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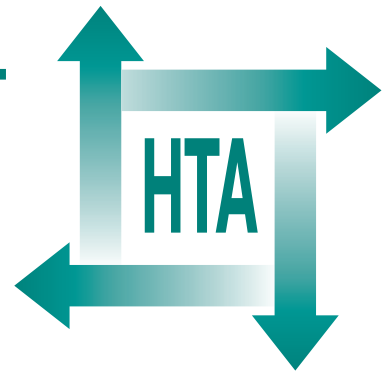

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Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis

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Dedication: This report is dedicated to the memory of Gill Ferris, who tragically died before it was completed

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The research reported in this monograph was commissioned by the HTA Programme as project number 93/10/01. The contractual start date was in May 1997. The draft report began editorial review in February 2004 and was accepted for publication in May 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

Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis

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Objectives: To assess the benefits in terms of reductions in the risks of deep vein thrombosis (DVT) and of pulmonary embolism (PE), and hazards in terms of major bleeding, of: (i) mechanical compression; (ii) oral anticoagulants; (iii) dextran; and (iv) regional anaesthesia (as an alternative to general anaesthesia) in surgical and medical patients.

Data sources: Electronic databases, search of Antithrombotic Trialists' Collaboration database, contact with trialists and manufacturers.

Review methods: All trials identified as fitting the selection criteria were independently assessed. The primary outcomes were DVT, PE and major bleeding events, and proximal venous thrombosis (PVT) and fatal PE were secondary outcomes. Trials were subdivided into those that had assessed a method as the only means of thromboprophylaxis ('monotherapy') and those that had assessed the effects of adding a method to another form of thromboprophylaxis ('adjunctive therapy').

Results: Mechanical compression methods reduced the risk of DVT by about two-thirds when used as monotherapy and by about half when added to a pharmacological method. These benefits were similar irrespective of the particular method used (graduated compression stockings, intermittent pneumatic compression or footpumps) and were similar in each of the surgical groups studied. Mechanical methods reduced the risk of PVT by about half and the risk of PE by two-fifths. Oral anticoagulants, when used as monotherapy, reduced the risk of DVT and of PVT by about half, and this protective effect appeared similar in each of the surgical groups studied. There was an apparently large four-fifths reduction in the role of PE, but not only was the magnitude of this reduction statistically uncertain, but also pulmonary embolism was reported by a minority of trials, so it may be subject to selection bias. Oral anticoagulant regimens approximately doubled the risk of major bleeding and appeared less effective at preventing DVT than heparin regimens, although were associated with less major bleeding. Dextran reduced the risk of DVT and of PVT by about half, again irrespective of the type of surgery, but too few studies had reported PE to provide reliable estimates of effect on this outcome. Dextran appeared to be less effective at preventing DVT than the heparin regimens studied. Dextran was associated with an increased risk of bleeding, but too few bleeds had occurred for the size of this excess risk to be estimated reliably. Compared with general anaesthesia, regional anaesthesia reduced the risk of DVT by about half, and this benefit appeared similar in each of the surgical settings studied. Regional anaesthesia was associated with less major bleeding than general anaesthesia.

Conclusions: In the absence of a clear contraindication (such as severe peripheral arterial disease), patients undergoing a surgical procedure would be expected to derive net benefit from a mechanical compression method of thromboprophylaxis (such as graduated compression stockings), irrespective of their absolute risk of venous thromboembolism. Patients who are considered to be at particularly high risk of venous thromboembolism may also benefit from a pharmacological thromboprophylactic agent, but since oral anticoagulant and dextran regimens appear less effective at preventing DVT than standard low-dose unfractionated heparin or low molecular weight heparin regimens, they may be less suitable for patients at high risk of venous thromboembolism, even though

they are associated with less bleeding. Whenever feasible, the use of regional anaesthesia as an alternative to general anaesthesia may also provide additional protection against venous thromboembolism.

There is little information on the prevention of venous thromboembolism among high-risk medical patients (such as those with stroke), so further randomised trials in this area would be helpful.

Contents

List of abbreviations

ATT	Anti-thrombotic Trialists
CI	confidence interval
df	degrees of freedom
DVT	deep vein thrombosis
EH	elective hip surgery
FP	footpump
FUT	fibrinogen uptake test
GA	general anaesthesia
GCS	graduated compression stocking
HF	hip fracture surgery
INR	international normalised ratio
IPC	intermittent pneumatic compression
LMWH	low molecular weight heparin
NCEPOD	National Confidential Enquiry into Peri-operative Deaths
NS	not significant
PE	pulmonary embolism
PEP	Pulmonary Embolism Prevention
PVT	proximal venous thrombosis
RA	regional anaesthesia
RCT	randomised controlled trial
SE	standard error
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

Objectives

The objectives of this study were to assess the benefits in terms of reductions in the risks of deep vein thrombosis (DVT) and of pulmonary embolism (PE), and hazards in terms of major bleeding, of: (i) mechanical compression (graduated compression stockings, intermittent pneumatic compression, footpumps); (ii) oral anticoagulants; (iii) dextran; and (iv) regional anaesthesia (as an alternative to general anaesthesia) in surgical and medical patients.

Search strategy

The strategy involved a systematic search of electronic databases (MEDLINE, EMBASE, BIOSIS, Derwent), search of the Antithrombotic Trialists' Collaboration database, contact with trialists and manufacturers, and scrutiny of bibliographies of identified papers and reviews of thromboprophylaxis.

Selection criteria

Properly randomised trials were selected, including those reported in a non-English language, with at least one unconfounded comparison of the effect of one of the methods under review versus control, or a direct comparison between different versions of a method, or a direct comparison between a pharmacological agent (dextran or an oral anticoagulant) and low molecular weight or unfractionated heparin. Trials were included only if systematic assessment of DVT by radiological methods was planned.

Data collection and analysis

All trials identified as fitting the selection criteria were independently assessed by at least two review authors for methodological quality and the numbers of patients with primary and secondary outcomes were recorded. The primary outcomes were DVT, PE and major bleeding events, and proximal venous thrombosis (PVT) and fatal PE were secondary outcomes. Trials were subdivided into those that had assessed a method as the only means of thromboprophylaxis ('monotherapy') and those that had assessed the effects of adding a method to another form of thromboprophylaxis ('adjunctive therapy').

Main results

Mechanical compression methods reduced the risk of DVT by about two-thirds when used as monotherapy and by about half when added to a pharmacological method. These benefits were similar irrespective of the particular method used (graduated compression stockings, intermittent pneumatic compression or footpumps) and similar in each of the surgical groups studied. Mechanical methods reduced the risk of PVT by about half and the risk of PE by two-fifths.

Oral anticoagulants, when used as monotherapy, reduced the risk of DVT and of PVT by about half, and this protective effect appeared similar in each of the surgical groups studied. There was an apparently large four-fifths reduction in the role of PE, but not only was the magnitude of this reduction statistically uncertain, but also pulmonary embolism was reported by a minority of trials, so it may be subject to selection bias. Oral anticoagulant regimens approximately doubled the risk of major bleeding. Oral anticoagulant regimens appeared less effective at preventing DVT than heparin regimens [64% (standard error [SE] 8) greater risk of DVT], although were associated with less major bleeding [35% (10) risk reduction for major bleeds].

Dextran reduced the risk of DVT and of PVT by about half, again irrespective of the type of surgery, but too few studies had reported PE to provide reliable estimates of effect on this outcome. Dextran appeared to be less effective at preventing DVT than the heparin regimens studied. Dextran was associated with an increased risk of bleeding, but too few bleeds had occurred for the size of this excess risk to be estimated reliably.

Compared with general anaesthesia, regional anaesthesia reduced the risk of DVT by about half,

and this benefit appeared similar in each of the surgical settings studied. Regional anaesthesia was associated with less major bleeding than general anaesthesia.

