was removed (OR 19.43; 95% CI 11.42 to 33.06 and I^2 = 0.00%). The exclusion of the cohort study also had a significant impact on the analysis on prothrombin G20210A and oral contraceptive use. A significant increase in risk of VTE was estimated (OR 15.66; 95% CI 4.44 to 55.18). No evidence of heterogeneity was shown (p = 0.22) and a moderate amount of inconsistency was found (I^2 = 33.1%).

Hormone replacement therapy

Two studies on hormone replacement therapy were included in the review (*Table 4*). One was a nested case-control study[43] ($n = 160$) conducted among participants of the Heart and Estrogen/Progestin Replacement Study (HERS)[44] and the Estrogen Replacement and Atherosclerosis (ERA) trial.[45] In these two studies, postmenopausal women with documented coronary artery disease were randomly assigned to receive oral conjugated equine oestrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg per day or placebo and followed up for an average of 4.1 and 3.25 years in HERS and ERA, respectively. All VTE events reported were objectively confirmed. In this nested case–control study, all participants were tested for the presence of the FVL mutation. In another case–control study,[46] women aged 45–64 years with a first, idiopathic VTE event ($n = 77$) compared with women admitted to hospital for diagnoses unrelated to VTE and hormone replacement therapy, acting as controls ($n = 163$). All participants were tested for FVL and prothrombin G20210A mutation. Only four patients carried prothrombotic mutations (two cases and two controls) and none were users of hormone replacement therapy. Therefore, no analysis was carried out for the prothrombin G20210A mutation.

Meta-analysis for FVL, the use of hormone replacement therapy and VTE events was conducted (*Figure 4*). The results reported in both studies were consistent ($I^2 = 0.00\%$) and tests for heterogeneity were non-significant ($p = 0.89$ hormone replacement therapy, 0.77 FVL and 0.78 hormone replacement therapy and FVL). The use of hormone replacement therapy was associated with a three-fold increased risk in VTE events (pooled OR 3.16; 95% CI 1.90 to 5.23). A similar effect was observed with the presence of FVL mutation (pooled OR 3.58; 95% CI 1.43 to 8.97). Patients who had both risk factors had much greater odds of developing VTE events (pooled OR 13.16; 95% CI 4.28 to 40.47).

Pregnancy

The initial search yielded 234 studies, of which 162 were excluded (*Figure 5*). The studies that were retrieved for detailed evaluation but subsequently excluded are listed in Appendix 5. Thus, 72 studies were included, which were quality-rated in our analysis (*Table 5*). The methodological quality of the studies varied. The major limitation common to most studies was the failure to measure or adjust for confounding factors.

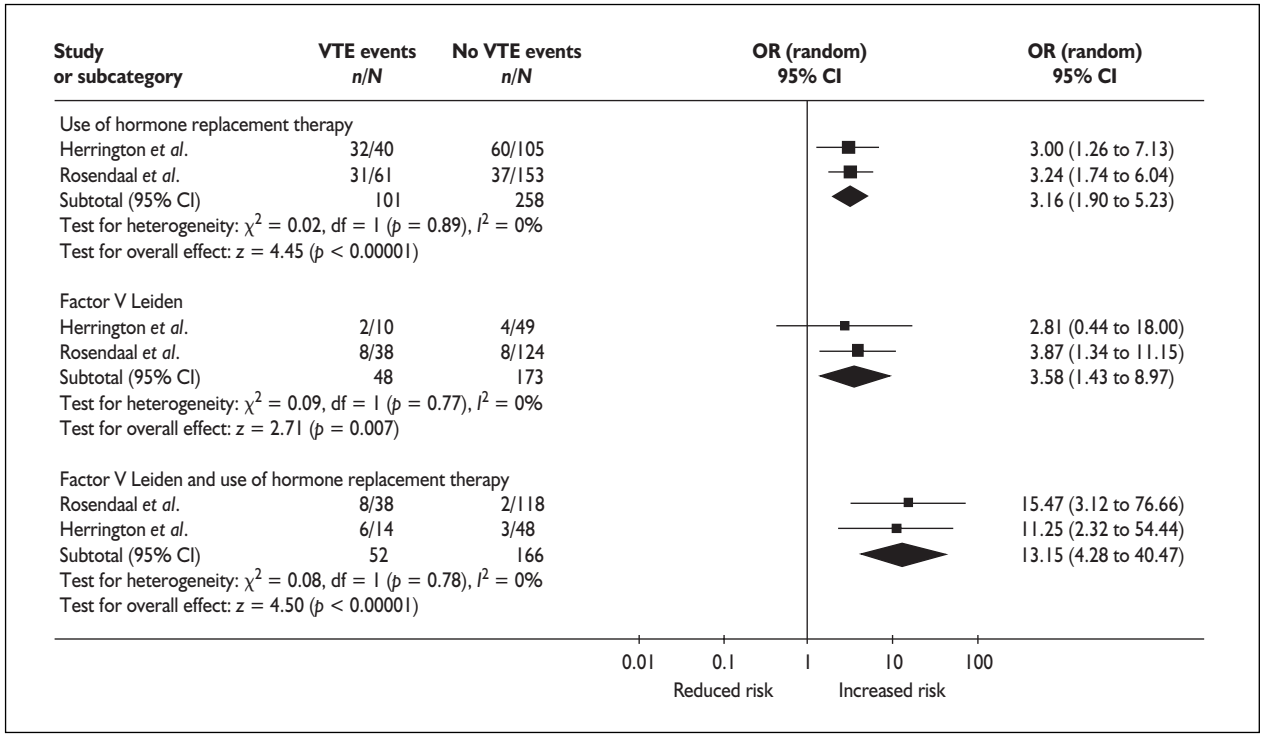

FIGURE 4 *Odds ratios for factor V Leiden and the risk of VTE in hormone replacement therapy use and no hormone replacement therapy use*

TABLE 4 *Study characteristics of studies on thrombophilia and hormone replacement therapy included in the review*

Source and type of study	Participants	Hormones	Thrombophilia	Outcome measures	Results	Quality criteria[a]
Herrington *et al*. (2002); US[43] Nested case–control study	Participants of the HERS and ERA trial. Postmenopausal women, <80 years old with documented coronary artery disease Cases (n = 48) – women who had a thrombotic event during the trial. Controls (n = 112) – those who did not have a thrombotic event	Hormone replacement therapy – participants in the HERS trial received oral conjugated equine oestrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily. Participants in the ERA trial received oral conjugated equine oestrogen 0.625 mg, oestrogen plus medroxyprogesterone acetate 2.5 mg	FVL	VTE events A diagnosis of DVT was confirmed by venography, impedance plethysmography or ultrasound. A diagnosis of PE was confirmed by a segmental or larger ventilation/perfusion mismatch on a nuclear lung scan or an intraluminal filling by pulmonary angiography	Factor V Leiden was present in 8/48 cases and 7/112 controls (OR 3.3, 95% CI 1.1 to 9.8). In non-FVL carriers, the risk associated with HRT use was significantly increased (OR 3.7, 95% CI 1.4 to 9.4). However, in FVL carriers, the risk associated with HRT use increased nearly six-fold (OR 5.7, 95% CI 0.6 to 53.9). The OR for women with FVL assigned to HRT compared with non-carriers given placebo was 14.1 (95% CI 2.7 to 72.4)	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = Yes 6 = Yes 7 = NA
Rosendaal *et al*. (2002); UK[46] Case–control study	Cases (n = 77) – women admitted with a main diagnosis of a first episode of DVT or PE Controls (n = 163) – women admitted for diagnoses unrelated to thrombosis and HRT. Up to two controls were chosen per case, matched by 5-year age group, district and date of hospitalisation	Hormone replacement therapy (all types) – current users were defined as the use of HRT at any time in the month prior to hospital admission	Prothrombotic mutations: FVL, prothrombin G20210A	VTE events Idiopathic DVT and PE, classified as definite (objectively confirmed), probable, possible or other	Among the cases, 51% were receiving HRT at the time of thrombosis compared with 24% of the control group (OR 3.3, 95% CI 1.8 to 5.8). A prothrombotic mutation (FVL or prothrombin G20210A) was observed in 23% of the cases compared with 7% of controls (OR 3.8, 95% CI 1.7 to 8.5). None of the prothrombin G20210A carriers used HRT. Women who had FVL and HRT use had a 15-fold increased risk of thrombosis (OR 15.5, 95% CI 3.1 to 7.7)	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NA

DVT, deep vein thrombosis; ERA, the Estrogen Replacement and Atherosclerosis; FVL, factor V Leiden; HERS, the Heart and Estrogen/Progestin Replacement Study; HRT, hormone replacement therapy; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Quality criteria: 1 = representative inception cohort; 2 = comparator group reliability ascertained; 3 = blinded assessment of outcomes; 4 = confounding factors comparable; 5 = adjust for confounding; 6 = appropriate follow-up; 7 = description of drop-outs; NA, not applicable NS, not stated.

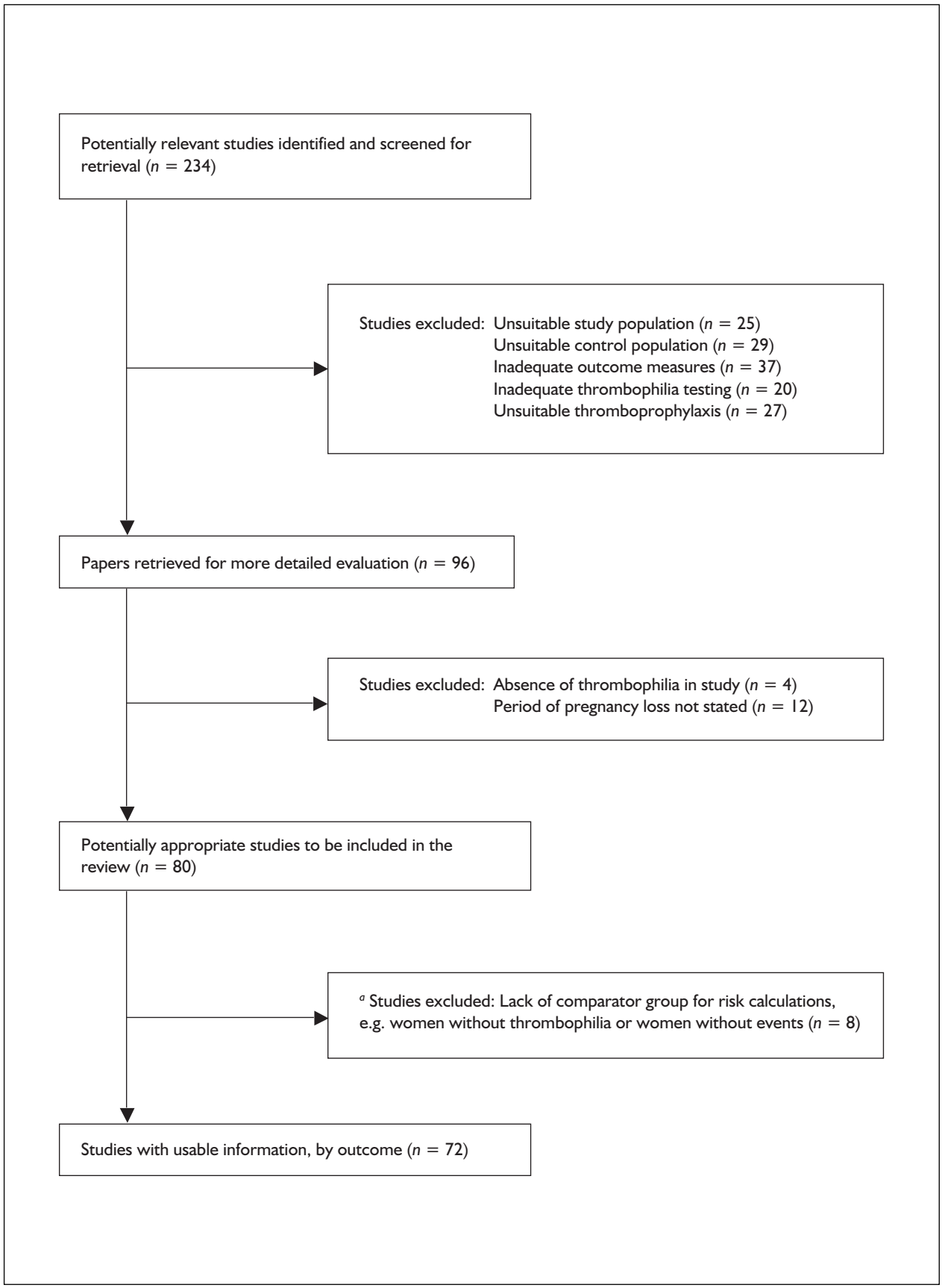

FIGURE 5 *'Trial flow' – selection of studies for systematic review in pregnancy*

[a] *Studies with usable information, by outcome for the review of effectiveness of prophylactic interventions in pregnant women with thrombophilia*

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Agorastos *et al.* (2002)[86]	Retrospective case–control	FVL FII G20210A	8 women with stillbirth 16 women with preeclampsia 7 women with placental abruption 15 women with IUGR Controls = 100 women with ≥1 uneventful pregnancy + no history of thrombosis	Stillbirth = fetal death >24 weeks Preeclampsia = BP >160/110 mmHg+ proteinuria >5 g/24 h Placental abruption = grade 2/3 IUGR = birth weight <10th centile for gestational age	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = NS 7 = NS
Alfirevic *et al.* (2001)[83]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS aCL, LA APCR Hyperhomocysteinaemia	18 women with unexplained stillbirth 63 women with preeclampsia 23 women with placental abruption 25 women with IUGR Controls = 44 women with uncomplicated pregnancies	Stillbirth = fetal death >23 weeks Severe preeclampsia defined by Davey and MacGillivray[163] Placental abruption requiring immediate delivery IUGR requiring delivery <36 weeks	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = Yes 7 = NS
Allen *et al.* (1996)[93]	Retrospective case–control	aCL	Cases = 100 women with preeclampsia Controls = 100 normotensive pregnant women with no proteinuria	Preeclampsia = BP >140/90 mmHg >20 weeks + proteinuria >100 mg/dl	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Alonso *et al.* (2002)[91]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS aCL, LA Hyperhomocysteinaemia	Cases = 8 women with IUFD Controls = 75 women with ≥1 successful pregnancy + no gestational complications	IUFD = fetal death ≥23 weeks	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Balasch *et al.* (1997)[70]	Retrospective case–control	FVL PC, PS APCR	Cases = 55 women with unexplained RSA Controls = 50 women with ≥1 child + no previous abortion	RSA = ≥2 spontaneous abortions in 1st trimester	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Bare *et al.* (2000)[87]	Retrospective cohort	FVL	489 women 128 FVL carriers + 461 non-FVL carriers	Spontaneous abortion Intrauterine death	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Benedetto *et al.* (2002)[98]	Retrospective case–control	FVL FII G20210A	Cases = 111 women with preeclampsia Controls = 111 normal pregnant women with no history of VTE	Preeclampsia = diastolic BP ≥90 mmHg + proteinuria ≥300 mg/24 >20 weeks gestation	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Bocciolone *et al.* (1994)[84]	Retrospective case–control	aCL, LA	Cases = 99 women with unexplained IUFD Controls = 85 women with normal pregnancies + no history of pregnancy loss	IUFD = fetal death ≥20 weeks	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Carp *et al.* (2002)[75]	Retrospective case–control	FVL FII G20210A MTHFR	Cases = 108 women with RSA Controls = 82 women without miscarriages	RSA = ≥3 pregnancy losses ≤26 weeks	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = Yes 7 = Yes
Chakrabarti *et al.* (1999)[63]	Retrospective case–control	aCL, LA	Cases = 50 pregnant women with unexplained RSA Controls = 30 pregnant women with no history of pregnancy loss	RSA = ≥ 2 pregnancy loss in 1st and 2nd trimester	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Cohen (1996)[162]	Randomised trial	aCL, LA	Participants = 90 women with history ≥3 consecutive pregnancy losses in association with aCL and LA Intervention = low-dose aspirin or low-dose aspirin plus unfractionated heparin	Live birth rate Gestational age at delivery Birth weight VTE	1 = Yes 2 = NA 3 = NS 4 = Yes 5 = NA 6 = NS 7 = No
Currie *et al.* (2002)[99]	Prospective cohort	FVL	Cases = 48 maternal–infant pairs with preeclampsia Controls = 46 maternal–infant pairs where pregnancy was normal	Preeclampsia = BP ≥ 140/90 mmHg >20 weeks gestation + proteinuria ≥300 mg/24 h	1 = Yes 2 = Yes 3 = NS 4 = Yes and no 5 = No 6 = Yes 7 = NS
D'Elia *et al.* (2002)[100]	Retrospective case–control	FVL FII G20210A MTHFR	Cases = 58 women with preeclampsia Controls = 74 pregnant normotensive women	Preeclampsia = BP ≥ 140/90 mmHg + proteinuria ≥300 mg/24 h	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Das *et al.* (1991)[66]	Retrospective case–control	LA	Cases = 50 pregnant women with previous RSA Controls = 50 pregnant women with ≥2 live births + no spontaneous abortion	RSA = ≥3 spontaneous abortions in 1st or 2nd trimester	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
De Carolis *et al.* (1994)[64]	Retrospective case–control	aCL	Cases = 181 women with RSA + 75 women with IUFD Controls = 106 women with no previous pregnancy loss	RSA = ≥2 spontaneous abortions <20 weeks IUFD = fetal loss >20 weeks	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
De Groot *et al.* (1999)[108]	Retrospective case–control	FVL	Cases = 163 women with preeclampsia Controls = 163 women with no preeclampsia	Preeclampsia = rise in BP ≥30 mmHg systolic or ≥15 mmHg diastolic ≤20 weeks + proteinuria ≥2+(100 mg/dl)	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = Yes 6 = Yes 7 = NS
Dilley *et al.* (2000)[47]	Retrospective case–control	FVL FII G20210A MTHFR	Cases = 41 women with VTE in previous pregnancy Controls = 76 women with normal pregnancies	VTE confirmed by ultrasonography, V/Q scan or MRI	1 = Yes 2 = Yes 3 = NS 4 = No 5 = Yes 6 = Yes 7 = NS
Dizon-Townson *et al.* (1996)[101]	Retrospective case–control	FVL	Cases = 158 women with severe preeclampsia Controls = 403 normotensive gravid women	Severe preeclampsia = BP >160/110 mmHg + proteinuria ≥25 g/24 h	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Dreyfus *et al.* (2001)[94]	Retrospective case–control	aCL, LA	Cases = 180 pregnant women with preeclampsia Controls = 360 pregnant women with no hypertension or proteinuria	Preeclampsia = BP ≥140/90 mmHg >20 weeks gestation + proteinuria ≥300 mg/24 h	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Farquharson *et al.* (2002)[127]	Randomised controlled trial	aCL, LA	Participants = 98 women with ≥3 consecutive pregnancy losses diagnosed with aCL or LA Intervention = low-dose aspirin or low-dose aspirin plus low molecular weight heparin	Live birth rate Gestation at delivery Birth weight Preterm delivery Pregnancy-induced hypertension	1 = Yes 2 = NA 3 = Yes 4 = Yes 5 = No 6 = Yes 7 = Yes