Conclusion

In the absence of a clear contraindication (such as severe peripheral arterial disease), patients undergoing a surgical procedure would be expected to derive net benefit from a mechanical compression method of thromboprophylaxis (such as graduated compression stockings), irrespective of their absolute risk of venous thromboembolism. Patients who are considered to be at particularly high risk of venous thromboembolism may also benefit from a pharmacological thromboprophylactic agent, but since oral anticoagulant and dextran regimens appear less effective at preventing DVT than standard low-dose unfractionated heparin or low molecular weight heparin regimens, they may be less suitable for patients at high risk of venous thromboembolism, even though they are associated with less bleeding. Whenever feasible, the use of regional anaesthesia as an alternative to general anaesthesia may also provide additional protection against venous thromboembolism. There is little information on the prevention of venous thromboembolism among high-risk medical patients (such as those with stroke), so further randomised trials in this area would be helpful.

Chapter 1
Background

During prolonged general anaesthesia or any other period of limited mobility, thrombus formation may be initiated in the deep veins of the leg. Such thrombosis is precipitated by the presence, to varying degrees, of components of Virchow's triad of risk factors (damage to the venous wall, change in blood flow and hypercoagulability). Venous stasis of the lower limbs is a consequence of immobility, whereas hypercoagulability may be secondary to tissue damage, inflammation or malignant disease. Moreover, during orthopaedic surgery to the lower limb or pelvic surgery, direct venous wall damage may occur as a consequence of the procedure.

Deep vein thrombosis (DVT) does not generally produce symptoms, and resolves when mobility is restored, but some episodes produce long-term valvular damage leading to chronic venous insufficiency. Some deep venous thrombi propagate proximally and may embolise to the lungs as 'pulmonary emboli' (PEs). PEs may be asymptomatic or associated with mild clinical symptoms, but when extensive they produce serious clinical sequelae and may be fatal. Venous thromboembolism (VTE) remains an important cause of morbidity and mortality in surgical and immobilised medical patients.[1–4] The 1993 National Confidential Enquiry into Peri-operative Deaths (NCEPOD) Report indicated, for example, that pulmonary embolus was the commonest cause of postoperative death after hysterectomy and elective hip operations.[1] It is important, therefore, to ensure that patients at high risk of VTE are offered appropriate forms of venous thromboprophylaxis when undergoing surgical procedures.

Various mechanical and pharmacological methods of prophylaxis have been used to prevent VTE in high-risk patients, and numerous randomised controlled trials (RCTs) have been conducted among patients undergoing different forms of surgery, and to a lesser extent among medical patients at high risk of VTE. Several systematic reviews of particular methods have been conducted, but the literature remains incomplete in some areas and contradictory in others. For example, some thromboprophylactic methods have not been reviewed at all, whereas others have been reviewed more than once but with conflicting findings,[5,6] and there have been reviews which did not restrict attention to properly randomised trials or compared agents indirectly after pooling risks in single arms.[7–9] Furthermore, since most reviews consider just those trials conducted within a single surgical specialty, where relatively small numbers of thromboembolic events may have been recorded, most treatment estimates in those reviews are statistically uncertain, and there is a need for systematic reviews which compare and contrast efficacy (and safety) across different clinical specialties. Finally, some practitioners believe that the absolute risks of VTE are now much smaller than those observed in earlier trials, perhaps because of improvements in surgical and anaesthetic practice, and hence question whether potentially hazardous thromboprophylactic methods such as antithrombotic agents will produce greater benefit than harm.

In spite of these difficulties, numerous guidelines and consensus statements have been produced.[3,10–12] Perhaps as a result of this plethora of often contradictory advice, there is significant variation in surgical practice, both between and within surgical specialties.[13–15]

The aim of this set of meta-analyses was to address some of the uncertainties regarding the effects of thromboprophylactic methods currently available. First, we reviewed three mechanical methods of thromboprophylaxis:

1. Graduated compression stockings (GCSs), also called TED stockings, which compress the lower leg veins in a graded fashion, reducing venous distension and increasing venous return to the deep venous system, hence improving the flow within it. They can extend from the foot to the knee only or they may compress the whole leg, including the thigh.
2. Intermittent pneumatic compression (IPC) devices, which use a cycle of compression and relaxation of pumped air. They may compress chambers sequentially from the ankle proximally or may have a single chamber. As is the case for stockings, they may extend from the foot to the knee or may encompass the whole leg. Different pressures can be used, and

the duration of compression/relaxation and the overall cycle can vary. Their mechanism of action is not fully understood but, as with stockings, they increase venous return and may, in addition, act via biochemical mediators which potentiate the fibrinolytic system.[16]

3. Footpumps (FPs) deliver external compression to the venous system of the foot, increasing venous return and thereby reducing venous stasis in the lower limb.

These methods were assessed in two separate clinical contexts. In the first, a method used as the only form of thromboprophylaxis ('monotherapy') was assessed among trials comparing that method versus no treatment. Alternatively, if a method was used as an additional protective agent ('adjunctive therapy') among patients already receiving a pharmacological method of thromboprophylaxis, then this was examined among trials comparing X + method versus X, where X is the background pharmacological thromboprophylactic agent.

Second, we reviewed two pharmacological methods of thromboprophylaxis which had not previously been reviewed:

1. Oral anticoagulants, such as warfarin and other coumarins, which prevent thrombosis by inhibiting the action of vitamin K-dependent coagulation factors. Warfarin can be given either as a fixed low-dose regimen, which requires no monitoring of the degree of anticoagulation, or as an adjusted-dose regimen, which generally aims to achieve a 'therapeutic level' of anticoagulation, typically equivalent to the international normalised ratio (INR) remaining within the range 2–3.
2. Dextran, which comprises a mixture of polysaccharides exerting colloid osmotic pressure to increase plasma volume and hence blood flow. Dextran is given by intravenous infusion during the perioperative and postoperative periods. Dextran infusions contain molecules of varying molecular weight, ranging from dextran 40, which contains molecules of ~40 kDa, to dextran 70, which contains molecules of ~70 kDa. Different sized molecules exert different colloid pressures, which may (it has been suggested) influence the effectiveness of different dextran preparations.

Assessments of these pharmacological agents included meta-analyses of trials comparing oral anticoagulant or dextran versus a heparin regimen (either unfractioned or low molecular weight).

Finally, we reviewed trials comparing regional anaesthesia (RA) versus general anaesthesia (GA). RA is achieved by means of a spinal or epidural local anaesthetic block, which impairs function of afferent and efferent nerves at the surgical site. It has been postulated that RA as an alternative to GA may prevent adverse outcomes after surgery through earlier mobilisation, greater lower limb blood flow,[17] inhibition of platelets[18] and a greater degree of fibrinolysis than with GA.[19]

We have not reviewed low molecular weight heparins (LMWHs) as they have been subject to two major systematic reviews.[5,6] Antiplatelet agents are the other major class of pharmacological agents – they were reviewed in 1994, and the Pulmonary Embolism Prevention (PEP) trial report included an updated meta-analysis.[20,21] We did not review dihydroergotamine as it is unlicensed in the UK and the USA because of its vasospastic side-effects.

Chapter 2
Methods

The methods used in this meta-analysis were broadly similar to those used in a previously reported meta-analysis of the effects of antiplatelet therapy on the venous thromboembolic events DVT and PE.[20]

Identification of trials

We aimed to identify all RCTs, published or otherwise, that were available by December 2001, and had compared one of the four methods of interest with a control, or with another such method, for the primary prevention of venous thromboembolism among surgical and medical patients. Such patients included adults undergoing a surgical procedure (e.g. general surgery, elective hip or knee replacement, hip fracture, trauma, urology, gynaecology, neurosurgery and cardiac/vascular surgery) or with a medical condition associated with a high risk of venous thromboembolism.

Trials were excluded if it could be ascertained that they had used a randomisation method that might allow foreknowledge of the next treatment to be allocated. This resulted in the exclusion of some studies that had used non-randomised methods of allocation, that is: sealed envelopes that were not sequentially numbered or opaque; allocation by alternation; allocation by date of birth; use of an allocation list that was visible to investigators; or the use of historical controls. Randomised trials with an unspecified or ill-defined method of randomisation were not excluded, but sensitivity analyses were prospectively planned in order to assess the contribution of such trials to the overall findings.