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Fatini *et al.* (2000)[59]	Retrospective case–control	FVL AT, PC Hyperhomocysteinaemia	Cases = 59 women with RSA Controls = 70 women with normal pregnancies	RSA = ≥3 fetal losses in the 1st trimester (7–12 weeks gestation)	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Finan *et al.* (2002)[55]	Retrospective case–control	FVL FII G20210A	Cases = 110 women with RSA Controls = 267 parous women with uncomplicated pregnancies	RSA = ≥2 confirmed pregnancy losses of unknown cause in the 1st trimester	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Foka *et al.* (2000)[79]	Retrospective case–control	FVL FII G20210A MTHFR	Cases = 80 women with RSA Controls = 100 women with ≥1 successful pregnancy + no pregnancy loss	RSA = ≥2 fetal losses in the 1st or 2nd trimester	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = Yes 7 = NS
Franklin and Kutteh (2002)[126]	Prospective cohort	aCL, LA	Participants = 79 women with ≥2 consecutive pregnancy losses who were positive for aCL or LA Intervention = aspirin alone or aspirin plus heparin	Live birth rate Gestational age at birth Birth weight Minor bleeding Thrombocytopenia Major bleeding Fractures	1 = Yes 2 = NA 3 = No 4 = Yes 5 = No 6 = Yes 7 = No
Gerhardt *et al.* (2000)[27]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS LA	Cases = 119 women with VTE in pregnancy or postpartum period Controls = 233 women	Objective diagnosis of DVT or PE confirmed by Doppler ultrasonography or venography	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Goddijn-Wessel *et al.* (1996)[112]	Retrospective case–control	Hyperhomocysteinaemia	Cases = 84 women with placental abruption Controls = 46 women with normal pregnancy outcome	Placental abruption = presence of tender, hypertonic uterus and disseminated intravascular coagulation and/or retroplacental haematoma with/without signs of infarction	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Grandone *et al.* (1997)[71]	Retrospective case–control	FVL	Cases = 27 women with RSA Controls = 118 parous women with no fetal loss	RSA = ≥2 unexplained fetal loss in the 1st trimester	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Grandone *et al.* (1997)[103]	Retrospective case–control	FVL MTHFR	Cases = 96 women with preeclampsia Controls = 129 parous women with uneventful pregnancies	Preeclampsia = BP ≥ 140/90 mmHg + proteinuria ≥300 mg/24 h	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Grandone *et al.* (1998)[53]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS aCL, LA	Cases = 42 women with VTE in previous pregnancy or postpartum period Controls = 213 parous women with no venous or arterial thrombosis	DVT confirmed by phlebography or ultrasonography PE confirmed by angiogram or V/Q scan	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = Yes
Grandone *et al.* (1999)[102]	Retrospective case–control	FVL FII G20210A MTHFR	Cases = 140 women with gestational hypertension with or without proteinuria Controls = 216 normotensive gravid women	Preeclampsia = BP≥140/90 mmHg + proteinuria ≥300 mg/24 h	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = Yes 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Grandone *et al.* (2002)[114]	Retrospective case–control	FVL FII G20210A	Participants =755 women ever pregnant, 194 with history of RSA, 202 with gestational hypertension with/without proteinuria and 359 with ≥1 uneventful pregnancy	RSA = ≥3 fetal losses ≤24 weeks Preeclampsia = BP >140/90 mmHg + proteinuria >300 mg/24 h IUGR = birth weight <10th centile for gestational age	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = Yes 6 = Yes 7 = NS
Gris *et al* (1999)[81]	Retrospective case–control	FII G20210A MTHFR AT, PC, PS aCL, LA APCR	Cases = 232 women with ≥1 unexplained late fetal loss Controls = 464 women with successful pregnancies	Late fetal loss = intrauterine fetal death >22 weeks	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Hatzis *et al.* (1999)[67]	Retrospective case–control	FII G20210A AT, PC, PS LA APCR	Cases = 56 women with unexplained RSA Controls = 48 women with no pregnancy loss	RSA = ≥2 pregnancy loss <16th week of amenorrhea	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Higashino *et al.* (1998)[65]	Retrospective case–control	aCL	Cases = 476 women with RSA Controls = 100 women with no pregnancy complications	RSA = ≥2 pregnancy losses in 1st trimester	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Holmes *et al.* (1999)[76]	Retrospective case–control	MTHFR	Cases = 173 women with recurrent fetal loss Controls = 67 healthy parous women with no pregnancy loss or VTE	Recurrent fetal loss = ≥3 consecutive miscarriages ≤23 weeks	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Infante-Rivard *et al.* (1991)[68]	Retrospective case–control	aCL, LA	Cases = 289 women with fetal loss and 867 control women with no fetal loss Cases = 42 women with pregnancy loss >21 weeks and 126 controls women with no fetal loss	Spontaneous abortion = fetal loss ≤20 weeks Pregnancy loss = fetal loss >21 weeks	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = Yes 6 = Yes 7 = NS
Infante-Rivard *et al.* (2002)[117]	Retrospective case–control	FVL FII G20210A MTHFR	Cases = 493 newborns with IUGR Controls = 472 newborns with no IUGR	IUGR = birth weight <10th centile for gestational age	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = Yes 6 = Yes 7 = NS
Kim *et al.* (2001)[104]	Retrospective case–control	FVL MTHFR	Cases = 281 women with preeclampsia Controls = 360 women with ≥2 term pregnancies unaffected by preeclampsia	Preeclampsia = BP ≥140/90 mmHg + proteinuria ≥300 mg/24 h	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Kupferminc *et al.* (1999)[16]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS aCL, LA	12 women with stillbirth 34 women with severe preeclampsia 20 women with placental abruption Controls = 110 women with normal pregnancies	Stillbirth = fetal death >23 weeks gestation Preeclampsia = BP >160/110 mmHg + proteinuria >5 g/24 h Placental abruption = grade 2 or 3	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Kupferminc *et al.* (2000)[95]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS aCL	Cases = 63 women with severe preeclampsia Controls = 126 women with normal pregnancies	Severe preeclampsia= BP >160/110 mmHg + proteinuria >5 g/24 h	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Kupferminc *et al.* (2000)[72]	Retrospective case–control	FII G20210A	27 women with pregnancy loss 16 women with stillbirth 80 women with preeclampsia 27 women with placental abruption 72 cases with IUGR Controls = 156 women with normal pregnancies	Pregnancy loss = fetal loss <22 weeks Stillbirth = fetal death >23 weeks gestation Severe preeclampsia = BP >160/110 mmHg + proteinuria >5 g/24 h Placental abruption = requiring immediate delivery Birth weight <10th centile for gestational age	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Kutteh and Ermel (1996)[129]	Prospective cohort	aCL, LA	Participants = 50 women with ≥3 consecutive, spontaneous pregnancy losses who were positive for aCL and LA Intervention = low-dose aspirin and either low-dose heparin (10,000 U) or high-dose heparin (20,000 U) twice daily	Live birth rate Gestational age at birth Birth weight Minor bleeding episodes Thrombocytopenia Preeclampsia IUGR Major bleeding	1 = Yes 2 = NA 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Kutteh (1996)[128]	Prospective cohort	aCL, LA	Participants = 50 women with ≥3 consecutive, spontaneous pregnancy losses who were positive for aCL and LA Intervention = low-dose aspirin or low-dose aspirin plus heparin	Live birth rate Gestational age at birth Birth weight Minor bleeding episodes Thrombocytopenia Preeclampsia IUGR Major bleeding	1 = Yes 2 = NA 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Lissak *et al.* (1999)[77]	Retrospective case–control	MTHFR	Cases = 41 women with RSA Controls = 18 women with ≥2 live term deliveries + no pregnancy loss	RSA = ≥2 fetal loss ≤16 weeks	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Many *et al*. (2002)[82]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS aCL	Cases = 40 women with IUFD Controls = 80 women with uneventful pregnancies	IUFD = pregnancy loss ≥27 weeks	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Martinelli *et al*. (2000)[88]	Retrospective case–control	FVL FII G20210A MTHFR	Cases = 67 women with unexplained late fetal loss Controls = 232 women with ≥1 normal pregnancies and no fetal losses	Late fetal loss = fetal death ≥20 weeks	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = No 6 = Yes 7 = NS
Martinelli *et al*. (2001)[48]	Retrospective cohort	FVL FII G20210A AT, PC, PS	15 women homozygous for FVL 39 women double heterozygous for FVL + FII G20210A 182 women with normal coagulation	DVT by Doppler ultrasound or venography	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Martinelli *et al*. (2001)[115]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS aCL, LA	Cases = 61 women with previous history of IUGR Controls = 93 parous women with uneventful pregnancies	IUGR = birth weight <10th percentile for gestational age	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Martinelli *at el*. (2002)[49]	Retrospective case–control	FVL FII G20210A AT, PC, PS	Cases = 119 women with first episode of DVT and/or PE in pregnancy or postpartum period Controls = 232 women with ≥1 pregnancy and no thrombosis	DVT diagnosed by ultrasonography PE diagnosed by ventilation/perfusion scan	1 = Yes 2 = Yes 3 = Yes 4 = No 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Meinardi *et al.* (1999)[89]	Retrospective cohort	FVL	Participants = 228 carriers of FVL and 122 non-carrier relatives	Miscarriage = fetal loss ≤20 weeks Stillbirth = fetal loss >20 weeks	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Mello *et al.* (1999)[96]	Retrospective case–control	FVL AT, PC, PS aCL, LA APCR	Cases = 46 women with preeclampsia Controls = 80 women with normal pregnancies	Preeclampsia = BP ≥140/90 mmHg + proteinuria ≥300 mg/24 h	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Morrison *et al.* (2002)[109]	Retrospective cohort	FVL FII G20210A MTHFR	Participants = 404 women with preeclampsia, 303 with gestational hypertension and 164 with no raised BP	Preeclampsia = BP ≥90 mmHg + proteinuria ≥0.3 g/24 h	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = Yes 7 = Yes
Murphy *et al.* (2000)[50]	Prospective cohort	FVL AT, PC, PS aCL, LA	Participants =593 primigravid women	VTE diagnosed by Doppler or ventilation perfusion scan Recurrent fetal loss = ≥2 previous unexplained losses at any point during pregnancy Preeclampsia = BP >140/90 mmHg + proteinuria ≥1 by Dipstick IUGR = birth weight <10th percentile for gestational age	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Nagy *et al.* (1998)[105]	Retrospective case–control	FVL	Cases = 69 women with severe preeclampsia Controls = 129 women with no preeclampsia	Severe preeclampsia = BP >160/110 mmHg + proteinuria >1000 mg/24 h	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Nelen *et al.* (1997)[78]	Retrospective case–control	MTHFR	Cases =185 women with unexplained Unexplained recurrent early pregnancy loss Controls = 113 women with no pregnancy loss	Recurrent early pregnancy loss = ≥2 fetal loss <17 weeks	1 = Yes 2 = Yes 3 = No 4 = Yes 5 = No 6 = Yes 7 = NS
O'Shaughnessy *et al.* (1999)[106]	Retrospective case–control	FVL MTHFR	Cases = 283 women with preeclampsia Controls = 100 women with pregnancies uncomplicated by preeclampsia	Preeclampsia = BP ≥140/90 mmHg + proteinuria ≥300 mg/24 h	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Ogasawara *et al.* (1996)[69]	Retrospective case–control	LA	Cases = 195 women with unexplained recurrent miscarriage Controls =100 women	Recurrent miscarriage = ≥3 pregnancy loss in 1st or 2nd trimester	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Ogunyemi *et al.* (2003)[54]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS aCL, LA Hyperhomocysteinaemia	Cases = 30 pregnant women with DVT or PE Controls = 30 pregnant women without VTE	DVT diagnosed by Doppler PE diagnosed by ventilation perfusion scan	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Owen *et al.* (1997)[113]	Retrospective case–control	Hyperhomocysteinaemia	Cases = 21 women with placental abruption Controls = 19 women	No definition of placental abruption given	1 = Yes 2 = No 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Pabinger *et al.* (2000)[51]	Retrospective case–control	FVL	Cases = 64 women homozygous for FVL with ≥1 pregnancies Controls = 52 women with no FVL with ≥1 pregnancies	VTE by phlebography, Doppler or perfusion lung scanning. Miscarriage = fetal loss ≤23 weeks Stillbirth = intrauterine death >23 weeks	1 = Yes 2 = No 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Pattison *et al.* (2000)[132]	Randomised placebo-controlled trial	aCL, LA	Participants = 50 women with a history ≥3 recurrent miscarriages and positive for aCL and LA Intervention = identically packaged tablets of a placebo or aspirin (75 mg daily)	Live birth rate Gestational age at birth Birth weight Bleeding in pregnancy Hypertension or preeclampsia	1 = Yes 2 = NA 3 = Yes 4 = Yes 5 = No 6 = Yes 7 = Yes
Pauzner *et al.* (2001)[133]	Prospective cohort	aCL, LA	Participants = 42 women with previous fetal loss and/or previous VTE, in the presence of aCL and LA Intervention = low molecular weight heparin and low-dose aspirin or warfarin	Live birth rate Gestation at delivery Birth weight Teratogenicity Maternal bleeding Thrombotic events	1 = Yes 2 = NA 3 = No 4 = Yes 5 = No 6 = Yes 7 = NS
Pickering *et al.* (2001)[73]	Retrospective case–control	FII G20210A	Cases = 91 women with recurrent early pregnancy loss Controls = 66 women with no history of miscarriage or thrombosis	Early pregnancy loss = ≥3 fetal loss ≤12 weeks	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = Yes 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Pihusch *et al.* (2001)[74]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS aCL	Cases = 102 women with RSA Controls = 128 women without miscarriage	RSA = ≥2 fetal loss ≤25 weeks gestation	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = Yes 7 = NS
Rai *et al.* (1997)[130]	Randomised controlled trial	aCL, LA	Participants = 90 women with history ≥3 consecutive miscarriages with positive results for aCL and LA Intervention = low-dose aspirin or low-dose aspirin plus heparin (5000 U twice daily)	Live birth rate Gestation at delivery Birth weight VTE Thrombocytopenia Fractures Bruising at injection site	1 = Yes 2 = NA 3 = Yes 4 = Yes 5 = No 6 = Yes 7 = Yes
Rai *et al.* (2001)[61]	Retrospective case–control	FVL APCR	Cases = 904 women with a history of recurrent early miscarriage Controls = 150 women with no previous adverse pregnancy complication	Recurrent early miscarriage = ≥3 fetal loss <12 weeks	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Raijmakers *et al.* (2001)[110]	Retrospective case–control	MTHFR	Cases = 167 women with preeclampsia Controls = 403 population based control women with no preeclampsia	Preeclampsia = diastolic BP >90 mmHg + proteinuria >20 weeks gestation	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Raziel *et al.* (2001)[56]	Retrospective case–control	FVL FII G20210A MTHFR AT, PC, PS APCR Hyperhomocysteinaemia	Cases = 36 women with RPL Controls = 40 women with ≥1 successful pregnancy	RPL = ≥2 pregnancy losses in 1st or 2nd trimester	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Reznikoff-Etievan *et al.* (2001)[57]	Retrospective case-control	FVL FII G20210A AT, PC, PS, aCL, LA	Cases = 260 women with early unexplained recurrent miscarriage Controls = 240 healthy women	Early recurrent miscarriage = ≥2 fetal loss <10 weeks	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Rigo *et al.* (2000)[107]	Retrospective case–control	FVL MTHFR	Cases = 120 preeclamptic women Controls = 101 healthy pregnant women	Severe preeclampsia = BP >160/110 mmHg + proteinuria >3 g/24 h	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Rothbart *et al.* (1999)[90]	Retrospective case–control	FVL	Cases = 14 women with IUFD Controls = 14 women with no fetal death	IUFD = fetal demise ≥24 weeks without apparent explanation	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = Yes 7 = NS
Schjetlein *et al.* (1998)[97]	Retrospective case–control	aCL, LA	Cases = 200 women with preeclampsia Controls = 97 normotensive women	Preeclampsia = BP ≥140/90 mmHg	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = No 6 = Yes 7 = NS
Tal *et al.* (1999)[62]	Retrospective case–control	Acquired APCR (FVL negative) APCR caused by FVL	Cases = 125 women with pregnancy loss Controls = 125 women with ≥1 live birth but no past fetal loss	Pregnancy loss = 1st or 2nd trimester	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Tormene *et al.* (1999)[80]	Prospective cohort	FVL	Cases = 65 women with FVL Controls = 22 women with no FVL	Intrauterine fetal death >24 weeks	1 = Yes 2 = NS 3 = NA 4 = Yes 5 = No 6 = Yes 7 = Yes
Tormene *et al.* (2001)[52]	Retrospective case–control	FVL	Cases = 105 women with FVL Controls = 81 female non-carriers	VTE objectively diagnosed DVT confirmed by compression ultrasonography, impedance plethysmography or Doppler	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Van Pampus *et al.* (1999)[92]	Retrospective case–control	FVL aCL APCR Hyperhomocysteinaemia	Cases = 345 women with severe preeclampsia Controls = 67 women with uncomplicated pregnancies	Preeclampsia = diastolic BP ≥110 mmHg + proteinuria <34 weeks gestation	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS
Wiener-Megnagi *et al.* (1998)[111]	Retrospective case–control	FVL AT, PC, PS aCL, LA APCR	Cases = 27 women with placental abruption Controls = 29 women with normal medical and obstetric histories + no previous miscarriages	Placental abruption based on profuse vaginal bleeding in 3rd trimester of pregnancy + clinical observation of placenta after its expulsion or extraction	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Wouters *et al.* (1993)[60]	Retrospective case–control	Hyperhomocysteinaemia	Cases = 102 women with unexplained RSA Controls = 41 women	RSA = ≥2 pregnancy losses ≤16 weeks of menstrual age	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = NS

continued

TABLE 5 *Study characteristics of studies on thrombophilia and pregnancy included in the review (cont'd)*

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality criteria[a]
Yasuda *et al.* (1995)[85]	Prospective cohort	aCL	Participants = 860 pregnant women	Fetal death >24 weeks Preeclampsia (Definition by the International Society for the Study of Hypertension in Pregnancy) IUGR = birth weight <10th percentile for gestational age	1 = Yes 2 = NA 3 = NS 4 = Yes 5 = No 6 = Yes 7 = NS
Younis *et al.* (2000)[58]	Retrospective case–control	FVL APCR	Cases = 78 women with unexplained recurrent pregnancy losses Controls = 139 women with ≥1 successful pregnancy and no history of pregnancy loss	≥2 pregnancy losses in 1st or 2nd trimester	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = Yes 7 = NS

APCR, activated protein C resistance, AT, antithrombin deficiency; BP, blood pressure; CL, elevated anticardiolipins; FVL, factor V Leiden; IUGR, intrauterine growth restriction; LA, lupus anticoagulants; MTHFR, methylenetetrahydrofolate reductase; PC, protein C deficiency; PE, pulmonary embolism; PS, protein S deficiency; RSA, recurrent spontaneous abortion.

[a] Quality criteria: 1 = representative inception cohort; 2 = comparator group reliably ascertained; 3 = blinded assessment of outcomes; 4 = confounding factors comparable; 5 = adjust for confounding; 6 = appropriate follow-up; 7 = description of drop-outs; NA, not applicable; NS, not stated.

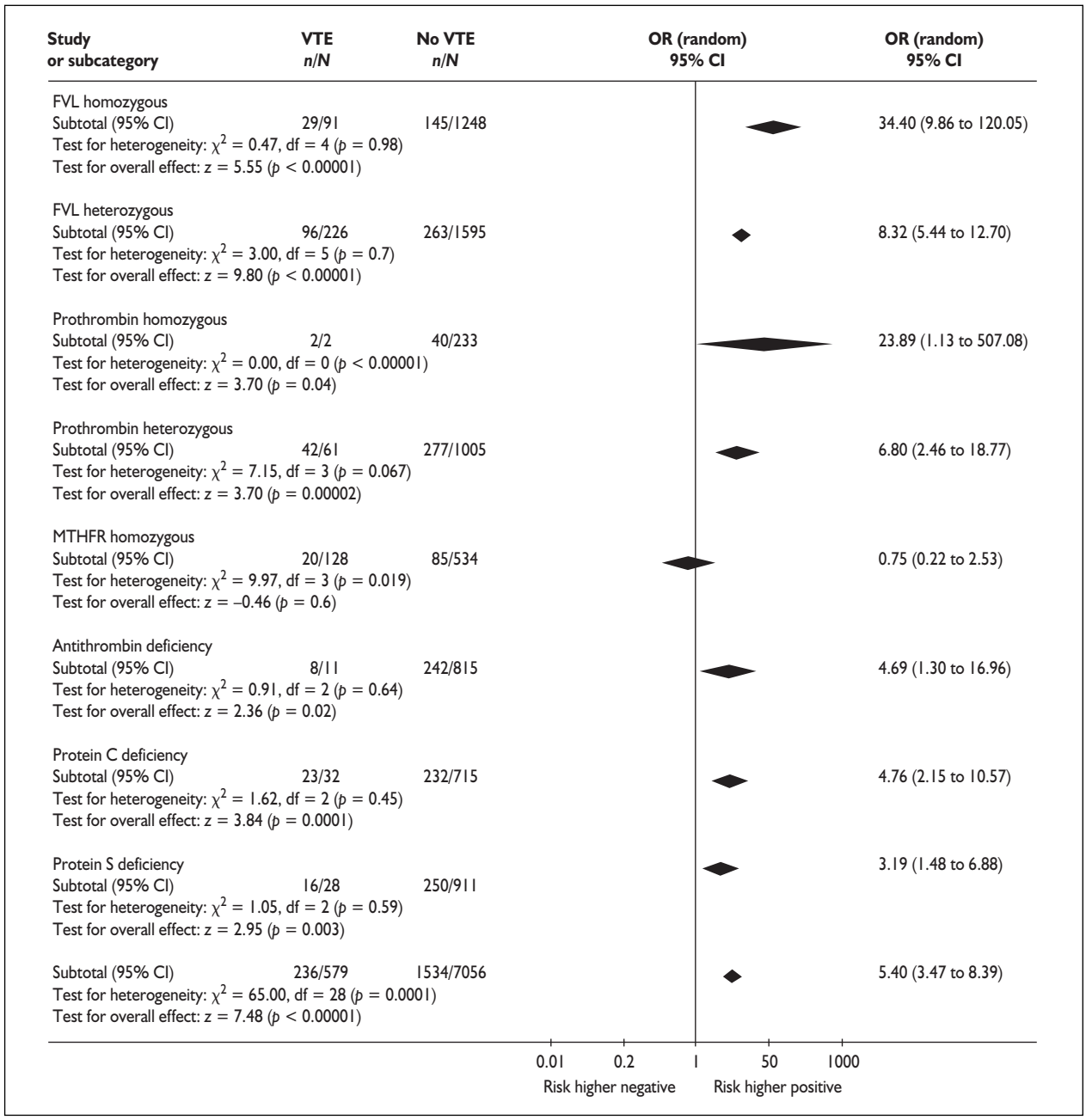

FIGURE 6 *Odds ratios for selected thrombophilias and risk of VTE in pregnancy*

Venous thromboembolism

Nine studies assessing the risk of VTE in pregnancy with heritable thrombophilia were included (*Figure 6*).[27,47–54] It was not possible to analyse the risk of DVT and pulmonary embolism separately as studies measured VTE as a single outcome.

A strong association between VTE in pregnancy and FVL was found. The OR for homozygous FVL carriers was 34.40 (95% CI 9.86 to 120.05).[27,48,50–52] Heterozygous carriers of this mutation were at a lower risk, with an OR of 8.32 calculated.[27,47,49,50,52,53] Only one study examined the risk in homozygous carriers of prothrombin G20210A (OR 26.36; 95% CI 1.24 to 559.32). The risks of VTE in pregnancy associated with other heritable thrombophilias were as follows; heterozygous prothrombin G20210A (OR 6.80) protein C deficiency (OR 4.76), antithrombin deficiency (OR 4.69) and protein S deficiency (OR 3.19).[27,47,49,53,54] Results of the association between homozygosity for methylene tetrahydrofolate reductase (MTHFR) and VTE in pregnancy indicated heterogeneity ($p = 0.02$) but was not significant (95% CI 0.22 to 2.53).[47,50,53,54]

Early pregnancy loss

Pregnant women homozygous for FVL or with hyperhomocysteinaemia were at highest risk of early pregnancy loss, with an OR of 6.25 obtained for each thrombophilia[55–60] (*Figure 7*). Data from three studies (n = 1521) indicated that acquired APC resistance in the absence of FVL was significantly associated with early pregnancy loss (OR 4.04; 95% CI 1.67 to 9.76).[58,61,62] The ORs for elevated anticardiolipin antibodies and lupus anticoagulants were 3.40 and 2.97, respectively.[63–69] However, pooled data on lupus anticoagulants indicated significant heterogeneity (p = 0.04). Sensitivity analysis was performed. One study had not excluded underlying causes of pregnancy loss[68] and another study compared cases with pregnancy loss to non-pregnant controls with non-recurrent losses.[67] After excluding these studies, the results were no longer heterogeneous. Heterozygosity for prothrombin and FVL were associated with a lower risk of early pregnancy loss compared with other thrombophilias. The respective ORs for these mutations were 2.49 and 1.59.[55,57,58,61,62,70–74] The remaining thrombophilias, including homozygous MTHFR, antithrombin and protein C and S deficiencies, were not significantly associated with an increased risk of early pregnancy loss.[56,67,74–78]

Early pregnancy loss was separated into recurrent loss in the first trimester and single pregnancy loss in the second trimester. FVL carriers were found to be at higher risk of pregnancy loss in the second than the first trimester (OR 4.12 and 1.91, respectively).[55,57,61,62,75,79,80] However, the results for recurrent first trimester loss indicated heterogeneity and remained so despite conducting sensitivity analysis (p = 0.00). The risk of second trimester pregnancy loss was also higher than recurrent first trimester loss in heterozygous carriers of prothrombin G20210A, with respective ORs of 8.60 and 2.70 calculated.[55,57,72–75,79] Homozygosity for MTHFR C677T showed a negative association with recurrent first trimester loss, but this finding was not significant (OR 0.86; 95% CI 0.44 to 1.69).[75–77] Anticardiolipin antibodies and hyperhomocysteinaemia were significantly associated with recurrent first trimester loss; however, these risks were established from only one study.[59,65] Acquired APC resistance was associated with a higher risk of recurrent pregnancy loss in the first trimester than non-recurrent loss in the second trimester.

Late pregnancy loss

The results show that pregnant women with protein S deficiency are at the highest risk of late pregnancy loss. Pooled data on two studies (n = 816) generated an OR of 20.09.[81,82] The risk of late pregnancy loss for anticardiolipin antibodies and lupus anticoagulants was lower than that obtained for early pregnancy loss, with ORs of 3.30 and 2.38, respectively.[64,68,81,83–85] FVL is associated with a higher risk of late pregnancy loss than early pregnancy loss (*Figure 7*).[82,86–90] An OR of 2.06 was obtained for late pregnancy loss compared with 1.59 for early pregnancy loss within carriers of the mutation. Additionally, results indicated that heterozygous carriers of prothrombin are more likely to suffer late pregnancy loss than early pregnancy loss (OR 2.66 for late loss compared with 2.49 for early loss).[72,81,82,88,91] Antithrombin deficiency, protein C deficiency, and homozygosity for MTHFR C677T were also associated with late pregnancy loss; however, these findings were not significant.[16,81–83,88,91] Hyperhomocysteinaemia and acquired APC resistance were not associated with late pregnancy loss; however, these risks came from only one study involving 62 women and were found to be not significant.[83]

Preeclampsia

Pooled data showed that pregnant women with hyperhomocysteinaemia are more likely to develop preeclampsia than women with other thrombophilias (OR 3.49; 95% CI 1.21 to 10.11)[83,92] (*Figure 8*). The acquired thrombophilias, elevated anticardiolipin antibodies and lupus anticoagulants were associated with a lower risk for preeclampsia than for pregnancy loss.[83,85,92–97] FVL homozygotes were found to be at lower risk of developing preeclampsia than heterozygous carriers of the mutation (OR 1.87 and 2.34, respectively). However, the result for FVL homozygotes was not significant.[83,92,96,98–108] Following the same pattern for other adverse pregnancy outcomes, MTHFR was associated with the lowest risk of preeclampsia (OR 1.32; 95% CI 1.05 to 1.66).[50,83,95,100,102–104,106,107,109,110] Deficiencies of antithrombin, protein C and protein S were not significantly associated with preeclampsia.

Placental abruption

Homozygosity for FVL was associated with the highest risk of placental abruption, but this finding was not significant (95%CI 0.41 to 171.21). Therefore, the risk of placental abruption was the highest with heterozygous prothrombin G20210A (OR 7.71), followed by heterozygous FVL (OR 4.70) and hyperhomocysteinaemia (OR 4.26) (*Figure 9*).[16,72,86,111–113] Homozygosity for MTHFR, deficiencies of antithrombin, protein C and protein S, elevated anticardiolipin antibodies

Early pregnancy loss before 24 weeks gestation

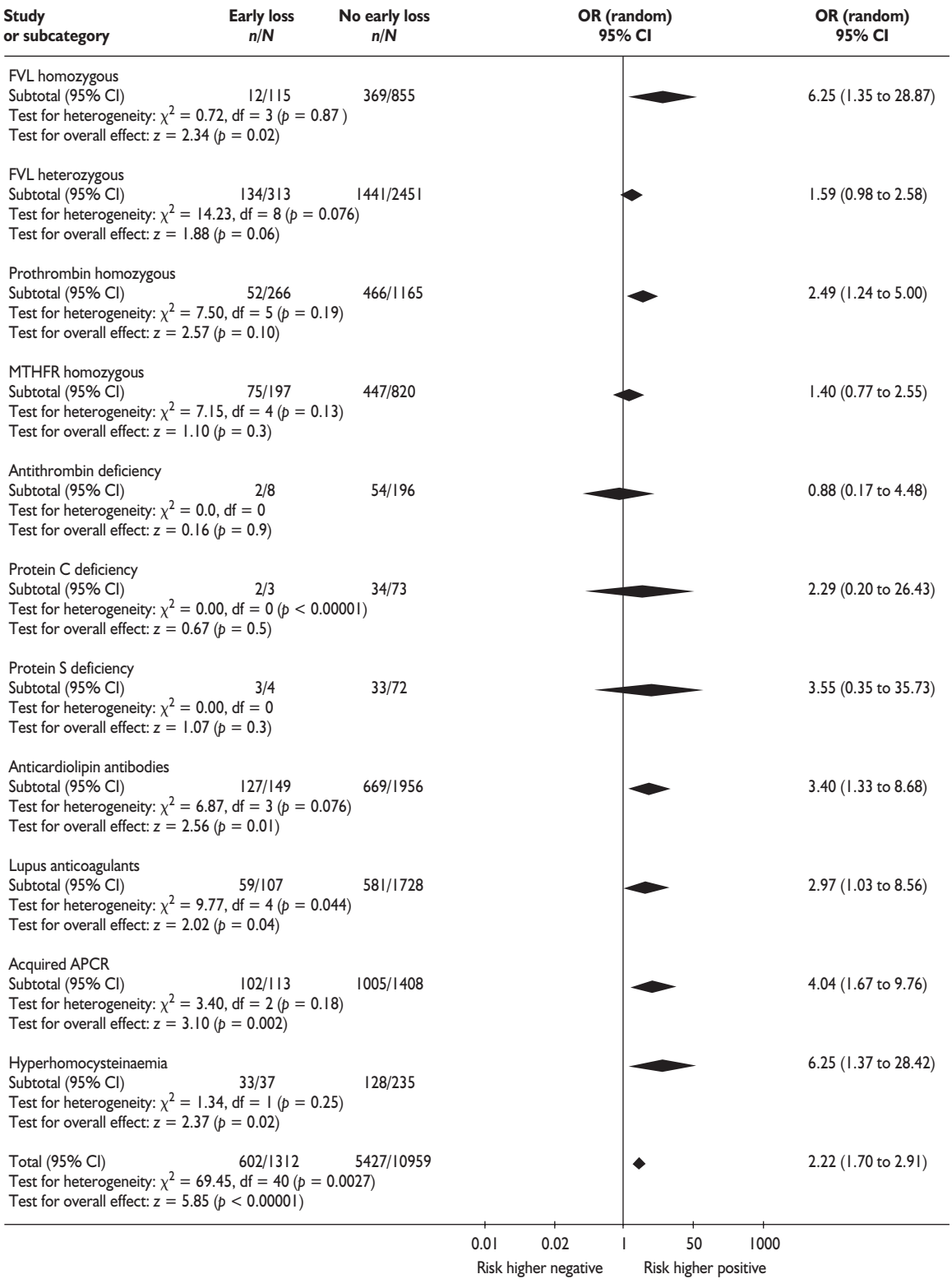

FIGURE 7 *Odds ratios for selected thrombophilias and risk of pregnancy loss*

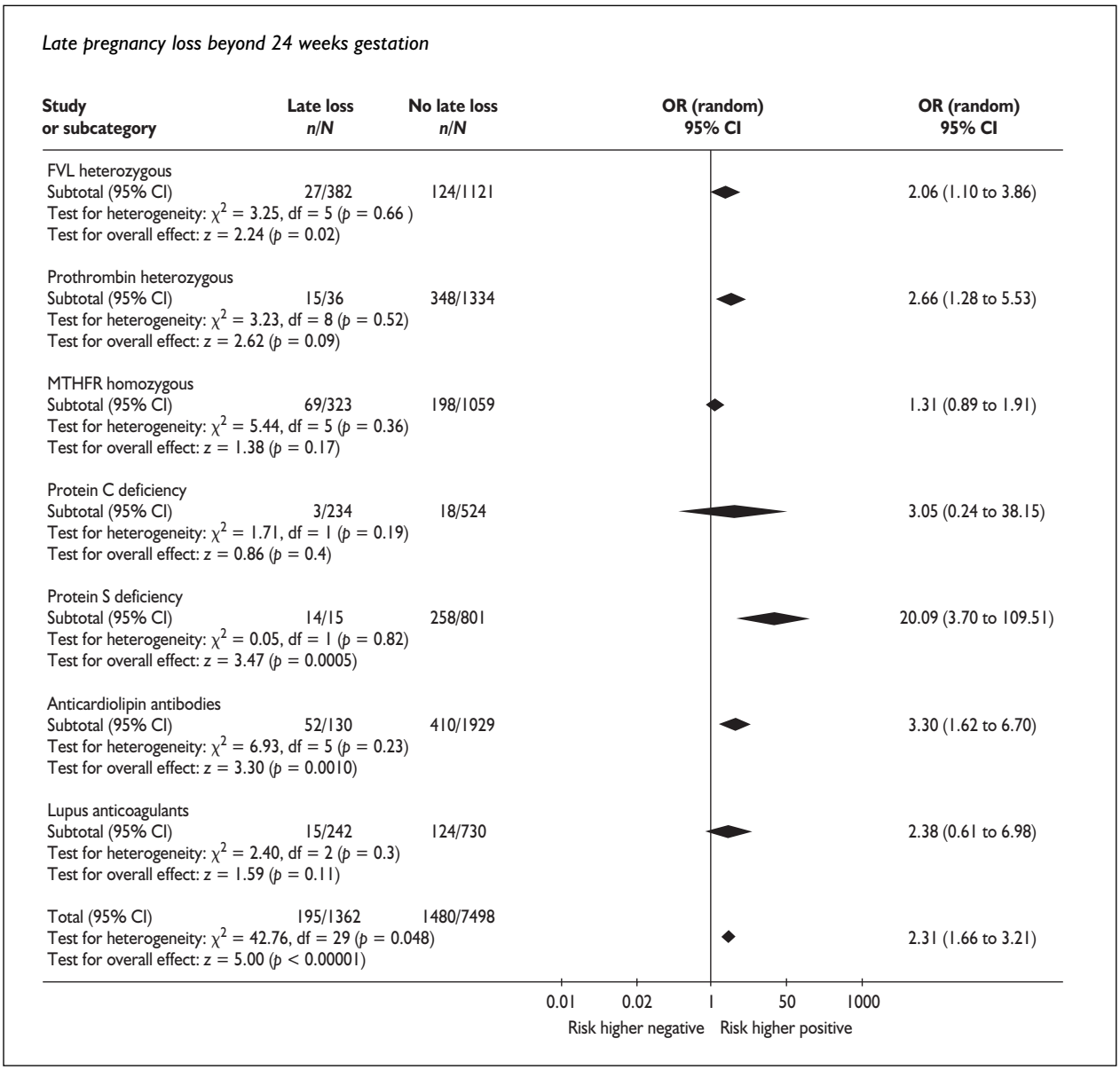

FIGURE 7 *(cont'd)*

and acquired APC resistance were not significantly associated with placental abruption.