Trials were included in an analysis only if the comparison under review was 'unconfounded', i.e. the two randomised groups being compared differed only in respect of the thromboprophylactic method under investigation. Trials were not excluded, however, when the duration of treatment differed between randomised groups, provided that the duration of follow-up for primary outcomes was similar in both arms.

We identified potentially eligible trials from four electronic databases (MEDLINE, EMBASE, BIOSIS and the Derwent drug file) using the method developed by the Cochrane Collaboration (see Appendix 1). Trials were also identified through: cross-checking bibliographies for identified trials; checking existing Cochrane systematic reviews, textbooks and consensus statements; searching the records of the Anti-thrombotic Trialists' (ATT) Collaboration, the Cochrane Controlled Trials Register and the reference list from the Cochrane Peripheral Vascular Disease Group; by consulting with manufacturers of thromboprophylactic devices and agents; and by discussion with trialists. The main searches were performed in June 1997 and subsequently updated to December 2001 in order to identify large trials that had been published in the interim period. A list of trials and their main design features is provided in *Tables 1–4*.

Definition of outcomes

The primary outcomes were DVT and PE. Primary outcomes were counted only if they occurred during the period of systematic assessment (which usually coincided with the treatment period). Trials were included in analyses of DVT only if they used either systematic venography or one of the following systematic diagnostic methods (with or without confirmatory venography): fibrinogen labelled iodine; plethysmography; duplex ultrasound scanning; thermography; or labelled plasmin. Trials were excluded if DVT had been identified only through clinical signs and symptoms (or if there were no episodes of DVT or PE recorded, raising the suspicion that the diagnostic method may not have been used systematically).

In order to avoid the potential for bias through selective reporting, analyses of PE were conducted only among those trials that had sought DVT systematically. Trials were included in analyses of PE only if events were identified by systematic radiological assessment using ventilation/perfusion lung scans or by clinical suspicion that was subsequently confirmed (or refuted) with a ventilation/perfusion lung scan, angiography or *post mortem*.

Proximal venous thrombosis (PVT) (defined as extension of thrombus to above the knee) and fatal PE (ascertained by clinical course or autopsy) were prespecified to be secondary outcomes. Deaths other than those due to PE were not examined in detail, other than to identify deaths due to intracranial or extracranial bleeding.

Bleeding events were considered to be 'major' on the basis of the authors' own classifications (typically those requiring transfusion or resulting in disability, although some authors included bleeding necessitating reoperation, or wound haematoma), or if the episode was fatal. We tried to clarify such data with the investigators (see below).

Data requested

We asked the lead author of each potentially eligible trial for details about the method of randomisation; any blinding of treatment allocation; the method of DVT assessment and the scheduled duration of systematic surveillance for DVT; whether venography was used as confirmation; the method of PE assessment and the scheduled duration of surveillance for PE; any blinding of DVT and PE assessment; and the definition of major bleeding used in the trial. Each trial was asked to provide a tabular summary of the numbers of patients originally allocated to each treatment group (that is, before any post-randomisation exclusions), the number of patients without information on DVT outcomes and the numbers of patients with primary or secondary outcomes.

Statistical methods

Proportional and absolute effects of treatment

Analyses employed a modified Mantel–Haenszel method of combining data from different studies, with comparisons stratified by trial to avoid direct comparisons between individuals in different studies. Statistical tests for heterogeneity were performed using the chi-squared (χ^2) distribution. We calculated the observed minus the expected (O–E) number of adverse outcomes, and its variance, from standard 2×2 tables of outcome by treatment allocation. Wherever possible we sought to perform these calculations among all patients originally randomised (that is, an 'intention-to-treat' analysis) and, if necessary, the relevant numbers were requested by correspondence with the study authors. However, if this information was not available, the numbers of patients actually assessed for DVT were used as denominators for the relevant calculations. In a few trials, compression was randomly allocated to the left or right limb. In this instance identical methods can be used to estimate the effects of the treatment on the odds of leg-specific DVT, and the O – Es and their variances thus generated can be combined with those generated by the other trials. Such trials were therefore included in meta-analyses of the effects of compression methods on DVT. These trials are excluded, however, from analyses of systemic outcomes, such as PE or major bleeding, which are not leg-specific. These O – E numbers and their variances were then summed across all trials to give the grand total for O – E and its variance (V). Significance tests were based on comparison of $z = (O-E)/\sqrt{V}$ with the standard normal distribution. The odds ratio was calculated as $\exp(b)$, where $b = (O-E)/V$.[20,22]

The data are presented as Forest plots. Here the vertical line of the inverted T represents the line of equivalence between the methods being compared (i.e. odds ratio = 1). Individual trials and groups of trials are presented horizontally; the squares for each trial or group of trials represent the point estimate with the area of the square being proportional to the amount of information, and the line represents the 99% confidence interval (CI). Point estimates to the left of the vertical are in favour of the intervention and those to the right are in favour of the control arm. Summary measures are represented by diamonds, where the width of the diamond corresponds to the 95% CI. Two-sided p-values are used throughout, and denoted $2P$.

Effects in specific categories of trials

We compared different trials or groups of trials using standard χ^2 tests for heterogeneity or, where appropriate, tests for trend. However, even where there is significant heterogeneity, groups of patients in whom treatment is particularly advantageous or relatively ineffective can be difficult to identify reliably. Especially when small numbers of patients in a particular category (e.g. a specific type of surgical procedure) have been studied, it is important that 'lack of evidence of benefit' when that category is considered on its own is not misinterpreted as 'evidence of lack of benefit'. Consequently, unless there are good prior reasons for expecting large differences between the effects of treatment in particular circumstances, the approximate benefits of the methods under investigation in some particular

subgroup may be best assessed indirectly, not from an analysis that is restricted to just that subgroup but, instead, by approximate extrapolation from the proportional effect that is observed in a much wider class of patients.

This principle is particularly important when considering possible differences in the effects of a method according to whether it is used as monotherapy or as adjunctive therapy. We applied χ^2 tests for heterogeneity to examine whether there was evidence that an intervention was any less (or more) effective when added to another treatment (that is, when used as adjunctive therapy) as compared with when it was used alone (that is, as monotherapy). In the absence of statistically significant heterogeneity for a given treatment, we combined monotherapy and adjunctive therapy trials in subsequent analyses. If evidence of heterogeneity of the effects of a method for a particular outcome was found to be present, however, then the monotherapy and adjunctive therapy trials were considered separately. In particular, in the presence of such heterogeneity, analyses in specific categories of patients (e.g. different surgical operations) or according to different types of that method (e.g. different doses of a thromboprophylactic agent) were conducted only among trials of monotherapy in order to avoid the potential confounding effects of background therapy.

We undertook preplanned sensitivity analyses on several aspects of trial quality to see how variations in the independent variables affected the behaviour of the models. For each thromboprophylactic agent, we investigated: (i) the use of venography to confirm or diagnose DVT; (ii) the use of a placebo compared with open controls; (iii) whether allocation was definitely concealed or not; and (iv) the use of tabular data received from trialists compared with published data.

Description of trials

In our initial search to June 1997, we identified 3236 potentially informative references through electronic literature searches and, after removing duplicates, 2447 references remained. The titles and abstracts were then assessed, yielding 455 references describing potentially eligible studies.

These references were assessed independently by two reviewers (GF and PR) using a standard form (available on request). Discrepancies were resolved by discussion and joint reassessment of the study. If further clarification was required, a third experienced reviewer (CB) provided the final assessment. We tried to contact the authors of 288 studies, either to confirm the methodology or results or to assess eligibility in cases where we were uncertain, usually about the method of randomisation. Responses were received from 96 (33%) authors, which led to the exclusion of 17 studies.

Fifty-nine foreign language references to potentially eligible trials were identified from the literature search. Where possible these trials were assessed for eligibility via their English abstracts. For those trials without an English abstract, a translation of their methods and results sections was performed to enable an assessment of their eligibility.