Intrauterine growth restriction

Seven studies (n = 4487) were included (*Figure 10*).[83,85,86,114–117] The highest risk for IUGR and thrombophilia was for homozygous FVL (OR 15.20; 95% CI 1.32 to 174.96).[114,115] Pregnant women heterozygous for prothrombin G20210A were also at increased risk of experiencing a pregnancy complicated by IUGR (OR 2.91). The remaining thrombophilias studied were not significantly associated with IUGR.

Postpartum haemorrhage

Of the 72 studies included in this review, none measured or recorded postpartum haemorrhage as an outcome. Therefore, it was not possible to calculate the risk of developing this complication with thrombophilia.

Orthopaedic surgery

Of 149 studies identified from the searches, only eight met the inclusion criteria (*Figure 11*). Those studies which were retrieved for detailed evaluation but subsequently excluded from the review are listed in Appendix 6.

Overall, the studies included a total of 4218 patients undergoing total hip and/or knee replacement surgery (*Table 6*). No studies on patients undergoing neck of femur repairs were

TABLE 6 *Study characteristics of studies on thrombophilia and orthopaedic surgery included in the review*

Source	Type of study	Participants	Prophylaxis	Thrombophilia	Outcome measures	Quality criteria[a]
Lindahl *et al.* (1999)[118] Sweden	Prospective cohort	Cohort (n = 645) – patients undergoing elective hip or knee replacement	LMWH throughout hospitalisation	APCR functional analysis (predilution) for the FV R506Q mutation	VTE events up to 3 months postoperatively Venography, ultrasonography or pulmonary scintigraphy requested for symptomatic patients	1 = Yes 2 = Yes 3 = NS 4 = NS 5 = No 6 = Yes 7 = Yes
Lowe *et al.* (1999)[119] UK, The Netherlands and Italy	Prospective cohort	Cohort (n = 480) – patients undergoing elective hip replacement surgery	LMWH, dextran, UFH, stockings, antiplatelet agents and other prophylaxis One patient had no records of prophylaxis	APCR (APC sensitivity ratios <0.70) associated with the presence of FVL, FVL, high factor VIIIc (>150%)	DVT Bilateral ascending venography on all patients 8–14 days after surgery	1 = Yes 2 = Yes 3 = Yes[b] 4 = Yes 5 = Yes 6 = Yes 7 = Yes
Philipp *et al.* (1998)[122] USA	Retrospective case–control	Cases (n = 30) – patients who underwent elective total hip arthroplasty and had confirmed diagnosis of VTE Controls (n = 55) – patients who underwent elective hip arthroplasty with no evidence of VTE, matched for age, sex and date of operation	Warfarin and/or enoxaparin and intermittent pneumatic compression during hospitalisation	FVL, MTHFR genotypes	VTE events. Surveillance bilateral lower extremity venous B-mode duplex ultrasonography with Doppler examination 4 days after surgery	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = NA 6 = Yes 7 = NA
Ryan *et al.* (1998)[123] USA	Prospective cohort Retrospective analysis	Cohort (n = 825) – patients undergoing total hip or knee replacement	Warfarin, heparin and external compression	FVL	DVT Bilateral ascending venography between days 5 and 9 after surgery (>90% patients)	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = NA 6 = Yes 7 = Yes

continued

TABLE 6 *Study characteristics of studies on thrombophilia and orthopaedic surgery included in the review (cont'd)*

Source	Type of study	Participants	Prophylaxis	Thrombophilia	Outcome measures	Quality criteria[a]
Svensson *et al.* (1997)[124] Sweden	Retrospective cohort (selected from RCT)	Cohort (n = 198) – patients undergoing elective primary hip arthroplasty	Enoxaparin during hospitalisation. Subsequently randomised into extended enoxaparin for 3 weeks or placebo group	FVL	DVT Bilateral ascending phlebography between 19 to 23 days after discharge from hospital	1 = Yes 2 = Yes 3 = Yes 4 = NS 5 = No 6 = Yes 7 = NA
Wahlander *et al.* (2002)[121] Sweden	Retrospective cohort (selected from RCT)	Cohort (n = 1876) – patients scheduled for elective total hip or knee replacement therapy	Randomised to receive either dalteparin or melagatran and oral ximelagatran	FVL Prothrombin G20210A	VTE events Bilateral venography on days 8–11. Patients were followed for 4–6 weeks after surgery	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = NA 6 = Yes 7 = Yes
Westrich *et al.* (2002)[120] USA	Retrospective case–control	Cases (n = 14) – patients with documented PE after total hip arthroplasty Controls (n = 14) matched, undergone hip arthroplasty without any clinical indication of thromboembolism	Aspirin, mechanical compression, heparin, warfarin	Prothrombin G20210A AT Homocysteine FVL PC PS	PE Documented by ventilation–perfusion lung scanning or by spiral computed tomography	1 = Yes 2 = Yes 3 = NS 4 = Yes 5 = NA 6 = Yes 7 = NA
Woolson *et al.* (1998)[125] USA	Retrospective case–control	Cases (n = 36) – patients who had undergone primary or revision total hip arthroplasty Controls (n = 45) – patients who had undergone total hip arthroplasty and had negative findings on surveillance ultrasound tests were randomly chosen	Intra- and postoperative intermittent pneumatic compression, aspirin, warfarin	FVL	DVT Post discharge surveillance for proximal DVT between postoperative day 5 and 7 using compression duplex ultrasound	1 = Yes 2 = Yes 3 = NS 4 = No 5 = No 6 = NS 7 = NA

APCR, activated protein C resistance; AT, antithrombin III; DVT, deep vein thrombosis; FVL, factor V Leiden; LMWH, low molecular weight heparin; PC, protein C; PE, pulmonary embolism; PS, protein S; RCT, randomised controlled trial; UFH, unfractionated heparin; VTE, venous thromboembolism (DVT + PE).

[a] Quality criteria: 1 = representative inception cohort; 2 = comparator group reliability ascertained; 3 = blinded assessment of outcomes; 4 = confounding factors comparable; 5 = adjust for confounding; 6 = appropriate follow-up; 7 = description of drop-outs; NA, not applicable; NS, not stated.

[b] Personal communication – blinded assessment of outcome was not stated in the article.

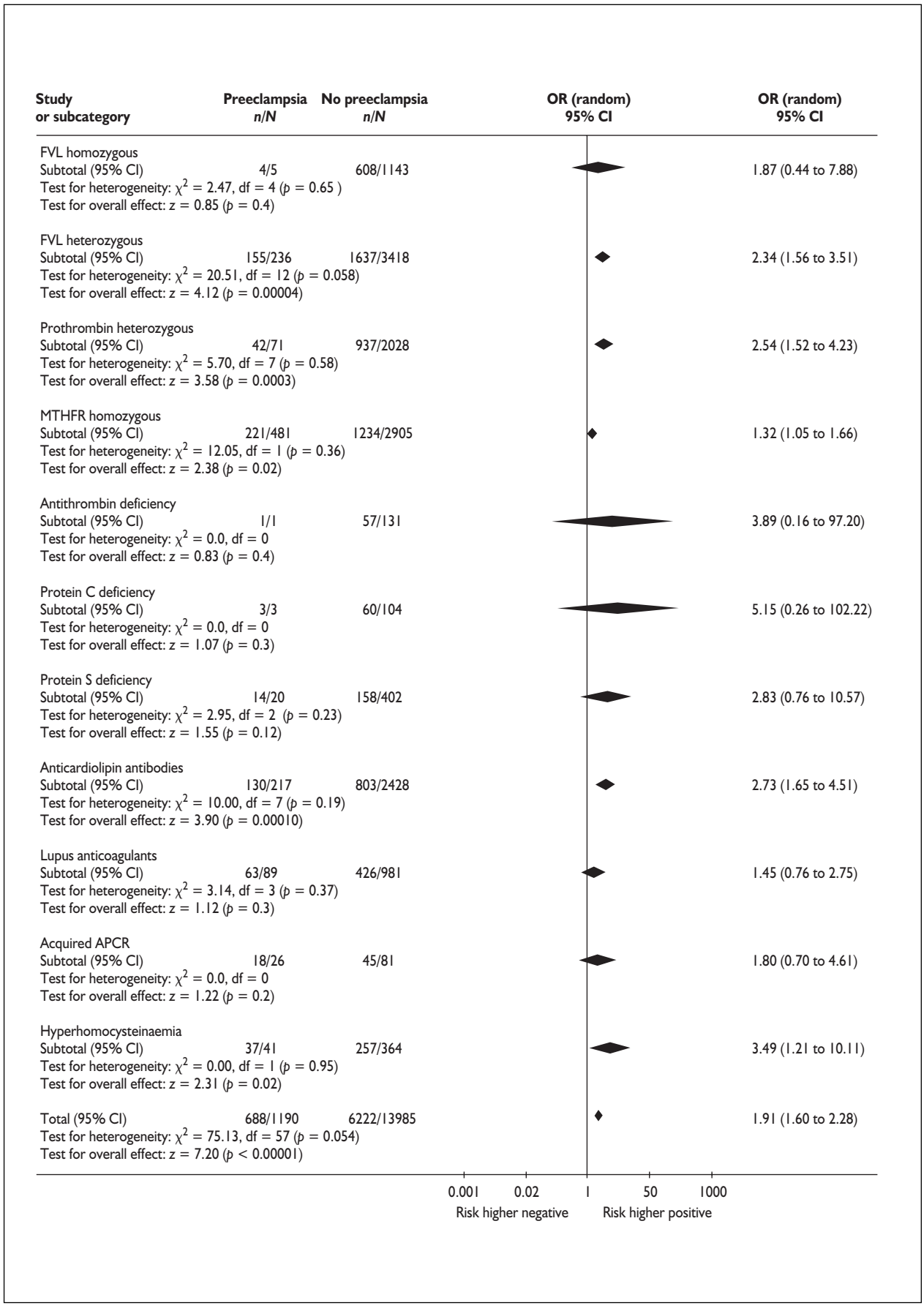

FIGURE 8 *Odds ratios for selected thrombophilias and risk of preeclampsia*

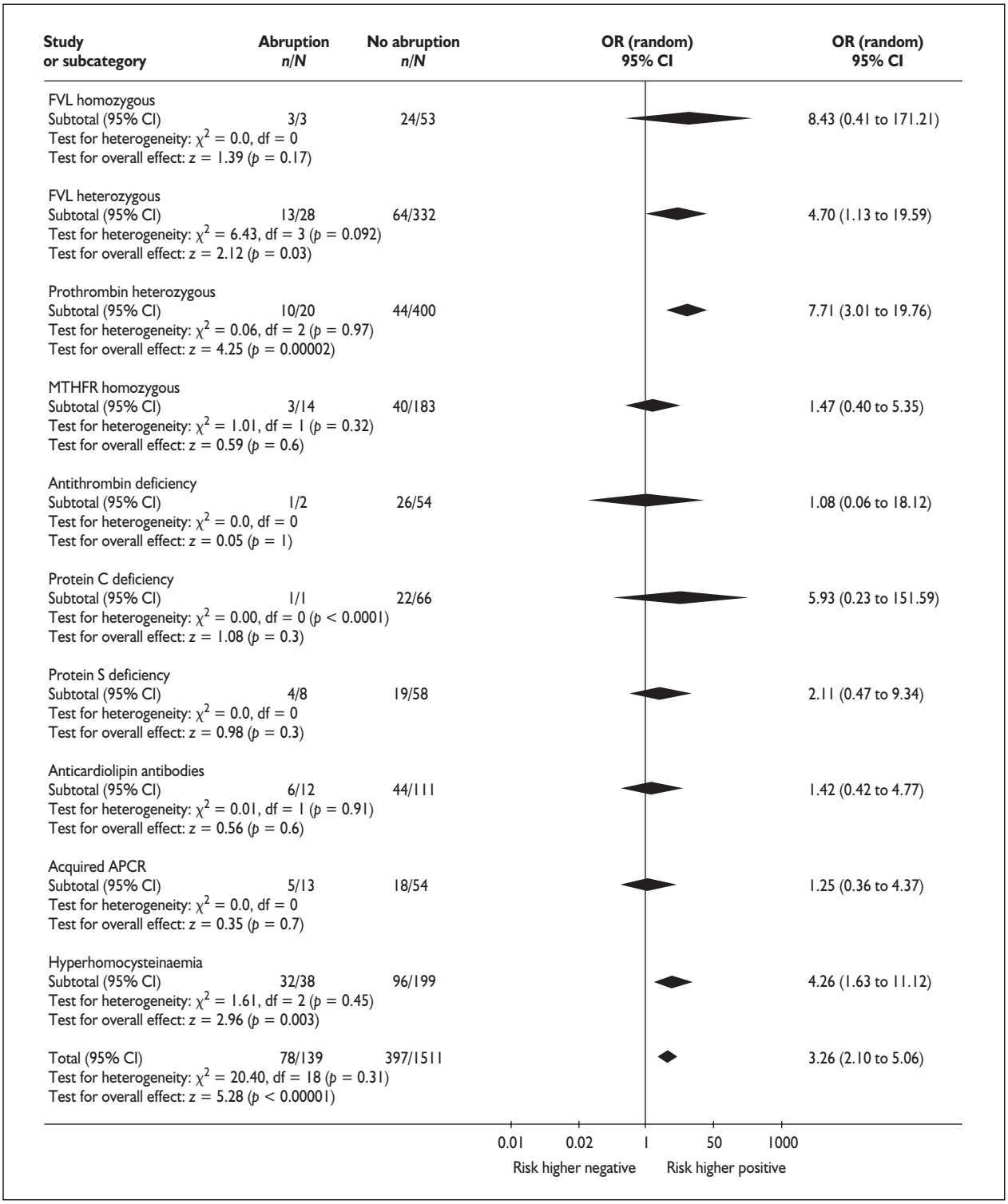

FIGURE 9 *Odds ratios for selected thrombophilias and risk of placental abruption*

found. All the included studies measured FVL. Prothrombin G20210A was measured in two studies. Other thrombophilic defects such as antithrombin deficiency, hyperhomocysteinaemia, MTHFR and elevated factor VIIIc were only reported in individual studies.

The methodological quality of the studies varied (*Table 6*). The major limitation common to most studies was the failure to measure or adjust for confounding factors. Three studies failed to describe blinded assessment of outcomes; however, this does not necessarily equate to the absence of

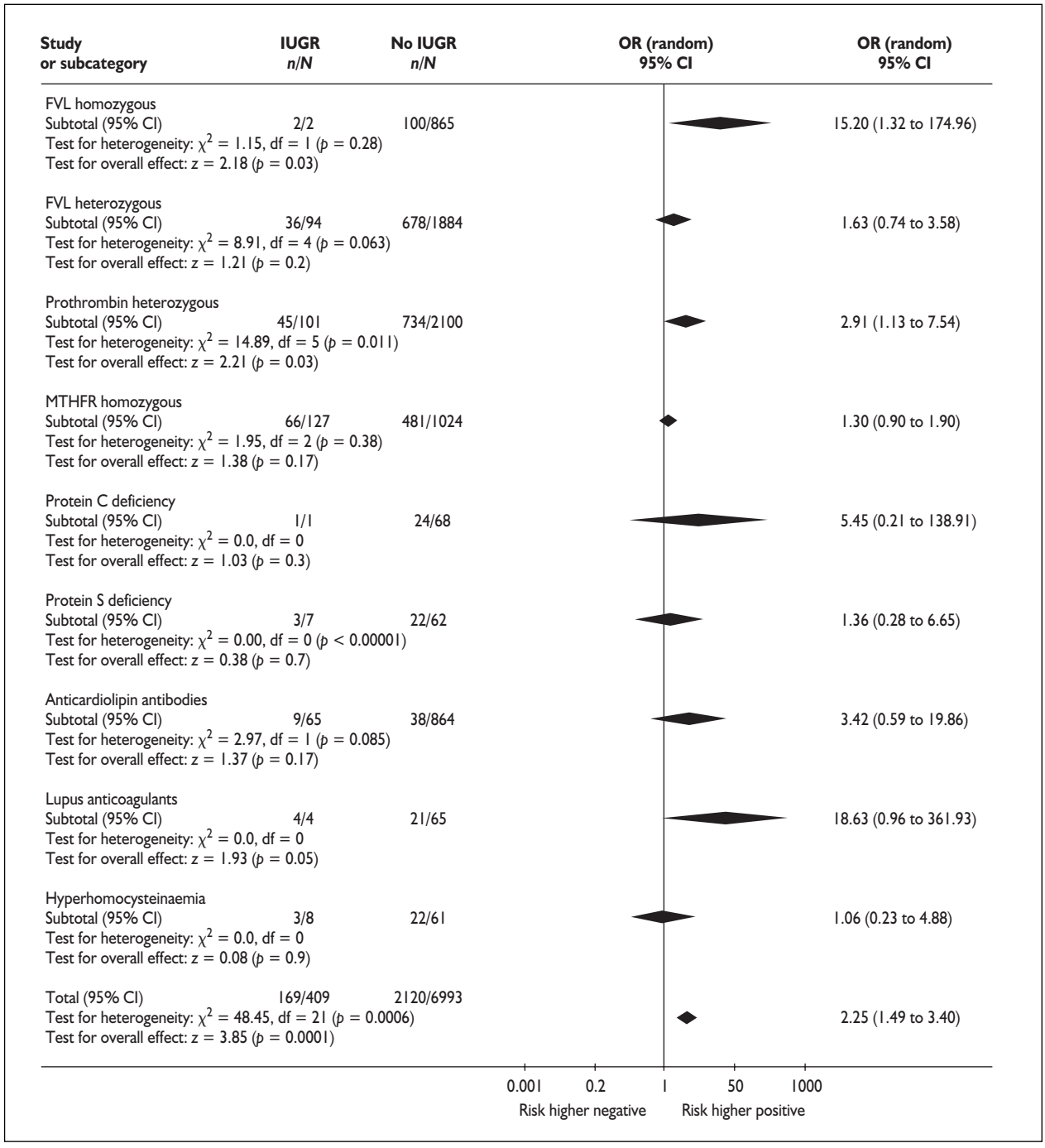

FIGURE 10 *Odds ratios for selected thrombophilias and risk of IUGR*

blinding. In the test for heterogeneity, stratified by individual thrombophilic defects, there was little evidence of the methodological quality of the studies influencing the results ($p > 0.10$).