Of 455 potentially eligible studies identified, 350 were excluded for one or more of the following reasons: non-randomised allocation method (103 citations); inappropriate or confounded comparisons (135 citations); meta-analysis or review article (38 citations); no outcome of interest (28 citations); secondary prevention (18 citations); other reason for exclusion (13 trials). We identified a further 18 eligible trials by other means. This left 123 eligible trials. Details of the design of trials are shown for compression methods, anti-coagulants, dextran and RA in *Tables 1–4* and the respective numbers of events in *Tables 5–8*. An update of the original searches in 2001 yielded two additional trials, both comparing oral anticoagulant versus LMWH.

TABLE I *Trial characteristics – compression methods*

Author, year	Ref. No.	Unit of randomisation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
GCS vs control																
Allan, 1983	23	P	None	ns	1 d preop–d7 postop	None	None	GS	FUT	N	Y	d 1,2,3,5,7 postop	None	None	N	Rand nk
Barnes, 1978	24	P	None	Thigh-length	Duration of hospn (inc surgery)	None	None	EH	DUS	Y	N	Preop–discharge (alternate days)	Scan	N	Y	Seq
Holford, 1976	25	P	None	Thigh-length	1 d preop–full ambulation (d 4–5 postop)	None	None	GS	FUT	N	ns	Preop, then d 1–6 postop (daily)	Scan	None	N	Env nk
Inada, 1983	26	L	None	Thigh-length	1 d preop–d 8 postop	None	None	GS	FUT	Y	ns	1 h preop–d 1,3,5 postop	None	None	N	Rand ns
Muir, 2000	27	P	None	Thigh-length	Adm–d 7	None	None	MED	DUS	N	Y	d 1, d 7	Scan	N	N	Env nk
Rosengarten, 1970	28	P	None	Knee-length	Preop-discharge or d 14 postop	None	None	GS	FUT	N	ns	d 1–14 postop/discharge (daily)	None	None	N	Rand ns
Shirai, 1985	29	L	None	Thigh-length	1 d preop – mobile	None	None	GS	FUT	N	ns	No details	None	None	N	Rand ns
Turner, 1984	30	P	None	ns	Admission–discharge	None	None	GY	FUT	N	Y	d 1 postop discharge (daily)	None	None	N	Rand c
Turpie, 1989	31	P	None	Thigh-length	Admission–discharge or d 14 postop	None	None	NR	FUT/IPG	Y	Y	Study entry–discharge/d 14 postop (daily)	Fatal pm	Y	Y	Seq
GCS combination																
Bergqvist, 1984	32	L	Dex	Thigh-length	1 d preop–d 7 postop (total 7 d)	None	None	GS	FUT	N	Y	Preop then d 1,3,5,7 postop (daily if FUT+); obs 30 d	None	None	Y	Rand c
Fredin, 1989	33	P	Dex	Thigh-length	1 d preop–d 14 postop	None	None	EH	FUT	Y	Y	Preop, d 1,3,5,7; veno d 10	Scan/pm	Y	Y	Seq

continued

TABLE I *Trial characteristics – compression methods (cont'd)*

Author, year	Ref. No.	Unit of randomisation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
Kalodiki, 1996	34	P	LMWH	Thigh-length	preop–discharge (8–12 d)	None	None	EH	Veno	N	Y	d 8–12 post-op (once)	Scan sys	Y	Y	Pharm
Kierkegaard, 1993	35	L	Aspirin	Thigh-length	Adm–discharge (≥8 d)	None	None	MED	FUT	Y	ns	d 2 postop–adm–discharge (alternate; daily if FUT+)	None	None	Y	Seq
Mellbring, 1986	67	L	IPC	Thigh-length	Preop–mobile	None	None	GS	FUT	N	ns	Preop then d 1,3,5,7,9 postop (daily if FUT+)	None	None	Y	Env
Ohlund, 1983	36	P	Dex	Knee-length	ns	None	None	EH	FUT	Y	N	d 1–10 postop (4–5x/patient)	None	None	Y	Rand c
Rasmussen, 1988	37	P	Hep	Knee–length	1 d preop–mobile (or ≥ d 5 postop)	None	None	GS	Tc Plasmin	N	ns	d 4–5 postop (once)	None	None	N	Rand ns
Scurr, 1987	68	L	IPC	Thigh-length	Preop (adm)–full ambulation	None	None	GS	FUT	Y	ns	1 d preop (DUS/IPG), d 1,3,5,7 post-op (FUT), d 5–7 (DUS/IPG)	None	None	N	Rand ns
Wille-Jorgensen I, 1985	38	P	Hep	Thigh-length	preop–discharge/ d 7 postop	None	None	GS	FUT	Y	Y	Preop, immediately postop, d 1,3,5,7 postop	Scan if FUT+	Y	Y	Seq
Wille-Jorgensen II, 1991	39	P	Hep	Thigh-length	Preop–mobile	None	None	GS	FUT	Y	Y	d 1,3,5,7 postop	Scan/ Xray	None	Y	Seq
IPC vs control				*Length, type*	*IPC*											
Bachmann, 1976	40	P	None	ns, single	Preop (nol)–postop (ol)–not specified	None	None	EH/EK	FUT	Y	Y	ns	Scan	Y	Y	Rand nk

continued

TABLE I *Trial characteristics – compression methods (cont'd)*

Author, year	Ref. No.	Unit of randomisation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
Blackshear, 1987	41	L	None	ns, sequen	Periop–24 h postop	None	None	GS	DUS	N	ns	Preop + postop	None	None	N	Rand nk
Butson, 1981*	42	P	None	Knee-length, single	Anaesthesia–2–4 d postop/ambulation	None	None	GS	FUT	Y	ns	d 1–d 14 postop	Fatal only pm	None	N	Env nk
Bynke, 1987	43	L	None	Thigh-length, single	Periop	None	None	NR	FUT	Y	ns	Preop, d 3, d 7 postop	None	None	N	Rand c
Clark, 1974	44	L	None	Knee-length, single	Anaesthesia for 17–23 h	None	None	GS	FUT	N	Y	Preop, d 1, d 3 postop	None	None	Y	Seq
Clarke–Pearson A, 1984	45	P	None	Knee-length, single	Anaesthesia–5 d postop	None	None	GY	FUT/IPG	Y	Y	FUT: d 1 postop–discharge (alternate), IPG: preop, d 5 postop	Scan angio	Y	Y	Seq
Clarke-Pearson B, 1984	46	P	None	Knee-length, single	Periop	None	None	GY	FUT/IPG	Y	Y	IPG preop–disch (alternate), FUT preop–disch (daily)	Scan angio	Y	Y	Seq
Coe, 1978	47	P	None	Knee-length, single	Anaesthesia–discharge	None	None	UR	FUT	Y	Y	d 1 postop–discharge (daily)	Scan or angio	None	N	Rand nk
Fisher, 1995	48	P	None	Thigh-length, sequen	Postop–ambulation	None	None	HF/PF	Dopp	Y	Y	Dopp: adm, every 5 d postop to ambulation, Scan: d 3–d 5 postop	Scan sys	Y	N	Seq
Gallus, 1983	49	P	None	Knee-length, single	Intraop–d 7 postop	None	None	EH	IPG/FUT	Y	Y	FUT daily postop, IPG d 7 postop, Veno d 7 postop	None	None	Y	Seq
Hills, 1972	50	P	None	Knee-length, single	Periop–ambulation (1 d postop)	None	None	GS	FUT	N	ns	d 1–d 7 postop	None	None	N	Env nk