Venous thromboembolism

The association between thrombophilia and VTE was modest and non-significant (*Table 6*). Significant differences in the incidence of VTE between patients with and without thrombophilia were observed in one study[118] with FVL (OR 5.42; 95% CI 2.18 to 13.47) and another with elevated factor VIIIc[119] (OR 1.65; 95% CI 1.06 to 2.58). Meta-analysis was carried out on studies that measured FVL and prothrombin G20210A (*Figure 12*).

All eight studies investigated the association between FVL and VTE in patients undergoing hip or knee replacement. All patients received postoperative thromboprophylaxis throughout hospitalisation. The most common endpoint used was asymptomatic DVT, detected by early

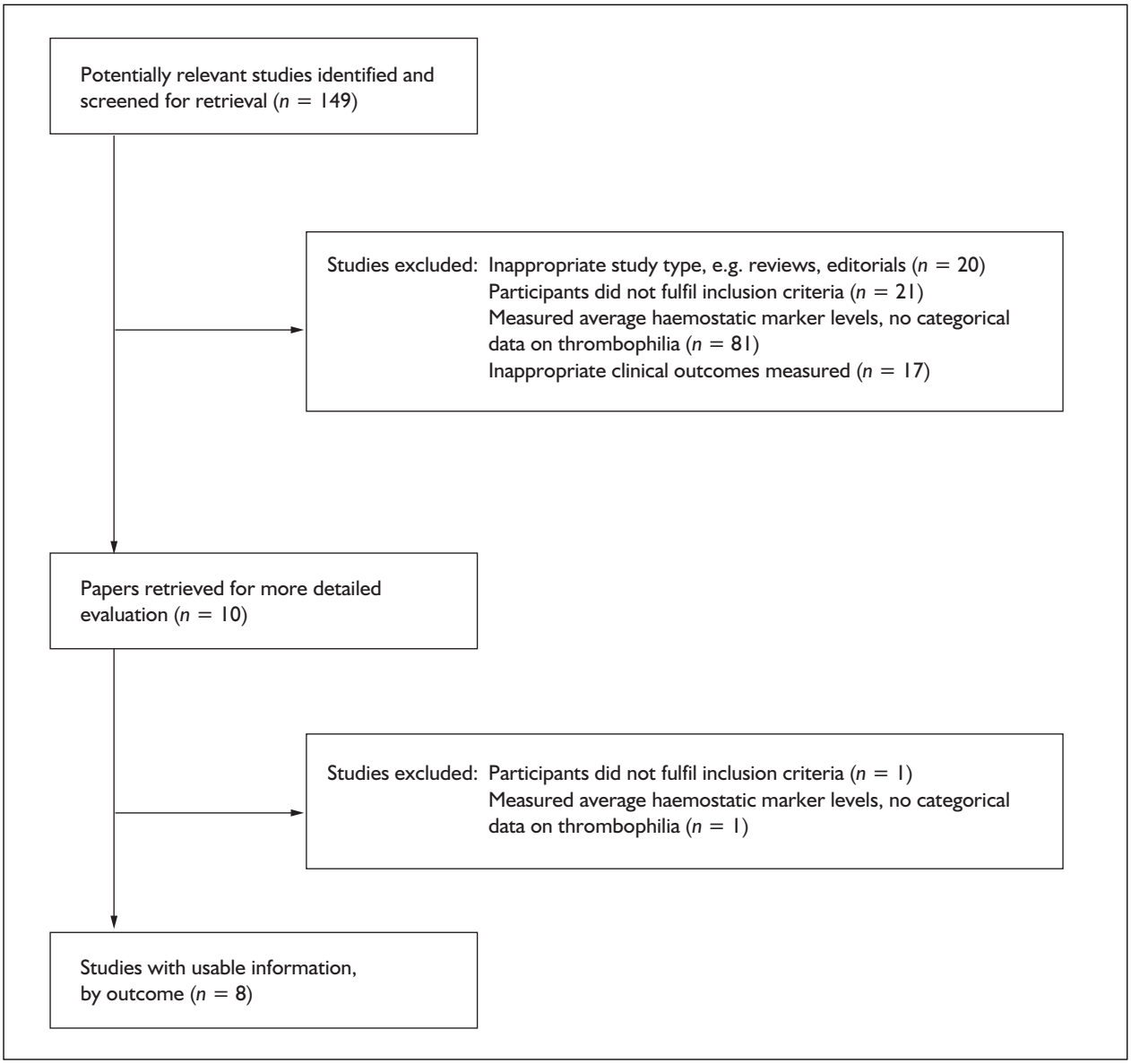

FIGURE 11 *'Trial flow' – selection of studies for systematic review in orthopaedic surgery*

venographic screening, between 4 and 23 days after surgery. In contrast, Lindahl and colleagues[118] recorded symptomatic VTE up to 3 months after surgery and Westrich and colleagues[120] recorded pulmonary embolism as the sole clinical outcome. Only one study[118] showed evidence of significant association between FVL and VTE post-hip or -knee replacement (*Table 6*). Meta-analysis was carried out on seven studies as one study[120] reported no patients with FVL in any participants and was excluded from the analysis. Despite variations in study methodology, there was no evidence of heterogeneity ($p = 0.29$) and the results from the studies showed low inconsistency ($I^2 = 18.70\%$). Significant association was observed between FVL and VTE (pooled OR 1.86; 95% CI 1.27 to 2.74).

Prothrombin G20210A was described in two studies on patients undergoing total hip or knee replacement (*Figure 13*). One study ($n = 14$) showed no evidence of association between prothrombin G20210A and pulmonary embolism (OR of 12.43; 95% CI 0.60 to 256.66).[120] In another study ($n = 1255$), assessing prothrombin G20210A and asymptomatic VTE,[121] OR 1.04 (95% CI 0.48 to 2.25) was observed. However, significant association was detected when examining the data on PE in isolation (OR 8.42; 95% CI 1.75 to 40.53). When considering pulmonary embolism only, a pooled OR of 9.14 (95% CI 2.27 to 36.89) was observed. There was no evidence of heterogeneity ($p = 0.79$) or inconsistency between the results of the two studies ($I^2 = 0.00\%$).

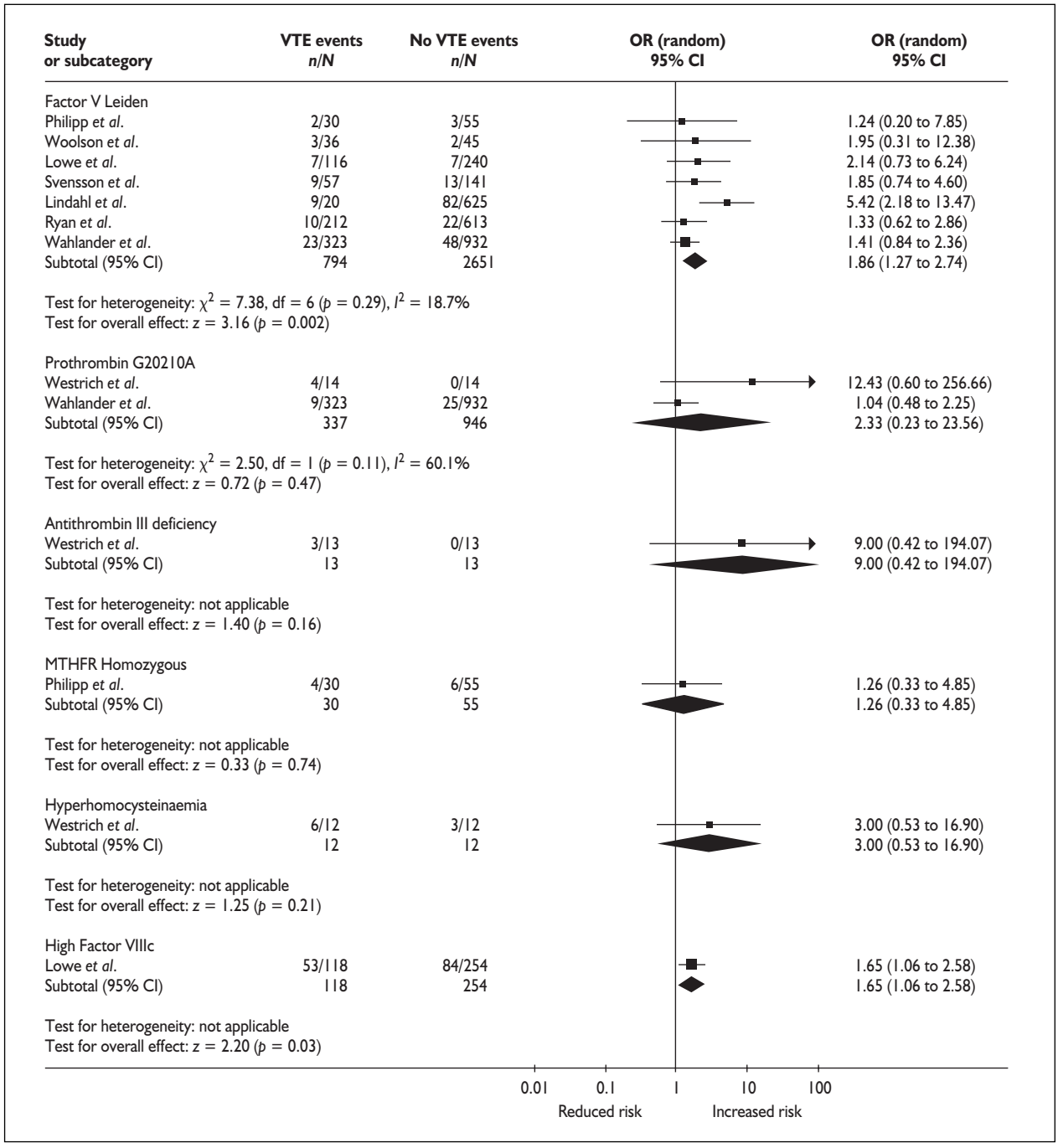

FIGURE 12 *Odds ratios for selected thrombophilias and the risk of VTE after major elective orthopaedic surgery*

Antithrombin deficiency and hyperhomocysteine were also measured in the same study, producing ORs of 9.00 (95% CI 0.42 to 194.07) and 3.00 (95% CI 0.53 to 16.90), respectively. However, these results were non-significant and severely limited by power in detecting any association. Similarly, no significant association was found between MTHFR and postoperative asymptomatic VTE (OR 1.26; 95% CI 0.33 to 4.85), which was reported in one study (n = 85).[122] Significant association between high factor VIIIc and asymptomatic DVT was shown by Lowe and colleagues (OR 1.65; 95% CI 1.06 to 2.58).[119] However, this association became non-significant when the results were adjusted for confounding factors including age, sex, body mass index, varicose veins, use of compression stockings, blood group for factor VIIIc, study centre and assay batch.

Sensitivity analysis of asymptomatic outcomes included data on asymptomatic DVT from four studies.[119,123–125] The exclusion of the data on symptomatic outcomes reduced the degree of

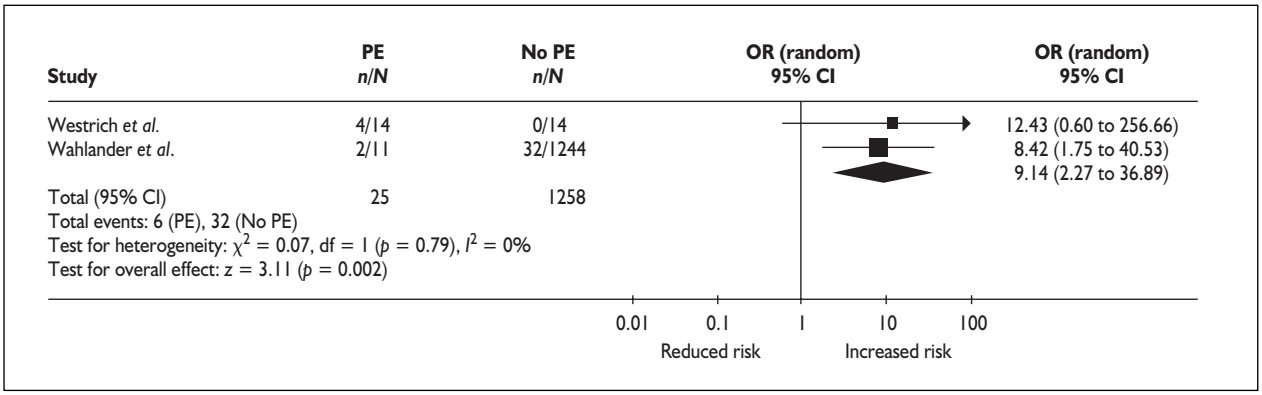

FIGURE 13 *Odds ratios for prothrombin G20210A mutation and the risk of pulmonary embolism (PE) after major elective orthopaedic surgery*

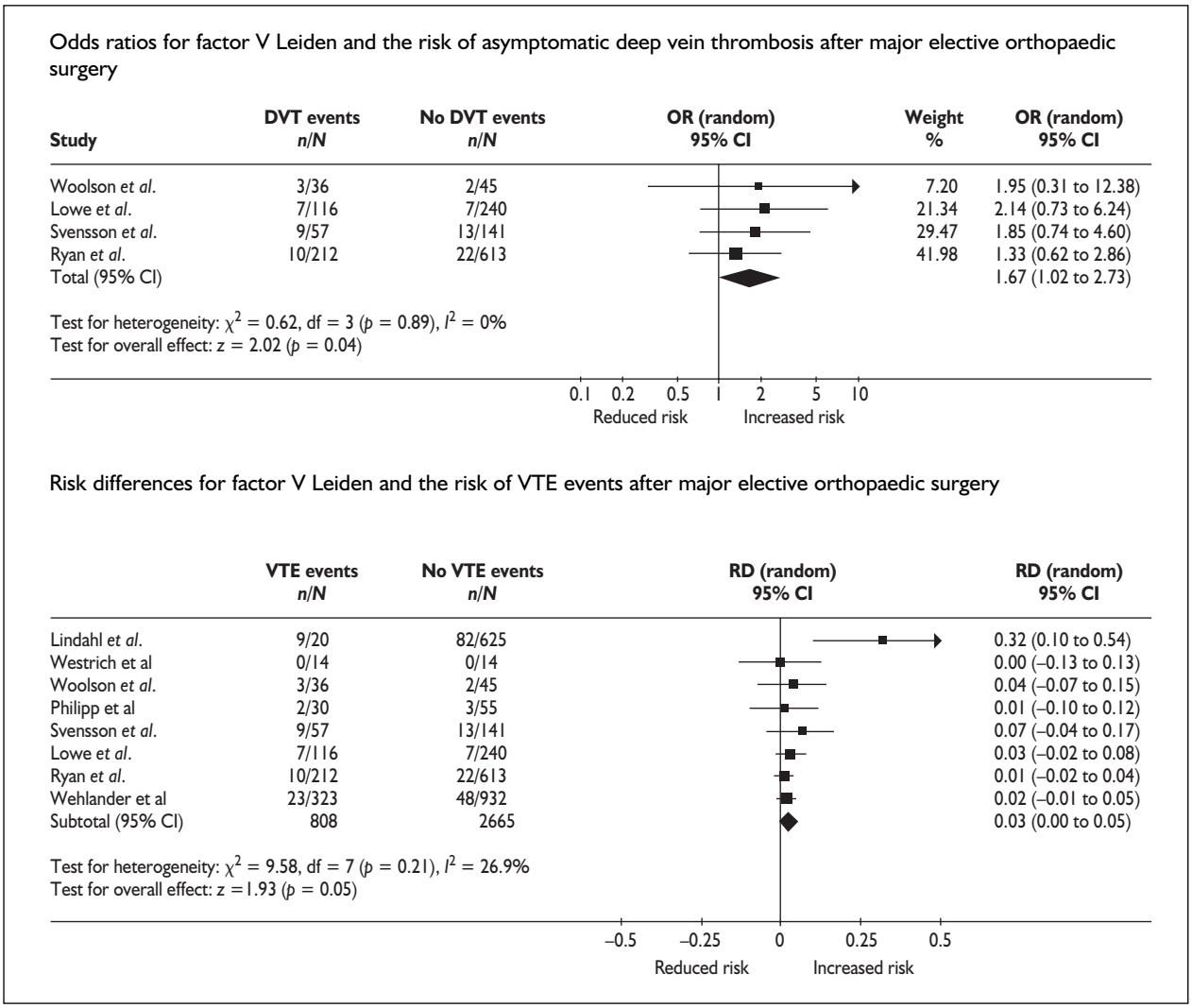

FIGURE 14 *Sensitivity analysis – orthopaedic surgery review*

inconsistency among the study results ($p = 0.95$; $I^2 = 0.00\%$). In addition, similarly to the results of the meta-analysis, significant association was observed between FVL and asymptomatic DVT only (OR 1.67; 95% CI .02 to 2.73).