continued

TABLE I *Trial characteristics – compression methods (cont'd)*

Author, year	Ref. No.	Unit of randomisation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
Hull I, 1979	51	P	None	Knee-length, single	Postop–discharge/ 17 d	None	None	EK	FUT	Y	Y	Veno d 7–d 10 or d 14–17 postop	None	None	N	Seq
Hull II, 1990	52	P	None	Thigh-length, sequen	Postop–discharge/ 14 d	None	None	EH	FUT/IPG	Y	Y	FUT d 1– d 14 postop, IPG d 5 postop then alt d until disch, veno d 14 postop or disch	Scan	Y	N	Rand ns
Knudson, 1994	53	P	None	Thigh-length, sequen	Within 24 h or admiss, dur ns	None	None	TR	DUS	N	ns	d 1–d 21 postop (at 5–7 d intervals)	Angio	ns	N	Rand ns
Kosir, 1996	54	P	None	ns, sequen	Intra-op–48 h postop	None	None	GS	DUS	N	Y	Preop then d 1, d 3, d 30 postop	None	None	Y	Rand ns
Skillman, 1978	55	P	None	Knee-length, single	Anaesthesia–ambulation (<17 d postop)	None	None	NR	FUT	Y	Y	d 1 postop–discharge	None	None	N	Rand ns
Turpie I, 1977	56	P	None	Knee-length, single	NoI: admission, oI: d 1–d 5 post-op	None	None	NR	FUT	N	ns	Preop–d 5 postop (14 d if non ambulant)	notsys pm only	ns	Y	Seq
Turpie II, 1979	57	P	None	Knee-length, sequen	d 1–<d 14 postop	None	None	NR	FUT/IPG	Y, not all	ns	FUT preop–<d 14 postop, IPG: preop–d 3, d 5, d 7, d 10, d 14	notsys pm only	ns	Y	Seq
Weitz, 1986	58	P	None	Knee-length, ns	Periop–d 6 postop	None	None	NR	FUT	Y	ns	ns	None	None	N	Rand ns

continued

TABLE I *Trial characteristics – compression methods (cont'd)*

Author, year	Ref. No.	Unit of randomisation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
IPC combination																
Caprini, 1983	69	P	GCS	Thigh-length, sequen	Preop–3 d postop/ ambulant	None	None	MixS	FUT/DUS	N, some	ns	FUT: preop, postop then alt till amb, DUS: preop, postop then every 3 d till amb	Angio	ns	Y	Env nk
Lieberman, 1994	59	P	Aspirin	Thigh-length, sequen	Postop–d 6–8 postop	None	None	EH	Veno	N	Y	d 6–d 8 postop	None	None	N	Rand nk
Pambianco, 1995	70	P	GCS	Thigh-length, single	8 h per night	None	None	MED	DUS	N	ns	Twice a week for 28 d/discharge	None	None	N	Rand nk
Rokito, 1996	71	P	GCS	Thigh-length, sequen	Preop–d 5/7	None	None	SP	DUS	Y	Y	d 5–d 7 postop	None	None	N	Rand ns
Siragusa, 1994	60	P	Heparin	ns, ns	ns	None	None	EH	Veno	N	Y	d 10 postop	Scan, angio	Y	Y	Comp
Smith, 1978	61	P	Dextran	ns, ns	Intraop	None	None	GS	FUT	N	Y	Preop–discharge/d 7 (alternate)	Scan	ns	N	Rand nk
Turpie, 1989	31	P	GCS	Thigh-length, sequen	Periop–d 7	None	None	NR	FUT/IPG	Y	Y	FUT preop–d 14, IPG d 3, d 5, d 7, d 9, d 11, d 14	None	None	Y	Seq
Wautrecht, 1996	72	P	GCS	Thigh-length, ns	Preop–d 10/ambulant	None	None	NR	Veno	N	Y	d 8–d 10 postop	Scan	ns	Y	Env
Footpump vs control																
Scurr, 1981	62	P	None	Bilateral	Periop	None	None	GS	FUT	Y	ns	d 1, 2, 3, 5, 7 postop	None	None	N	Rand ns
Wilson, 1992	63	P	None	Foot of op leg	Postop–d 9–10	None	None	EK	Veno	N	Y	d 9–10 postop (once)	Scan	ns	N	Rand ns
Footpump combination																
Fordyce, 1992	73	P	GCS	Foot of op leg	Postop during sitting and bed rest	Bilateral	Postop–ns	EH	Veno	N	Y	d 6–9 postop	None	None	N	Seq

continued

TABLE 1 *Trial characteristics – compression methods (cont'd)*

Author, year	Ref. No.	Unit of randomisation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
Stannard, 1996	64	P	Hep/aspirin	Bilateral	Postop–discharge	H5000, A325	H d 1, 3 A d 4, disch	EH	DUS	Y	Y	Preop, d 7, d 14 postop	None	None	N	Rand ns
Above vs below knee-length																
Porteous, 1989	65	None	None	None	Preop–discharge	None	Preop–disch	GS	FUT	Y	ns	Postop–discharge (alternate)	None	None	N	Rand ns
Williams, 1988	66	None	None	None	ns	None	ns	GS	FUT	N	ns	ns	None	None	N	Env

Key to all tables

Missing data

na, not applicable; ns, not stated; nr, not recorded

Unit of randomisation

L, legs; P, patients

Clinical setting

CS, cardiac surgery, EH, elective hip; EK, elective knee; G, gynaecology; GS, general surgery; HF, hip fracture; MED, medical; MixS, mixed; NR, neurosurgery; PF, pelvic fracture; SP, spinal; TR, trauma; U, urology; VS, vascular surgery

Venography method

DUS, Doppler ultrasound; FUT, fibrinogen uptake; IPG, impedance phlethysmograph; veno, venography. For PE: angio, angiography; fatal pm, PEs identified at post-mortem.

Anticoagulant adjustment method

INR, international normalised ratio; PT, prothrombin time; TT, thrombotest

Randomisation method

comp, on-site computer; env, sealed not opaque envelope; env nk, envelope not known if sealed or opaque; pharm, pharmacy coded container administered sequentially; rand c, closed list of random numbers; rand nk, list of random numbers not known if closed or open; rand ns, randomisation method not specified; rand o, open list of random numbers; seq, sequentially numbered sealed opaque envelope

Treatment detail

aceno, acenocoumarin; adj, adjusted dose; adm, admission; alt, alternate; bd, twice daily; d, day; dex, dextran; dic, dicoumarol; disch, discharge; fxd, fixed dose; h, hour; intraop, during surgery; LMWH, low molecular weight heparin; nol, non-operated leg; obs, observed; od, once daily; ol, operated leg; pd, postdischarge; periop, around time of surgery; phen, phenprocoumon; plac, placebo; po, by mouth; postop, post surgery; preop, before surgery; nic, nicoumalone; sequen, sequential; sc, subcutaneously; tds, three times daily; war, warfarin; w, week.

Other

amb, ambulant; pm, post-mortem; notsys, no systematic assessment of pulmonary embolism; pmnch, found at post-mortem but not cause of death.