Studies that recorded no events in both groups are generally excluded from meta-analysis. Sensitivity analysis was also carried out to investigate the impact by including the study with no events in the analysis (*Figure 14*). However, any measure of

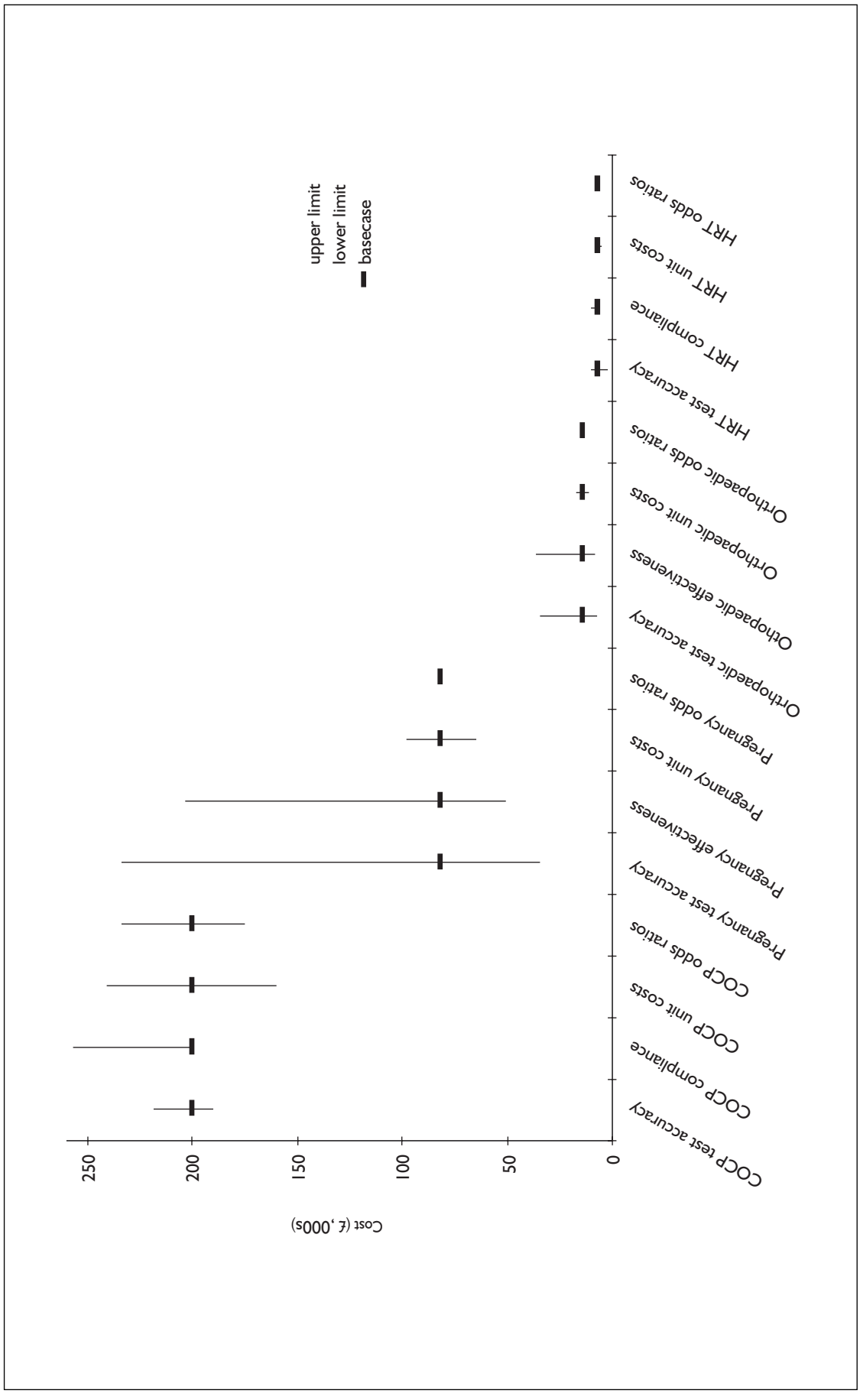

FIGURE 15 *Sensitivity analysis for the cost-effectiveness model. COCP, combined oral contraceptives; HRT, hormone replacement therapy. Test accuracy, sensitivity and specificity varied between 50% and 100%; COCP and HRT compliance tested at 50%; orthopaedic and pregnancy prophylaxis effectiveness varied between 20% and 80%; unit costs were inflated and deflated by 20%; odds ratios, extreme values of the 95% CI used.*

effect calculated as a ratio is undefined when event rates are zero. Therefore, this analysis compared effects expressed as risk difference, on an absolute scale. A significant difference in absolute risk difference was only observed in the study conducted by Lindahl and colleagues (risk difference 0.32; 95% CI 0.10 to 0.54).[118] The pooled risk difference between FVL carriers with and without VTE events was 0.03 (95% CI 0.00 to 0.05), indicating an excess risk of VTE events. The results showed that the exclusion of the zero event study had little effect on the overall results.

Mortality

Mortality was recorded in two studies.[118,121] One study (n = 645) reported four deaths (one myocardial infarction and three undetermined causes) in the whole study population,[118] one of whom was FVL positive. In another study (n = 1600), four deaths were reported (pulmonary embolism, myocarditis, heart failure and pneumonia).[121] The patient who died of pneumonia was FVL positive.

Effectiveness of prophylaxis

Pregnancy

Eight studies (n = 619) were found to evaluate the effectiveness of prophylactic interventions in pregnant women with thrombophilia in the prevention of pregnancy loss.[126–133] No studies on the prevention of VTE events were found. Of the above eight studies, four assessed the effectiveness of heparin plus aspirin versus aspirin alone for recurrent pregnancy loss associated with antiphospholipids.[126–128,130] An OR of 1.62 (95% CI 0.51 to 5.10) was found in favour of low-dose aspirin plus heparin in preventing recurrent pregnancy loss. No cases of thrombocytopenia, osteoporotic fractures, VTE or major bleeding occurred so ORs for these adverse outcomes were not calculated. However, minor bleeding (including haematuria, nosebleeds, gumbleeds and bleeding at the injection site) occurred in two of the studies and a pooled OR of 1.68 (95% CI 0.38 to 7.39) was estimated in favour of low-dose aspirin alone.[128,130]

In one study, Gris and colleagues[131] compared low-dose aspirin and LMWH in women with a single unexplained fetal loss from the 10th week of pregnancy. Patients treated with LMWH were more likely to have a healthy live birth (OR, 15.5; 95% CI 7.0 to 34.0). Small for gestational age infants were more frequent in patients treated with low-dose aspirin. No other side-effects of the treatment were evident in either patients or newborns. One study compared the effectiveness of low-dose aspirin versus a placebo,[132] one study compared low- and high-dose heparin[129] and another study compared warfarin and heparin.[133] Therefore, as the prophylactic therapies in these studies are not comparable, the results could not be combined in a meta-analysis.

Orthopaedic surgery

All eight studies included in the review of risk complications in patients with thrombophilia, undergoing major elective orthopaedic received thromboprophylaxis (*Figure 11*). Despite describing the use of prophylaxis in the study population, four studies failed to present sufficient data on prophylactic use and VTE events.[118,120–122] Woolson and colleagues[125] provided baseline data on prophylactic use of intermittent pneumatic compression alone, in combination with aspirin or with low-dose warfarin and Ryan and colleagues[123] recorded prophylactic use of warfarin, heparin and external compression. Both studies showed no significant differences in VTE rates among various prophylactic therapies. Similarly, Lowe and colleagues[119] recorded the use of prophylactic methods in all patients. Significant association between DVT rate and thromboprophylaxis was only observed with the use of stockings (adjusted OR 0.39; p = 0.00). Svensson and colleagues[124] examined the effects of prolonged prophylaxis (3 weeks after surgery) with enoxaparin, and showed potential benefit (OR 0.9; 95% CI 0.2 to 5.7) compared with short prophylaxis (OR 4.2; 95% CI 1.02 to 17.5).

Cost-effectiveness analysis

Delphi studies

Management of adverse clinical outcomes in pregnancy

Completed questionnaires were received from 27 respondents. A consensus relating to the management strategies of various adverse clinical events of interest for the economic model was established.

Deep vein thrombosis

Compression ultrasonography is most commonly used to confirm DVT, both in pregnancy and in the postpartum period. All pregnant women with a suspected DVT are managed as inpatients, the main treatment being LMWH, and the average length of hospital stay is 3 days (range from 1 to 10 days). Following a DVT, anticoagulant treatment usually lasts for 3 months postpartum

(range from six weeks to 6 months postpartum). Both LWMH and/or warfarin are the methods of anticoagulation administered in the postpartum period.

Pulmonary embolism
Pulmonary embolism is most commonly diagnosed by ventilation perfusion lung scans. In pregnant women, it is treated with LMWH and the average length of inpatient stay is 7 days (range from 3 to 14 days).

Miscarriage and stillbirth
If the patient is positive for thrombophilia, they are treated with aspirin alone or aspirin plus LMWH. In patients with miscarriage or stillbirth but no thrombophilia, they can receive either aspirin or no treatment.

Placental abruption
Placental abruption is managed by early vaginal or Caesarean section, depending on the circumstances.

Preeclampsia
Preeclampsia is monitored by regular urine analysis, blood pressure checks and ultrasounds of fetal weight and umbilical-blood flow. In cases of mild preeclampsia at <24 weeks gestation and severe preeclampsia at any week of gestation, patients are monitored by non-stress tests and may be given prophylactic steroids.

Postpartum haemorrhage
Prophylaxis is routinely administered in the third stage of labour to reduce the risk of postpartum haemorrhage. In general, patients with minor postpartum haemorrhage are monitored by blood test and blood pressure recording and receive crystalloid infusion. Patients with major postpartum haemorrhage are catheterised, receive Syntocinon and may undergo a blood transfusion or surgery in extreme cases.

Adverse drug reactions
In cases of drug-induced thrombocytopenia, anticoagulation is stopped and the patient is monitored. In severe cases, the haematologist is consulted and platelets are transfused. Where haemorrhage due to antithrombotic therapy has occurred, patients are monitored. If the haemorrhage is severe, anticoagulation may be stopped or changed or the dosage may be reduced.

Management of adverse clinical outcomes in orthopaedic patients
Completed questionnaires were received from 47 respondents. A consensus relating to the management strategies of various adverse clinical events of interest for the economic model was established.

Deep vein thrombosis
All patients undergoing major orthopaedic surgery are given thromboprophylaxis. Compression ultrasonography is most commonly used to confirm DVT. All orthopaedic patients with a suspected DVT are managed as outpatients, the main treatment being LMWH followed by warfarin. Anticoagulation treatment usually lasts 3 months.

Pulmonary embolism
Pulmonary embolism is most commonly diagnosed by ventilation perfusion lung scans. In orthopaedic patients, it is treated with LMWH followed by warfarin and the average length of inpatient stay is 7 days (range from four to 14 days).

Adverse drug reactions
In cases of drug-induced thrombocytopenia, anticoagulation is stopped and the patient is monitored. In severe cases, the haematologist is consulted and platelets are transfused. Where haemorrhage due to antithrombotic therapy has occurred, patients are monitored. If the haemorrhage is severe, anticoagulation may be stopped or changed or the dosage may be reduced.

Basecase analysis

Based on a hypothetical model of 10,000 patients in each screening scenario, in the absence of thrombophilia screening, adverse clinical complications would be found in approximately seven women on combined oral contraceptives, 104 women on hormone replacement therapy, 2921 pregnant women and 1265 patients undergoing major orthopaedic surgery, at costs of £119,147, £1,185,428, £513,591 and £1,217,935, respectively (*Table 7*). From a pure cost perspective, in this cohort, thrombophilia screening in women prior to prescribing combined oral contraceptives and restricting prescribing to those tested negative for thrombophilia was the least costly strategy to implement (approximately £708,640); and screening women at the onset of pregnancy and prescribing prophylaxis to those tested positive for thrombophilia was the most expensive (£5,374,352).

However, when taking effectiveness of screening into account, universal screening of patients prior to prescribing hormone replacement therapy and

TABLE 7 *Clinical complications averted, costs and ICERs by screening strategies*

	Clinical complications	Clinical complications prevented	Cost (£)	ICER (£)
Universal screening				
Combined oral oestrogen				
No screening	7		119,147	
Screening	4	3	709,640	200,402
Hormone replacement therapy				
No screening	104		1,185,428	
Screening	62	42	1,469,464	6,824
Pregnancy				
No screening	2921		509,364	
Screening	2862	59	5,374,890	81,554
Orthopaedic surgery				
No screening	1265		1,217,935	
Screening	1177	88	2,466,343	14,129
Selective screening				
Combined oral oestrogen				
No screening	7		119,147	
Screening	6	1	189,372	79,085
Hormone replacement therapy				
No screening	104		1,185,428	
Screening	89	15	1,220,316	2,446
Pregnancy				
No screening	2921		509,364	
Screening	2914	7	1,093,201	81,250
Orthopaedic surgery				
No screening	1265		1,217,935	
Screening	1238	26	1,459,103	9,136

restricting prescribing to those tested negative for thrombophilia would prevent 42 VTE events in this hypothetical population and was the most cost-effective screening strategy (ICER £6824). In contrast, screening women prior to prescribing combined oral contraceptives would prevent only three VTE events and was the least cost-effective strategy (ICER £200,402).

Irrespective of individual patient groups, selective screening based on the presence of previous personal or family history of VTE prevented fewer cases of adverse clinical complications than universal screening (number of clinical complications prevented were one, 15, seven and 26 in the oral oestrogen, hormone replacement therapy, pregnancy and orthopaedic surgery groups, respectively). However, selective VTE history-based screening was associated with lower ICERs than universal screening in all four screening scenarios, demonstrating increasing cost-effectiveness. The most significant improvement in cost-effectiveness was observed with the hormone replacement therapy and the combined oral contraceptives groups, when the ICERs for selective history-based screening were reduced by approximately 60% (from £6824 to £2447) and 64% (from £200,402 to £79,085), respectively.

Sensitivity analysis

One-way univariate sensitivity analysis showed that the results of the model were relatively robust (*Figure 15*). The model was most sensitive to test sensitivity and specificity, but changes in the key parameters do not alter the overall results. Screening women prior to prescribing hormone replacement therapy remained the most cost-effective strategy when test sensitivity and specificity, effectiveness of prophylaxis, unit costs and probabilities of developing adverse clinical complications were varied individually.

Scenario analysis was conducted to test the scenario of prescribing transdermal hormone replacement therapy in place of withholding therapy for those tested positive for thrombophilia. In this hypothetical population of 10,000, the prescription of transdermal preparations to those tested positive for thrombophilia would incur additional costs of approximately £491,434, resulting in a total cost of £1,676,862 and an ICER of approximately £12,404 for this strategy.

The purchasing cost of the second most commonly prescribed combined oral contraceptives were greater than the most commonly prescribed preparations (*Table 2*). However, this is not the case with oral hormone replacement therapy. Marginal improvement on cost-effectiveness (ICER = £186,905) was observed with combined oral contraceptives; however, substitution with the second most commonly prescribed hormone replacement therapy was less cost-effective than the basecase – the costs per event prevented were greater with oral hormone replacement therapy (ICER = £11,440). However, the relative cost-effectiveness between the groups remain unchanged.

Scenario analysis on no thrombophilia testing and prescribing prophylaxis to those with a VTE history resulted in ICERs of £192,728 and £15,317 for the pregnancy and the orthopaedic surgery group, respectively. The cost of prescribing prophylaxis to all patients who have a prior personal and/or family history of VTE without thrombophilia testing was less cost-effective than screening followed by prescribing prophylaxis to those tested positive.

Chapter 5
Discussion

This review was based on the hypothesis that women with thrombophilias who take oral oestrogen preparations such as oral contraceptives and hormone replacement therapy, women with thrombophilia who are pregnant and patients with thrombophilia undergoing major orthopaedic surgery are at increased risk of developing venous thromboembolism. Based on the current evidence available in the literature, the findings of this review generally support this hypothesis.

Risk of complications

Oral oestrogen preparations

Our results showed that certain thrombophilias, in particular FVL (OR 15.62; 95% CI 8.66 to 28.15), deficiencies of antithrombin (OR 12.60; 95% CI 1.37 to 115.79), protein C (OR 6.33; 95% CI 1.68 to 23.87) or protein S (OR 4.88; 95% CI 1.39 to 17.10), elevated levels of factor VIIIc (OR 8.80; 95% CI 4.13 to 18.75) and compound heterozygosity for FVL and prothrombin G20210A (OR 7.85; 95% CI 1.65 to 37.41) increase the risk of VTE users of oral contraceptives, and also that FVL (OR 13.16; 95% CI 4.28 to 40.47) increases the risk in users of hormone replacement therapy. Although we reviewed only studies with hormone users, the ORs for the increased risk of VTE were similar to those in studies of thrombophilia in the general population.[134,135]

With the exception of antithrombin deficiency, the reported odds for thrombophilic women developing VTE during the use of oral contraceptives varied substantially in individual studies. For instance, the reported odds of VTE among women with FVL who were oral contraceptive users ranged from 5.86 to 34.72.[37] One reason may be different inclusion criteria: the studies of Legnani and colleagues[41] and Santamaria and colleagues[36] were performed on women referred for a thrombophilia workup and women with familial thrombophilia, respectively; such women may have a higher risk of thrombosis.[136] The pooled OR estimated by our meta-analysis was 15.62, substantially less than the most commonly cited odds reported by Vandenbroucke and colleagues.[37] Our result is similar to a previous smaller meta-analysis of three studies (OR 10.25; 95% CI 5.69 to 18.45).[137] This meta-analysis also reported similar results to the present study for prothrombin G20210A (OR 7.14; 95% CI 3.39 to 15.04) and for its combination with FVL (OR 16.97; 95% CI 3.95 to 72.8).[137] The variations observed in other thrombophilic defects, such as deficiencies of protein C and protein S and combined thrombophilic defects, may be explained by the study type as the results were pooled from both case–control and cohort studies.

The thrombophilias described in this study represented primarily heterozygous mutations. Four studies did not define the genotypes,[38–40, 43] one study presented summed data for both heterozygous and homozygous mutations,[36] two studies excluded all homozygous carriers,[37,41] and one study had no homozygous carriers.[46] Separate analysis on individual genotypes was not carried out owing to the lack of data. However, some studies have speculated on the risk of homozygous prothrombotic mutations among oral contraceptive users. Vandenbroucke and colleagues suggested that, based on a multiplicative effect, the risk increase for homozygous FVL among oral contraceptive users may be >100-fold.[37]

The type of combined oral contraceptive has been shown to be an important factor in determining the risk increase in VTE. Third-generation oral contraceptives have been shown to incur greater risks than other classes of oral contraceptives.[14,138] Four of the studies included in this review described the distinction between third-generation and other oral contraceptives,[36,38,39,41] but separate data were presented in only one study.[38] Although this study showed that third-generation oral contraceptives had a greater effect than other oral contraceptives on the risk of VTE (OR 20.9 compared with 7.1), this effect was no longer observed in women with the FVL mutation. The risk of VTE was greater in first- and second-generation users compared with third-generation oral contraceptive users (OR 64.7 compared with 29.6).