TABLE 2 *Trial characteristics – anticoagulants*

Author, year	Ref. No.	Com-posi-tion	Unit of randomi-sation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomi-sation
OAC control/plac																	
Borgstrom, 1965	74	C	Open	None	Dic, PT 40 ms	Admission–mobile	None	None	HF	Veno	na	Y	3–4 w (once)	pm for fatal	ns	N	Rand c
Fordyce, 1991	75	C	Placebo	None	Fixed low war	1 w preop–3 w postop	None	None	EH	FUT	Y	ns	d 1–d 14 postop/disch	na	ns	N	Pharm
Hamilton, 1970	76	C	Open	None	Phen, PT 2–2.5	Postop–d 14	None	None	HF	Veno	na	N	d 5–d 12 postinjury	na	na	N	Env
MacCallum, 1990	77	C	Placebo	None	Fixed low war	1 w preop–disch	None	None	GY	FUT	Y	Y	d 5 postop, DUS/IPG d 5	na	ns	Y	Rand c
Morris, 1976	78	C	Placebo	None	War, TT 10%	Within 24 h admission–mobile/3 m	None	None	HF	FUT	N	ns	d 1–d 10 postop (daily)	X-ray	ns	N	seq
Pinto, 1970	79	C	Open	None	War, TT 5–15%	Premed–2 w po	None	None	HF/EH	FUT	Y	N	d 1–d 10 postop (daily)	na	na	N	Rand ns
Poller, 1987	80	C	Open	None	Fxd low + full	Mean 20 d preop–disch	None	None	GY	FUT/DUS	Y	ns	Immed. postop disch	na	na	N	Rand nk
Powers, 1989	81	C	Placebo	None	War, INR 2–2.7	Postop–21 d postop /dis	None	None	HF	FUT	Y	Y	FUT d 1–3 postop od, alt. IPG d 4–5 postop, alt. Veno 21 d postop/disch	Scan	ns	N	Seq
Taberner, 1978	82	C	Open	None	Nic, PT 2–4	5 d preop–d 14 postop	None	None	GY	FUT	N	Y	d 1–d 7 postop	na	na	Y	Rand o
OAC combination																	
Habersberger, 1973	83	W vs H	Open	HEP	War, PT 10–35%	Admission–ns	None	None	MED	FUT	N	ns	1st–7th/10th days (daily)	pm for fatal	ns	N	Rand ns
Hume, 1973	87	C	Open	GCS	War, PT 1.5	Recovery room–ns	None	None	EH	FUT	Y	ns	1 d pre-op, d 1, d 2, d3 postop, then alt days	na	na	N	Rand nk
Korvald, 1973	84	C	Open	DEX	War, TT 8–15%	Admission–ns	None	None	HF	Veno/FUT	Y	ns	2–3 w post op, 25 had FUT alt days until d 7–10 postop	pm for fatal	na	N	Rand ns

continued

TABLE 2 *Trial characteristics – anticoagulants (cont'd)*

Author, year	Ref. No.	Com-posi-tion	Unit of randomi-sation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomi-sation
Rokito, 1996	71	C	Open	GCS	Low war PT 1.3–1.5	Preop–d 4–5, postop	None	None	SP	DUS	Y	Y	d 5–d 7 postop	na	na	n	Rand ns
van Geloven, 1977	85	C	Placebo	HEP	Aceno adj	d 1 postop–30 d	None	None	MixS	FUT	N	ns	d 1–d 10 postop od	Scan if FUT	ns	N	Pharm
Woolson, 1991	86	C	Open	IPC/GCS	Low war PT 1.2–1.3	Preop–ns	None	None	EH	Veno/DUS	Most	N	7th postop day	Scan	ns	N	Rand c
OAC dose comparison					*Range*		*Dose*										
Feller, 1992	88	Adj W vs fxd	na	Calf stim	War adj INR 2–4	Night preop–d 3 postop (fixed) then adj	War 1 mg	Night preop–d 14 postop od	EH	Veno	na	Y	d 11–13 postop (once)	Scan	ns	Y	Env
Poller, 1987	80	Adj nic vs fxd	na	None	Nic adj INR 2.4	5 d preop–disch (av 7.2 d stay)	War 1 mg	Mean 20 d preop–disch	GY	FUT/DUS	Y	ns	Immed. postop–disch	na	ns	N	Rand nk
OAC vs heparins																	
Hume, 1973	87	LDH	na	GCS	War adj 1.5 PTT	Recovery room–?	H5000IU sc	2 h preop, postop tds	EH	FUT	Y	ns	1 d preop, d 1, d 2, d 3 postop then alt days	na	na	N	Rand ns
Poller, 1995	97	LDH	na	None	War 1 mg	7 d preop–venogram (d 9–14) od	H5000IU sc	2 h preop–veno (d 9–14) tds	EH/EK	Veno	na	Y	d 9–14 postop (operated limb)	na	na	N	Rand nk
Taberner, 1978	82	LDH	na	None	Nic adj 2–4 BCT	5 d preop–d 14 postop	H5000IU sc	2 h preop–d 7 postop bd	GY	FUT	N	Y	d 1–d 7 postop	na	na	Y	Rand o
van Geloven, 1977	85	LDH	na	PLAC DEX	Aceno adj plac hep	d 1 postop–?	H4-5000IU sc plac OAC	2 h preop–? bd	MixS	FUT	N	ns	d 1–d 10 postop od	Scan if FUT	ns	N	Pharm
Friedman, 1994	98	LMWH	na	None	War adj PT 1.2–1.5	Preop night–discharge or mobile (4–10 d)	H 50U/kg bd/90 od sc	Postop night–disch/mob (4–10 d)	EH/EK	IPG/DUS	Y	Y	d 4 postop disch (once)	Scan/angio	Y	Y	Rand c
Gerhart, 1991	90	LMWH	na	None	War adj PT 1–1.5	Adm–disch	LMWH 750U sc	Adm–d 9 postop bd + war d 7 postop–disch	HF	FUT/IPG	Y	Y	d 1 postop–disch(daily)	Scan	ns	N	Rand ns

continued

TABLE 2 *Trial characteristics – anticoagulants (cont'd)*

Author, year	Ref. No.	Composition	Unit of randomisation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
Hamulyak, 1995	91	LMWH	na	GCS	Aceno adj INR 2–3	Preop–d 10 postop	LMWH 60IU/kg sc	Preop–d 10 postop od	EH/EK	Veno	na	Y	d 10 postop (disch if earlier)	Scan/angio/pm	Y	N	Rand nk
Heit, 1997	92	LMWH	na	None	War adj INR 2–3	1 d preop–d 14 postop /disch	LMWH 60 iu/kg sc	1 d preop–d 14 postop/disch bd	EK	Veno	na	Y	d 5–14 postop	Scan/ang/Xray	ns	N	Rand ns
Hull III, 1993	93	LMWH	na	None	War INR 2–3 plac H	1st postop night–d 14 post /disch	LMWH 75 iu/kg sc, plac war	d 1 postop–d 14/disch od	EH/EK	Veno	na	Y	Mean d 9 postop (scheduled d 14)	Scan/angio/pm	ns	N	Comp
Hull IV, 2000	94	LMWH	na	None	War INR 2–3 plac H	Night of surgery–?	2500–5000 iu sc, plac war	2500 iu ± 2 h preop, 4 h postop, 5000 od	EH	Veno	na	Y	d 4–8 postop or at disch	na	na	N	Rand nk
Leclerc, 1996	95	LMWH	na	None	War INR 2–3 plac H	Night of surgery–d 14 postop /disch	LMWH 30 mg sc, plac war	d 1 postop–d 14 postop/disch bd	EK	Veno	DUS/IPG	Y	d 14 postop/disch	Scan	Y	Y	Pharm
Francis, 1997	96	LMWH	na	None	War PT 1.4–1.5	Preop night od postop –disch	LMWH preop, 5000 iu sc od	2 h preop od–disch	EH	Veno	N	Y	Mean d 7 ± 2	na	na	N	Rand ns
Fitzgerald, 2001	89	LMWH	na	None	War adj INR 2–3	8 h postop–d 4–14 postop	LMWH 30 mg sc	8 h postop–d 4–14 postop bd	EK	Veno	na	ns	No timing details	Scan/angio	na	N	Pharm

TABLE 3 *Trial characteristics – dextran*

Author, year	Ref. No.	Com-posi-tion	Unit of randomi-sation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomi-sation
Dextran vs control																	
Bergqvist I, 1979	100	C	Open	None	70, 500 ml	Periop, postop, d 1, d 3	None	None	HF	FUT	N	Y	Preop, d 1–10 postop (alt)	pm for fatal	na	N	Env nk
Bergqvist II, 1980	101	C	Open	None	70, 500 ml	Periop, postop, d 1, d 3	None	None	GS/UR	FUT	N	ns	Preop, d 1–7 postop (daily/ alternate)/ disch	pm for fatal	na	N	Rand nk
Carter, 1973	102	C	Placebo	None	70, 500 ml	Anaesthesia–discharge	None	None	GS	FUT	Y	ns	Preop–discharge (daily)	na	na	N	Rand nk
Evarts, 1971	103	C	Placebo	None	lmw, 500 ml	Periop–ns (daily)	None	None	EH	Veno	na	ns	preop and d 10–d 12 postop (once)	na	na	n	Env nk
Gruber, 1977	104	C	Open	None	40, 500 ml	Periop–d 1, d 2 postop	None	None	GS	FUT	N	ns	d 1–d 7 postop (daily)	pm for fatal	ns	N	Seq
Hefley, 1990	105	C	Placebo	None	40, 500 ml	Periop then d 2 and d 4	None	None	HF	Veno	na	ns	d 1–(d 5, d 6 or d7) postop	na	na	N	Seq
Hubens, 1976	106	C	Open	None	40, 500 ml	Anaesthesia–d 1 postop	None	None	GS	FUT	N	ns	Preop–d 7 postop (daily)	na	na	N	Rand nk
Hurson, 1979	107	C	Open	None	70, 500 ml	Postop–(d 2 and d 4) postop	None	None	EH	Veno	na	Y	d 4–d 6 (once) and d 10–d 12 (once) postop	Scan	Y	Y	Env
Huttunen, 1977	108	C	Placebo	None	40/70, 500 ml	Anaesthesia–periop	None	None	MixS	FUT	N	ns	d 1–d 7 postop (alternate)	na	na	N	Pharm
Johnsson, 1968	109	C	Open	None	70, 500 ml	Periop–d 1, d 2, d 6, d 9 and d 12 postop	None	None	HF	Veno	na	ns	Daily clinical assess, veno <3 m	na	na	N	Rand o
MacIntyre, 1974	110	C	Open	None	70, 500 ml	Anaesthesia, d 1, d 2 postop	None	None	MixS	FUT	N	ns	ns	pm for fatal	ns	N	Env nk
van Hospenthal, 1977	111	C	Placebo	None	70, 500 ml	Anaesthesia–d 1 postop	None	None	UR	FUT	N	ns	ns	na	na	N	Seq
Welin–Berger, 1982	112	C	Open	none	70, 500 ml	Periop–(d 1 and d 4) postop	None	None	EH	IPG	Y	ns	Preop and d 14 postop	Scan	ns	N	Rand nk

continued

TABLE 3 *Trial characteristics – dextran (cont'd)*

Author, year	Ref. No.	Com-posi-tion	Unit of randomi-sation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomi-sation
Dextran combination																	
Andersen, 1986	115	C	Open	GCS	70, 500 ml	Periop–mobile (alternate)	None	None	HF	Veno	na	Y	d 9–d 11 postop (daily)	na	na	N	Rand nk
Schondorf, 1980	113	C	Open	Heparin	40, 500 ml	Postop–d 1, d 3	None	None	EH	FUT	Y	ns	d 1–d 9/ d 10 postop (daily)	Scan	ns	N	Rand nk
Smith, 1978	61	C	open	IPC	70, 500 ml	Anaesthesia–8 h po for 4 h	None	None	GS	FUT	N	Y	Preop–d 7/ discharge postop (alternate)	Scan	ns	N	Env nk
Swierstra, 1984	114	C	Open	Aceno	40, 500 ml	Periop–d 1 postop	None	None	EH/EK	Veno	na	Y	d 7 postop	na	na	N	Seq
van Geloven, 1977	85	C	Placebo	Aceno	40, 500 ml	Periop–d 1 postop	None	None	MixS	FUT	N	ns	d 1–d 10 postop od	Scan if FUT+	ns	N	Pharm
Dextran vs heparin					*Dextran*	*Dextran*	*Heparin*	*Heparin*									
Bergqvist I, 1979	100	LDH	na	None	70, 500 ml	Periop, postop, d 1, d 3 postop	Heparin 5000 iu sc	Diagnosis–d 5 postop bd	HF	FUT	N	Y	Preop, d 1–10 postop (alt)	pm for fatal	na	n	Env nk
Bergqvist II, 1980	101	LDH	na	None	70, 500 ml	Periop, postop, d 1, d 3 postop	Heparin 5000 iu sc	Preop–d 5 postop bd	GS/UR	FUT	N	ns	Preop, d 1–7 postop (daily/ alternate)/disch	pm	ns	N	Rand nk
Gruber, 1977	104	LDH	na	None	40, 500 ml	Periop–d 1, d 2 postop	Heparin 5000 iu sc	2 h preop–d 7 postop tds	GS	FUT	N	ns	d 1–d 7 postop (daily)	pm for fatal	ns	N	Seq
Hohl, 1980	116	LDH	na	None	70, 500 ml	Periop–d 1 postop	Heparin 5000 iu sc	2 h preop–d 7 postop tds	GY	FUT	Y	Y	Preop–d 7 postop (daily)	na	ns	N	Env nk
Hubens, 1976	106	LDH	na	None	40, 500 ml	Anaesthesia, d 1 postop	Heparin 5000 iu sc	2 h preop–d 7 bd	MixS	FUT	N	ns	Preop–d 7 postop (daily)	na	na	N	Rand nk
MacIntyre, 1974	110	LDH	na	None	70, 500 ml	Anaesthesia, d 1, d 2 postop	Heparin 5000 iu sc	2 h preop–7 d postop bd	MixS	FUT	N	ns	ns	pm for fatal	ns	N	Env nk
Urbanyi, 1982	117	LDH	na	None	60, 500 ml	Preop–d 1, 2, 4, 6 postop	Heparin 5000 USP sc	Preop–d 1, 2, 3, postop tds	VS	FUT	Y	ns	d 1–7 postop (daily)	Scan if FUT pm for fatal	ns	N	Rand nk
Van Geloven, 1977	85	LDH	na	Aceno + plac dex	40, 500 ml	Periop and d 1 postop	Heparin 4000 iu sc	2 h preop–d 4.5 postop, bd	MixS	FUT	N	ns	d 1–10 postop (daily)	Scan if FUT+	ns	N	Pharm
Welin-Berger, 1982	112	LDH	na	None	70, 500 ml	Periop–(d 1 and d 4) postop	Heparin 5000 iu sc	Preop–d 7 postop bd	EH	IPG	Y	ns	Preop, day 14 postop	Scan	ns	N	Rand nk

continued

TABLE 3 *Trial characteristics – dextran (cont'd)*

Author, year	Ref. no	Com-posi-tion	Unit of randomi-sation	Background agent (all patients)	Treatment 1	Treatment regimen 1	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomi-sation
Wille-Jorgensen II,1991	39	LDH	na	GCS	70, 500 ml	Periop–(d 1 and d 3) postop	Heparin 5000 iu sc	Preop–d 7 or mob bd	GS	FUT	Y	ns	d 1, d 3, d 5, d 7	Scan	ns	Y	Seq
Dan Enox, 1991	99	LMWH	na	None	70, 500 ml	Periop–d 3/5 postop	LMWH 40.6 mg/0.4 ml sc	Preop–d 7 postop od	EH	Veno	na	Y	d 7–11 postop	na	na	N	Rand nk
Eriksson, 1988	118	LMWH	na	None	70, 500 ml	Periop, d 1, 3 postop	LMWH 2500 iu sc	Preop–d 7 bd postop	EH	FUT	Y	Y	d 1–14 postop (daily)	Scan	ns	Y	Seq
Matzsch, 1991	119	LMWH	na	None	70, 500 ml	Periop–d 1, 3, 5 postop	LMWH 50 u/kg sc	Preop–d 7 postop od	EH	FUT	Y	Y	d 1 postop–d 7/10 postop (at)	Scan	Y	Y	Seq
Oertli, 1992	120	LMWH	na	None	70, 500 ml	Anaes-24 hrs postop tds	LMWH 3000 iu sc	Preop–d 10 postop od	HF	FUT	Y	Y	d 1–d 7 postop (daily)	Scan	N	Y	Env
Wiig, 1995	121	LMWH	na	None	70, 500 ml + plac LMWH	Periop–d 1, 3, 5 postop	LMWH 20 mg sc plac dex	2 h preop–d 10 postop/mobile od	GS	Veno	na	Y	d 4–6 postop	Scan	ns	Y	Pharm