Few studies have investigated the relationship between thrombophilias and VTE in users of hormone replacement therapy. Since no data were

available on thrombophilias other than FVL, the results of this review have been restricted to women with FVL, who had a very similar increase in risk of VTE in two studies.[45,46] One of these studies[139] also reported significant increases in the risk of VTE in women with high levels of factor IX (OR 2.34; 95% CI 1.26 to 4.35), increased resistance to activated protein C (OR 4.06; 95% CI 1.62 to 10.21) or decreased antithrombin (OR 3.33; 95% CI 1.15 to 9.65) or protein C (OR 2.93; 95% CI 1.06 to 8.14).

There is some evidence in the literature indicating that different types of preparations may incur a lower level of risk than with other hormone preparations. Studies have shown higher risk of VTE in third-generation than second-generation oral contraceptive users.[140] Emerging evidence also suggests that oral contraceptives containing cyproteronacetate are associated with a risk increase of as much as 18-fold compared with non-users.[14] Similarly, a recent case–control study confirmed the increased risk of VTE among women who use oral hormone replacement therapy, whereas this effect was not observed with transdermal preparations.[141] Hormone preparations that are associated with lower risks of VTE, such as second-generation oral contraceptives and transdermal hormone replacement therapy, may therefore be considered in women with thrombophilias.

Pregnancy

This review has shown that both heritable and acquired thrombophilias are associated with VTE and adverse pregnancy outcomes, so confirming and extending results from previous systematic reviews which examined particular aspects of these associations.[142–144]

VTE was significantly associated with all inherited thrombophilias except in women homozygous for MTHFR C677T, where, in contrast to the non-pregnant situation, there was no risk. The mechanism underlying this lack of association in pregnancy is unclear. It is possible that folic acid supplements taken in pregnancy could reduce homocysteine levels in these women and so reduce the risk of VTE, but there are minimal data on the use of vitamin supplements in the studies reported and this possibility could not be examined with the available data. The risk of VTE with homozygous FVL was the highest risk observed for any thrombophilia, OR 34.4 (95% CI 9.86 to 12.05), reducing to 8.32 (95% CI 5.55 to 12.70) with heterozygous FVL. Of note, women heterozygous for FVL and homozygous for prothrombin G20201A were judged to be at a higher risk of VTE than any other pregnancy complication. No studies were found which measured the risk of pregnancy-related VTE in women with elevated anticardiolipin antibodies, lupus anticoagulants or acquired APC resistance; therefore, the risk of VTE in pregnancy with acquired thrombophilia remains unclear. Furthermore, the risk of DVT and pulmonary embolism could not be established separately as all studies measured VTE as a single outcome.

Pregnant women homozygous for FVL or hyperhomocysteinaemia were at a significantly higher risk of suffering an early pregnancy loss than women with other thrombophilias. Moreover, the risk of early pregnancy loss with hyperhomocysteinaemia was greater than the risk of any other pregnancy complication with this mutation. Of the inherited thrombophilias, homozygosity for FVL and heterozygosity for prothrombin G20210A were the only mutations significantly associated with early loss. The acquired thrombophilias, including elevated anticardiolipin antibodies, lupus anticoagulants and acquired APC resistance, were also significantly associated with pregnancy loss before 24 weeks' gestation. When early pregnancy loss was classified according to recurrent loss in the first trimester and non-recurrent loss in the second trimester, a higher risk of second trimester loss for both FVL and prothrombin G20210A was calculated. Although it was not possible to ascertain the risk of second trimester pregnancy loss with lupus anticoagulants, the risk of recurrent first trimester pregnancy loss was higher than for any other pregnancy complication with this acquired thrombophilia.

Of all thrombophilias, late loss was most strongly associated with protein S deficiency. Pregnant women heterozygous for either FVL or prothrombin or with lupus anticoagulants were also at significantly increased risk of loss beyond 24 weeks' gestation. The remaining thrombophilias studied were all found to have associations with late loss that were not significant. These findings are in line with the results of another systematic review by Alfirevic and colleagues,[145] who established that women with protein S deficiency were at the highest risk of unexplained stillbirth after 20 weeks. The ORs calculated in our review were higher for protein S deficiency and lower for other thrombophilias than the risk calculated by Alfirevic and colleagues. This could be explained by the fact that Alfirevic and colleagues defined stillbirth as unexplained fetal loss before 20 weeks,

whereas for the purpose of our review we defined stillbirth as fetal loss after 24 weeks' gestation.

In comparing early pregnancy loss before 24 weeks and late loss beyond this point of gestation, we found that in women heterozygous for either FVL or prothrombin G20210A, the risk of late pregnancy loss was higher than that for early loss. In the case of acquired thrombophilias, the reverse was true where elevated anticardiolipin antibodies and lupus anticardiolipins, were associated with higher risk of early pregnancy loss.

Our findings with regard to the pregnancy group are in line with the results of other systematic reviews in this area. Rey and colleagues conducted a systematic review on heritable thrombophilia and fetal loss.[144] They concluded that pregnant women with heritable thrombophilia were more likely to suffer an early pregnancy loss. However, they did not estimate the risk of early loss with acquired thrombophilia, hence it was not possible to compare our results with theirs.

Studies that did not specify the timing of pregnancy loss were excluded from the review. Data from these studies were pooled together to examine whether including these studies would have influenced the final results. The results from the 12 studies showed that FVL and prothrombin G20210A were associated with pregnancy loss. Therefore, as these results were obtained before exclusion of these studies, it is unlikely that excluding these studies would influence the final results.

Our findings indicated that all thrombophilias were associated with increased risk of preeclampsia; however, many of the results were not significant. The highest significant risk for preeclampsia was with hyperhomocysteinaemia. Elevated anticardiolipins, heterozygosity for FVL or prothrombin G20210 also had similar levels of risk. Preeclampsia was the only outcome for which a significant association with homozygosity for MTHFR was found. Our results differ from the findings from a systematic review performed by Morrison and colleagues,[109] which noted no evidence of an association of FVL, prothrombin G20210A or MTHFR C677T homozygosity with preeclampsia.

The highest significant risk of placental abruption was in heterozygous carriers of the gene-encoding prothrombin G20210A, followed by heterozygous FVL and hyperhomocysteinaemia. Our results are similar to those established by other reviews.[145]

Intrauterine growth restriction was most strongly associated with lupus anticoagulants, but this finding was not significant. Therefore, the highest risk for IUGR was in homozygous FVL carriers, followed by heterozygous prothrombin G20210A carriers. Alfirevic and colleagues concluded that pregnant women with elevated anticardiolipin antibodies and protein S deficiency were at highest risk of IUGR.[145] However, their findings were based on only three studies involving very small numbers of women. Additionally, they did not use a prespecified definition of IUGR.

Orthopaedic surgery

Based on current evidence, the findings of this study support the hypothesis that FVL contributes to postoperative VTE in orthopaedic surgery (OR 1.86; 95% CI 1.27 to 2.74). A positive association was also observed between the prothrombin G20210A mutation and pulmonary embolism (OR 9.14; 95% CI 2.27 to 36.89). In one study,[119] a high plasma level of factor VIIIc was also reported as a risk for postoperative orthopaedic VTE (OR 1.65; 95% CI 1.06 to 2.58). No significant associations were observed for other thrombophilias, which probably reflects a lack of published data.

Only one individual study showed a significant positive association between FVL and VTE.[118] Inconsistencies observed in individual study findings within a meta-analysis are most commonly due to study type and quality. However, this is unlikely to be the case as other prospective studies in the analysis did not report a significant association, or observe a similar magnitude of risk.[119,123] Bias associated with confounding factors may also have a significant impact on the findings. The five-fold increase in the odds of post-operative VTE in patients with FVL in the study by Lindahl and colleagues[118] could be explained, at least partly, by other unmeasured risk or confounding factors. In particular, in contrast to other studies in the review, which used venographic screening, Lindahl and colleagues used venographically confirmed, symptomatic DVT as the study end-point. The exclusion of patients with prior VTE[119,121] is another factor which could contribute to heterogeneity and inconsistency of study findings. However, sensitivity analysis has shown that the exclusion of symptomatic outcomes does not significantly affect the meta-analysis. In addition, the results from the sensitivity analysis would not support the suggestion that FVL is not associated with pulmonary embolism,[146] although this may reflect the relative lack of data on pulmonary embolism.

The quality of the studies also varied with regard to blinded assessment of outcomes, although studies that failed to describe blinded assessment of outcome do not necessarily equate to a failure of blinded assessment. In particular, in the two retrospective studies,[120,125] it is unlikely that those carrying out the thrombophilia analysis would have knowledge of the presence or absence of VTE, and this would therefore have little influence on the results. Despite these study differences, there was no evidence of heterogeneity and there was low inconsistency between the studies included in the meta-analysis, making the results relatively robust.

Effectiveness of prophylaxis

Studies measuring the effectiveness of thromboprophylaxis were lacking. Of the studies that were retrieved, different treatments were compared so it was not possible to group these studies together.

Limitations of the systematic reviews

The systematic review has several limitations, including selection bias and varying methodological quality of studies. All studies included in the review were independently judged as moderate to high quality using a standardised checklist. Laboratory methods for individual studies used standardised techniques and specific cut-off values to identify thrombophilia.

Publication bias can arise in systematic reviews. We restricted this review to studies that were published in English. However, it is believed that excluding non-English studies would make no significant difference to the results.[147]

As not all studies tested for all major thrombophilias, we cannot eliminate the possibility that some controls without the thrombophilia studied were carriers of other thrombophilias that were not tested for. This possibility could lead to underestimation of the association between thrombophilia and the adverse outcomes studied.

Despite strict inclusion criteria, there were instances of inter-study heterogeneity. A possible explanation for such heterogeneity is genetic variations between ethnic populations studied. The studies included in the review were conducted among participants of different ethnic backgrounds. Thrombophilia defects are known to vary according to race; in particular, thrombophilia is more prevalent in Caucasians.[145,148] This is supported by a study included in this review, where a higher OR was obtained when analysis was restricted to white women only.[47] Another factor that could contribute to the heterogeneous results is different sensitivity and specificity of the laboratory methods used in testing for thrombophilia.

Cost-effectiveness analysis

The total cost of screening for thrombophilia in a hypothetical population of 10,000 ranged from £708,640 (combined oral contraceptives group) to £5,374,352 (pregnancy group). In comparison with no screening, universal screening of women prior to prescribing hormone replacement therapy was the most cost-effective strategy at a net cost of £6824 per adverse clinical complication prevented. Selective VTE history-based screening was more cost-effective than universal screening in all the patient groups examined in this study. Subsequently, screening women who have personal or family history prior to prescribing hormone replacement therapy was shown to be the most cost-effective at a net cost of £2446 per adverse clinical complication prevented.

Thrombophilia is associated with a substantial increase in relative risk of VTE; in particular, in patient groups such as women on combined oral contraceptives and hormone replacement therapy, the ORs for the combined risk of FVL and taking oral oestrogen preparation were 15.62 and 13.16, respectively. However, in view of the prevalence of thrombophilia, the absolute risk remains low. Therefore, the absolute numbers of expected events and the estimated number of prevented events in these groups are low. This is particularly apparent with the combined oral contraceptives group, when only three VTE events would be prevented in the hypothetical population of 10,000, and subsequently resulting in a large ICER.

Selective screening based on prior personal or family history of venous thromboembolism has been recommended.[134] The results of this study support such recommendations and showed selective history-based screening to be more cost-effective than universal screening in all four clinical situations. Nonetheless, the effectiveness of history-based screening is highly dependent on

the reliability of the data source and the sensitivity of family history. The sensitivity of family history as a screening variable has been reported to be as low as 49%.[149]

This is the first study that attempted to evaluate the relative cost-effectiveness of a complete thrombophilia screen in various patient groups. Clark and colleagues[22] evaluated the cost-effectiveness of universal and selective screening for FVL in pregnancy, and gave results comparable to those for our pregnancy arm of the cost-effectiveness analysis.

This study has potential limitations that are inherent to all cost-effectiveness analyses. Based on a decision analysis, this study used estimates from several sources such as probabilities of clinical events reported in the medical literature and expert opinion on management of events. In an attempt to overcome the potential bias, a systematic review and meta-analyses were conducted to estimate probabilities of clinical events and a Delphi study was conducted to determine the average treatment strategy for all the adverse clinical complications, which is believed to reflect current clinical practice. In addition, extensive sensitivity analysis was carried out to examine the effect that variations of model inputs would have on the results. The results of the sensitivity analysis showed that the overall results were robust.

In this analysis, cost-effectiveness was expressed as 'cost per adverse clinical complication prevented'. In the oral oestrogen preparation and the orthopaedic surgery groups, the adverse clinical complications referred to VTE events. However, in the pregnancy group, adverse pregnancy outcomes were also considered, therefore, the 'adverse clinical events' referred to an aggregation of VTE events and adverse pregnancy events. Different clinical complications are of different significance to the NHS and to patients. Although such an aggregated measure of outcomes is not ideal, it allows standardised comparison across the patient groups and offers some prioritisation order. In order to take into account the different value of the different clinical events to the NHS and to patients, the method of calculating QALYs may be used. However, in the case of pregnancy, such a measure may be problematic as the QALYs associated with the fetus need also to be taken into account.

This cost-effectiveness model in this study was taken from the perspective of the NHS. Indirect costs such as loss of production and quality of life impairment associated with venous thromboembolism and adverse pregnancy outcomes were not taken into account. This model was designed to investigate the most cost-effective strategy for thrombophilia screening, based on the assumption that a decision has been made to undertake screening and does not consider the relative cost-effectiveness of screening compared with other uses of scarce NHS resources. In order to determine the cost and the relative value of a thrombophilia screening programme with respect to other healthcare programmes, alternative forms of economic evaluation, such as cost–benefit analysis, are required. Currently, there are insufficient data in the literature to allow us to do that. However, in addition to addressing the clinical and cost-effectiveness of screening, other important issues such as acceptability, psychological consequences deriving from the diagnosis of thrombophilia and potential consequences of false-positive and false-negative results need to be taken into account.

Chapter 6
Conclusions

Implications for clinicians and policy makers

Thrombophilia is associated with increased risks of VTE in women taking oral oestrogen preparations and patients undergoing major elective orthopaedic surgery, and of VTE and adverse pregnancy outcomes in women with thrombophilia during pregnancy. This study is the first to provide a comprehensive review and assessment of risk of all thrombophilia-related complications in a single study. The magnitude of risks associated with thrombophilia in these patient groups has been defined.

In women who are on combined oral contraceptives, the OR for VTE for the combined risk of FVL and taking oral oestrogen preparation was 15.62 (95% CI 8.66 to 28.15). However, in view of the prevalence of thrombophilia and the low prevalence of VTE in non-users of combined oral contraceptives, the absolute risk remains low. Therefore, the absolute numbers of expected VTE events are low.

In areas such as pregnancy, there is a large volume of data on some thrombophilia defects, but inconsistent findings of individual studies and methodological limitations of several reviews have made it difficult for clinicians to provide optimum advice to their patients in this situation. This systematic review addresses all the limitations of previous individual studies and systematic reviews. Significant risks for VTE and adverse pregnancy outcomes associated with individual thrombophilic defects were established and substantial risk increases are observed, with VTE associated with FVL, early pregnancy loss and preeclampsia associated with hyperhomocysteinaemia, recurrent pregnancy loss associated with prothrombin G20210A, late pregnancy loss associated with protein S deficiency and IUGR associated with homozygous FVL.

FVL, high plasma factor VIIIc levels and prothrombin G20210A are significantly associated with the occurrence of postoperative VTE in elective hip or knee replacement therapy. However, these associations are observed in patients who are already given thromboprophylaxis and are, therefore, of clinical significance.

Universal thrombophilia screening in women prior to prescribing oral oestrogen preparations, in women during pregnancy and in patients undergoing major elective orthopaedic surgery is not supported by the evidence. The findings from this study show that selective history-based screening is more preferable than universal screening.

Unanswered questions

This systematic review has highlighted the small number of relevant published studies available for inclusion in meta-analyses. Despite the growing evidence in the literature, there are still gaps in our knowledge of thrombophilia and adverse clinical outcomes. There is a lack of data for accurate estimates of the size of the risks of VTE and adverse pregnancy outcomes associated with the less prevalent thrombophilias such as deficiencies of antithrombin, proteins C or S and the combined thrombophilic defects. The calculated CIs of the estimated ORs for these thrombophilias are large and the results should be interpreted with caution. However, this may be due, in part, to the difficulty in collecting such data. We therefore recommend that larger cohort studies, including more thrombophilic patients and controls, be performed to provide more reliable estimates.

This study has not addressed the clinical utility of thrombophilia screening. Large cohort studies examining the likelihood that testing for thrombophilia would result in an improved health outcome need to be established. In addition, other important influencing factors such as screening acceptability, psychological consequences deriving from the diagnosis of thrombophilia and potential consequences of false-positive and false-negative results need all to be taken into account when conducting such studies.

The cost-effectiveness model in this study was designed to investigate the most cost-effective strategy for thrombophilia screening, based on the assumption that a decision has been made to undertake screening and does not consider the relative cost-effectiveness of screening compared

with other uses of scarce NHS resources. In order to determine the relative value of a thrombophilia screening programme to other healthcare programmes, a cost–benefit analysis is required.

However, the findings of this study are able to address some issues of the UK National Screening Committee's criteria for appraising a screening programme. With regard to the condition, thrombophilia as a whole has been shown to be an important health problem in terms of associated adverse clinical events such as VTE and adverse pregnancy outcomes. With regard to testing for thrombophilia, the tests are simple, safe, precise and validated. However, further research is needed to address issues such as the precise choice of the thrombophilic mutations to be tested and test acceptability to the patients. With regard to treatment, further studies are required to determine the relative effectiveness of prophylaxis, and optimum treatment needs to be defined. For instance, there is growing evidence in the literature advocating the use of extended thromboprophylactic treatment following major orthopaedic surgery. With regard to a screening programme, further research on the clinical utility and the relative value of thrombophilia screening to other healthcare programmes is needed before this can be addressed.

Trajectory of knowledge base

Thrombophilia and its associated adverse clinical events are a rapidly developing field that continues to be the subject of many recent studies. Large cohort studies are being carried out to evaluate thrombosis in patients with different thrombophilic defects, generating data on the less prevalent mutations, in particular the effects of combined thrombophilic defects. The diagnosis and management of VTE is also evolving. For instance, in addition to lung perfusion scan, which has been described in all the studies in this review, spiral computed tomographic pulmonary angiography is increasingly being used in the evaluation of patients with clinically suspected pulmonary embolism in current clinical practice. New studies are being carried out on the drug treatments for the prevention and the management of VTE, in particular relating to the duration of drug use.

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Contribution of authors

Olivia Wu (Research Assistant) and Lindsay Robertson (Research Assistant) conducted the meta-analysis and economic analysis. Sara Twaddle (Director, Scottish Intercollegiate Guidelines Network) primarily guided the approach and implementation of the economic analysis and assisted with all phases of the study design and implementation. Gordon Lowe (Professor of Vascular Medicine), Peter Clark (Consultant Haematologist), Mike Greaves (Head of School of Medicine), Isobel Walker (Consultant Haematologist) and Ian Greer (Regius Professor of Obstetrics and Gynaecology) wrote the original protocol and assisted with the phases of study design and implementation. Gordon Lowe, Ivan Brenkel (Clinical Director Orthopaedics), Lesley Regan (Clinical Professor) and Ian Greer also assisted in the design and implementation of the Delphi studies. Peter Langhorne (Professor of Geriatric Medicine) guided the design and implementation of the meta-analysis. All contributors took part in the final editing and production of the report.

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Appendix 1

Data extraction form

Reference ID ..... **Reviewer** .....
Author .....
Journal .....
Year .....

Objective

Study Design

Prospective Cohort	[ ]	Retrospective Case Control	[ ]
Retrospective Cohort	[ ]	RCT	[ ]
Prospective Case Control	[ ]	Other	[ ]

Other describe

Control [YES / NO / NOT APPLICABLE]
If 'YES',
Are the cases and controls taken from a comparable population? [YES / NO / UNCLEAR]
Are the same exclusion criteria used for both cases and controls? [YES / NO / UNCLEAR]
Are cases clearly defined and differentiated from controls? [YES / NO / UNCLEAR]
Matching [ ]
Matching describe

Randomisation [YES / NO / NOT APPLICABLE]
If 'YES',

Described as 'randomised'	[ ]	Appropriate process of randomisation	[ ]
Described randomisation sequence	[ ]	Inappropriate process of randomisation	[ ]

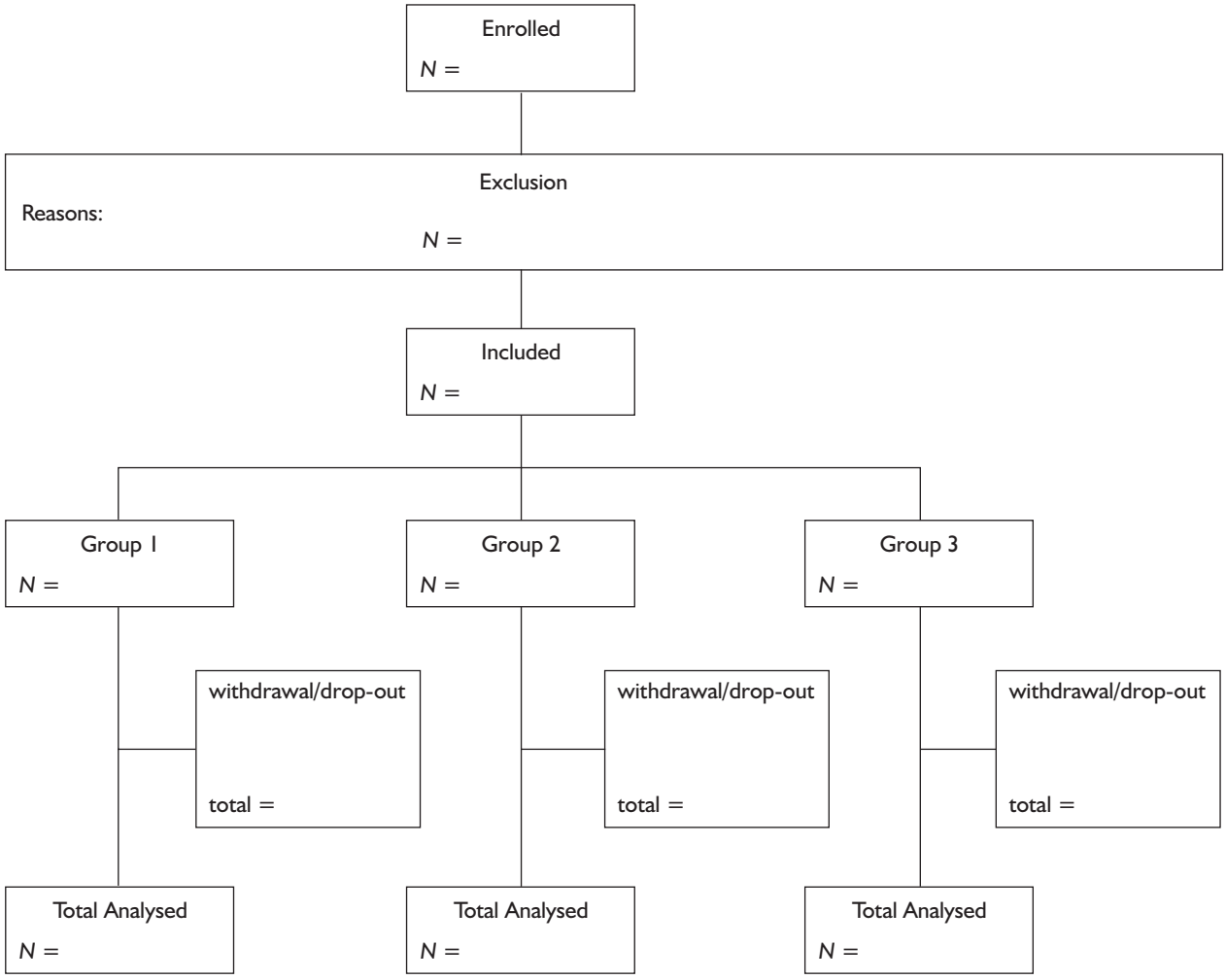
Blind [YES / NO / NOT APPLICABLE]
If 'YES',
Not described [ ]
Participants blinded [YES / NO / UNCLEAR]
Clinicians blinded [YES / NO / UNCLEAR]
Outcome assessors blinded [YES / NO / UNCLEAR]
Appropriate/effective blinding [ ]
Inappropriate/ineffective blinding [ ]

Participants
Setting
Inpatients [……..]
Outpatients [……..]
Clinic [……..]
Other [……..]
Other describe

Inception Cohort/Diagnostic Criteria (drug/dose/frequency/duration/started/stopped)

Group1	
Group2	
Group3	

Overall length of follow up .....



Compliance
Assessment of compliance not applicable [ ]
Assessment of compliance undertaken [YES / NO / UNCLEAR]
How was compliance measured? ……....

Outcome Measures

Baseline Characteristics			
	Group 1	**Group 2**	**Group 3**
N			
Age (years)			
Sex – Female/Male			
Clinical History – Personal/Family History of Thrombophilia, Smoking Status, BMI, Blood Group O, Anaesthetic, IVF, Previous Parity/Miscarriage, Co-morbidities, etc.			
Prior VTE Events (Number of Patients) – DVT, PE Only, PE & DVT, etc.			
Clinical Outcomes			
DVT Events (Number of Patients) – lower limb, upper limb, bilateral, other descriptions.			

	Group 1	Group 2	Group 3
PE Events (Number of Patients) – PE Only, with DVT, other descriptions.			
Postphlebitic Syndrome			
Other VTE Events (Number of Patients)			
Mortality			
Arterial Events (Number of Patients) – MI, Stroke, TIA, etc.			
Peripheral Vascular Death			
Adverse Pregnancy Outcomes (Number of Patients) – Miscarriage, Late Pregnancy Loss, Preeclampsia, Growth Retardation, Abruption, Post-partum Haemorrhage, etc.			
Adverse Events – Haemorrhage (major, minor, other descriptions), Injection site haematomas, Skin necrosis, Thrombocytopenia, Osteoporosis, etc.			

	Group 1	Group 2	Group 3
Other Factors			

Thrombophilia
APC resistance/FVL (heterozygous, homozygous), Deficiencies of AT/PC/PS, Prothrombin Variant, Raised FVIIIc/FIXc, Homocysteine, Antiphospholipid Antibodies, etc.

	Group 1	Group 2	Group 3
None			
No Data			

Notes

Appendix 2

Delphi study questionnaires sent to consultants of orthopaedics

Patient population: patients undergoing major orthopaedic surgery including both primary and revision procedures for total hip and knee replacement, and fractured neck or femur.

Please mark 'X' or type, where appropriate, within the brackets provided.

Deep Vein Thrombosis

1. What proportion of patients (no risk) would be given prophylaxis? [ ]

2. What proportion of patients tested positive for thrombophilia would be given prophylaxis? [ ]

3. In patients with symptoms for DVT, what routine investigations are used to exclude or confirm DVT?
   - Ultrasound [ ]
   - Colour duplex [ ]
   - Venography [ ]
   - Plethysmography [ ]
   - Others, please specify .....

4. In case of proven proximal DVT (popliteal or femoral), do you use:
   - LMWH alone [ ]
   - UFH alone [ ]
   - LMWH and then warfarin [ ]
   - UFH and then warfarin [ ]
   - Others, please specify .....

5. Following DVT associated with the following circumstances, for how long would you usually anticoagulate?
   - No risk [ ]
   - Patients with thrombophilia [ ]

6. Does your hospital have a set policy for DVT management?
   - Yes [ ]
   - No [ ]

7. Does your hospital have a set policy for calf vein DVT management?
   - Yes [ ]
   - No [ ]

Pulmonary Embolism

1. What would be the normal treatment strategy for pulmonary embolism?

   .....

2. What is the average length of additional stay due to treatment of pulmonary embolism?

   .....

Drug Induced Bleeding

1. What would be the normal treatment strategy of bleeding due to antithrombotic therapy induced bleeding?

   .....

2. What is the average length of additional stay due to treatment of antithrombotic therapy induced bleeding?

   .....

Drug Induced Thrombocytopenia

1. What would be the normal treatment strategy of bleeding due to antithrombotic therapy induced thrombocytopenia?

   .....

2. What is the average length of additional stay due to treatment of antithrombotic therapy induced thrombocytopenia?

   .....

Thank you very much for your time. If you have any questions regarding this survey, please contact:

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Appendix 3

Delphi questionnaires sent to consultants of obstetrics

This questionnaire applies to pregnant patients and women in the postpartum period.

Please mark an X within the brackets or, where appropriate, print your answer in the space provided.

Deep Vein Thrombosis

1. In your hospital, what is the routine method of diagnosing or excluding DVT in pregnancy?
   (a) Compression Ultrasonography [ ] (b) Contrast Venography [ ]
   (c) Magnetic Resonance Imaging [ ] (d) Impedance Plethysmography [ ]
   (e) Other……

2. In your hospital, what is the routine method of diagnosing or excluding DVT in the postpartum period?
   (a) Compression Ultrasonography [ ] (b) Contrast Venography [ ]
   (c) Magnetic Resonance Imaging [ ] (d) Impedance Plethysmography [ ]
   (e) Other……

3. What percentages of pregnant women with a suspected diagnosis of DVT are treated as inpatients and outpatients?
   (a) Inpatients [%] (b) Outpatients [%]

4. What is the average length of hospital stay for women treated as inpatients?
   ……

5. Once a diagnosis of DVT is confirmed, what method of treatment do you use antenatally?
   (a) Low molecular weight Heparin e.g. Certoparin, Dalteparin, Enoxaparin, Tinzaparin [ ]
   (b) Low molecular weight Heparinoid e.g. Danaparoid [ ]
   (c) Unfractionated Heparin e.g. Calciparine, Monoparin. Minihep [ ]
   (d) Warfarin [ ]
   (e) Other……

6. Following a DVT, how long does anticoagulation treatment last?
   ……

7. What method of anticoagulation is administered in the postpartum period?
   (a) Low molecular weight Heparin [ ] (b) Unfractionated Heparin [ ]
   (c) Low molecular weight Heparinoid [ ] (d) Warfarin [ ]
   (e) Other……

Pulmonary Embolism

8. What is the standard procedure for diagnosing pulmonary embolism in your hospital?

……

9. How is pulmonary embolism treated in pregnancy?
   (a) Low molecular weight Heparin [ ] (b) Unfractionated Heparin [ ]
   (c) Low molecular weight Heparinoid [ ] (d) Warfarin [ ]
   (e) Other……

10. What is the average length of inpatient stay for pulmonary embolism in pregnancy?
   ……

Labour and delivery

11. Do you stop anticoagulation until labour/caesarean section is complete?
   (a) Yes [ ] (b) No [ ]

12. If yes, how long before planned induction or caesarean section do you stop anticoagulation?
   ……

13. Do you reduce to prophylactic doses during labour?
   (a) Yes [ ] (b) No [ ]

14. Do you continue full anticoagulation during labour?
   (a) Yes [ ] (b) No [ ]

15. Does your unit withhold heparin for women requiring epidural anaesthesia?
   (a) Yes [ ] (b) No [ ]

16. If so, how much time must elapse before an epidural is used after:
   (a) Prophylactic doses?…….....
   (b) Therapeutic anticoagulation with heparin? …….....……

Pregnancy Complications

Miscarriage/Spontaneous abortion

17. Do you assess women with recurrent miscarriage for thrombophilia?
   (a) Yes [ ] (b) No [ ]

18. If so what thrombophilias do you screen for?
   ……

19. If the patient is positive for thrombophilia, what drugs do you use for the treatment of recurrent miscarriage?
   (a) Aspirin alone [ ] (b) Low molecular weight heparin alone [ ]
   (c) Unfractionated heparin [ ] (d) Aspirin *and* UF/LMW heparin [ ]

20. If the patient is negative for thrombophilia, what drugs, if any, do you use for the treatment of recurrent miscarriage?
   (a) Aspirin alone [ ] (b) Low molecular weight heparin alone [ ]
   (c) Unfractionated heparin [ ] (d) Aspirin *and* UF/LMW heparin [ ]
   (e) No treatment [ ] (f) Other……..

Stillbirth/Late pregnancy loss

21. Do you assess women with stillbirth for thrombophilia?
   (a) Yes [ ] (b) No [ ]

22. If so what thrombophilias do you screen for?
   ……

23. If the patient is positive for thrombophilia, what drugs do you use for the treatment of stillbirth?
    (a) Aspirin alone [ ] (b) Low molecular weight heparin alone [ ]
    (c) Unfractionated heparin [ ] (d) Aspirin *and* UF/LMW heparin [ ]

24. If the patient is negative for thrombophilia, what drugs, if any, do you use for the treatment of stillbirth?
    (a) Aspirin alone [ ] (b) Low molecular weight heparin alone [ ]
    (c) Unfractionated heparin [ ] (d) Aspirin *and* UF/LMW heparin [ ]
    (e) No treatment [ ] (f) Other .....

Placental abruption

25. Do you assess women with placental abruption for thrombophilia?
    (a) Yes [ ] (b) No [ ]

26. If so what thrombophilias do you screen for?

    .....

27. How do you usually treat a significant abruption during pregnancy?
    (a) Early delivery by vaginal delivery [ ] (b) Early delivery by Caesarean section [ ]
    (c) Internal fetal monitoring [ ] (d) Blood transfusion [ ]
    (e) Other.....

Preeclampsia

28. How is mild preeclampsia (significant proteinuria and hypertension) investigated and monitored before 24 weeks gestation?
    (a) Urine analysis [ ] (b) Blood pressure checks [ ]
    (c) Ultrasound of fetal weight [ ] (d) Ultrasound of umbilical blood-flow [ ]
    (e) Non-stress tests [ ] (f) Prophylactic steroids [ ]
    (g) Other.....

29. How is mild preeclampsia (significant proteinuria and hypertension) investigated and monitored after 24 weeks gestation?
    (a) Urine analysis [ ] (b) Blood pressure checks [ ]
    (c) Ultrasound of fetal weight [ ] (d) Ultrasound of umbilical blood-flow [ ]
    (e) Non-stress tests [ ] (f) Prophylactic steroids [ ]
    (g) Other.....

30. How is severe preeclampsia (significant proteinuria and hypertension) investigated and monitored before 24 weeks gestation?
    (a) Urine analysis [ ] (b) Blood pressure checks [ ]
    (c) Ultrasound of fetal weight [ ] (d) Ultrasound of umbilical blood-flow [ ]
    (e) Non-stress tests [ ] (f) Prophylactic steroids [ ]
    (g) Other.....

31. How is severe preeclampsia (significant proteinuria and hypertension) investigated and monitored after 24 weeks gestation?
    (a) Urine analysis [ ] (b) Blood pressure checks [ ]
    (c) Ultrasound of fetal weight [ ] (d) Ultrasound of umbilical blood-flow [ ]
    (e) Non-stress tests [ ] (f) Prophylactic steroids [ ]
    (g) Other.....

32. In what proportion of cases are the following therapies admitted?
    (a) Antihypertensive therapy [%] (b) Anticonvulsant therapy [%]

33. What is the average length of inpatient stay due to preeclampsia?

……n……

34. Following delivery, what is the standard care and follow-up procedure (e.g. postnatal visits)?

……n……

……

Postpartum haemorrhage

35. Is prophylaxis (Syntocinon/Syntometrine) routinely administered in the third stage of labour to reduce the risk of primary postpartum haemorrhage?
    (a) Yes [ ] (b) No [ ]

36. How is **minor** postpartum haemorrhage (500–1000 mls blood loss) monitored and treated (investigations, drug therapy)?
    (a) Crystalloid (e.g. Hartmanns) infusion [ ] (b) Blood test [ ]
    (c) Pulse/blood pressure recording [ ]
    (e) Other……

37. How is **major** postpartum haemorrhage (>1500 mls blood loss) monitored and treated (investigations, blood transfusion, drug therapy, surgery)?
    (a) Blood transfusion [ ] (b) Blood test [ ]
    (c) Pulse/blood pressure recording [ ] (d) Catheter [ ]
    (e) Syntocinon [ ] (f) Surgery [ ]
    (g) Other……

38. What is the average length of inpatient stay due to postpartum haemorrhage?

……

Adverse Drug Reactions

39. How are the following adverse side effects associated with anticoagulation usually treated?
    (a) Minor Thrombocytopenia (platelet count between 20-150 $\times 10^9$/L)

    ……
    (b) Major Thrombocytopenia (platelet count lower than 20×10^9/L)

    ……
    (c) Minor Haemorrhage

    ……
    (d) Major Haemorrhage (fall in haemoglobin of 2g/dL / bleeding leading to transfusion)

    ……

Please return your completed questionnaire in the stamped, self-addressed envelope.

Thank you very much for your time. If you have any queries regarding this survey, please contact:

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Appendix 4

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We look forward to hearing from you.

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