TABLE 4 *Trial characteristics – regional anaesthesia*

Author, year	Ref. No.	Unit of randomisation	Background agent (all patients)	Treatment 1	Duration of treatment 1	Treatment 2	Duration of treatment 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
Regional vs general anaesthesia					*RA*		*GA*									
Brichant, 1995	122	Open	LMWH+ GCS	Subarachnoid block	na	GA	na	EH	Veno	N	Y	d 10	na	N	N	Rand nk
Davis I, 1981	123	Open	None	Subarachnoid block	104 min	N_2O/O_2 + pancuronium	104 min	HF	FUT	N	Y	Duration 7 d; no timing details	na	N	Y	Seq
Davis II, 1989	124	Open	GCS	Hypobaric spinal anaes	73 min	Narcotic–halothane–relaxant GA	79 min	EH	FUT/IPG	Y	Y	postop d 4, 7, 11 postop (IPG) FUT od 7 d postop	Scan 4 FUT/IPG	N	Y	Seq
Fredin, 1986	125	Open	Dextran 70	Continuous epidural blockade	na	Neurolept anaesth	na	EH	Veno	na	Y	d 10–14 postop (once)	Scan systematic	Y	Y	Env
Hendolin I, 1981	126	Open	None	Continuous lumbar epidural	up to 24 h	GA	na	UR	FUT	N	ns	1 d preop, postop, d 1, 2, 3, 5, 7 postop	na	na	N	Env nk
Hendolin II, 1982	127	Open	None	Continuous thoracic epidural	24 h	GA	na	GS	FUT	Y	ns	1 d preop, postop, d 1, 2, 3, 5 postop	na	na	N	Rand nk
Jorgensen, 1991	128	Open	GCS	Continuous extradural anaesthesia	3 d	GA	Operation	EK	Veno	na	Y	d 9–11 postop (once)	Scan	N	Y	Env
McKenzie, 1985	129	Open	None	Subarachnoid block	93.5 min	GA	79 min	HF	Veno	na	N	d 7–10 postop (once) (1 pt on d 4 postop)	na	na	Y	Seq
Modig, 1986	17	Open	None	Continuous lumbar epidural	152 min	GA with parenteral analgesics	150 min	EH	Veno	na	Y	d 12–14 postop (once)	Scan systematic	Y	N	Env nk
Rodrigo, 1994	130	Open	Dextran 40 + 7500 IU H	Lumbar epidural	na	GA	na	EK	Veno	na	ns	d 10 postop	ns	ns	N	Rand nk
William-Russo, 1996	131	Open	ASA, GCS on non-op limb	na	na	na	na	EK	Veno	na	Y	d 4–5 postop (once)	Scan systematic	Y	Y	Seq

TABLE 5 *Trial events – compression methods*

Author, year	Ref. No.	Numbers randomised		DVT assessed		DVT		PVT		Non-fatal PE		Fatal PE		All PE		Major bleeds	
		A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C
GCS vs control																	
Allan, 1983	23	211 total		97	103	15	37	nr	nr	na	na	na	na	na	na	nr	nr
Barnes, 1978	24	8	10	8	10	0	5	0	4	0	3	0	0	0	3	nr	nr
Holford, 1976	25	50	48	48	47	11	23	1	3	0	1	0	0	0	1	nr	nr
Inada, 1983	26	110	110	110	110	4	16	nr	nr	na	na	na	na	na	na	nr	nr
Muir, 2000	27	65	32	65	32	7	7	3	2	0	0	0	0	0	0	nr	nr
Rosengarten, 1970	28	25	25	25	25	8	8	0	0	na	na	na	na	na	na	nr	nr
Shirai, 1985	29	126	126	126	126	5	17	nr	nr	na	na	na	na	na	na	nr	nr
Turner, 1984	30	104	92	104	92	0	4	nr	nr	na	na	na	na	na	na	nr	nr
Turpie, 1989	31	80	81	80	81	7	16	1	2	na	na	0	0	na	na	nr	nr
GCS combination																	
Bergqvist, 1984	32	88	88	80	80	0	8	0	1	na	na	na	na	na	na	nr	nr
Fredin, 1989	33	150/3arms		49	48	13	21	nr	nr	0	2	0	0	0	2	nr	nr
Kalodiki, 1996	34	39	38	32	32	8	12	4	9	2	3	0	0	2	3	nr	nr
Kierkegaard, 1993	35	80	80	80	80	0	8	0	0	na	na	na	na	na	na	nr	nr
Mellbring, 1986	67	114 total		54	54	7	6	nr total=1		na	na	na	na	na	na	nr	nr
Ohlund, 1983	36	63 total		31	31	7	15	nr	nr	na	na	0	0	na	na	nr	nr
Rasmussen, 1988	37	89	85	89	85	23	25	nr	nr	na	na	na	na	na	na	nr	nr
Scurr, 1987	68	78	78	78	78	1	7	0	0	na	na	na	na	na	na	nr	nr
Wille-Jorgensen I, 1985	39	94	102	86	90	1	7	nr	nr	2	5	0	1	2	6	nr	nr
Wille-Jorgensen II, 1991	38	94	84	79	81	2	12	nr	nr	0	0	1	0	1	0	nr	nr
IPC vs control																	
Bachmann, 1976	40	26	28	26	28	4	13	nr	nr	1	5	na	na	1	5	nr	nr
Blackshear, 1987	41	20	20	20	20	0	0	nr	nr	na	na	na	na	na	na	nr	nr
Butson, 1981	42	62	57	62	57	4	4	nr	nr	na	na	0	1	na	na	nr	nr
Bynke, 1987	43	31	31	31	31	0	6	nr	nr	na	na	na	na	na	na	nr	nr
Clark, 1974	44	36	36	36	36	0	7	nr	nr	na	na	na	na	na	na	nr	nr
Clarke-Pearson I, 1984	45	59	57	55	52	5	17	1	4	2	1	0	0	2	1	nr	nr
Clarke-Pearson II, 1984	46	104	105	97	97	14	11	5	1	3	0	1	1	4	1	nr	nr
Coe, 1978	47	31	24	29	24	1	5	nr	nr	0	1	0	0	0	1	nr	nr
Fisher, 1995	48	345 total		145	159	4	9	4	9	6	8	0	1	6	9	nr	nr
Gallus, 1983	49	95 total		43	47	15	25	10	12	na	na	na	na	na	na	nr	nr
Hills, 1972	50	155 total		70	70	7	23	nr	nr	na	na	na	na	na	na	nr	nr
Hull I, 1979	51	32	29	32	28	2	19	0	7	na	na	na	na	na	na	nr	nr

continued

TABLE 5 *Trial events – compression methods (cont'd)*

Author, year	Ref. No.	Numbers randomised		DVT assessed		DVT		PVT		Non-fatal PE		Fatal PE		All PE		Major bleeds	
		A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C
Hull II, 1990	52	152	158	124	135	36	77	22	42	0	1	1	0	1	1	nr	nr
Knudson, 1994	53	26	39	26	39	0	5	0	5	0	0	0	0	0	0	nr	nr
Kosir, 1996	54	137 in 3 arms		25	45	0	0	nr	nr	na	na	na	na	na	na	nr	nr
Skillman, 1978	55	47	48	47	48	4	12	nr	nr	0	0	0	0	0	0	nr	nr
Turpie I, 1977	56	82	79	65	63	8	13	0	2	na	na	0	0	na	na	nr	nr
Turpie II, 1979	57	112	106	102	97	8	20	3	8	na	na	na	na	na	na	nr	nr
Weitz, 1986	58	5	9	5	9	0	2	nr	nr	na	na	na	na	na	na	nr	nr
IPC combination																	
Caprini, 1983	69	102 total		38	39	1	5	0	1	1	1	0	1	1	2	nr	nr
Lieberman, 1994	59	130	130	113	118	7	9	0	1	na	na	0	0	na	na	nr	nr
Pambianco, 1995	70	117	115	116	115	8	6	nr	nr	na	na	na	na	na	na	nr	nr
Rokito, 1996	71	33	42	33	42	0	0	nr	nr	na	na	na	na	na	na	nr	nr
Siragusa, 1994	60	35	35	35	35	6	10	5	4	0	0	0	0	0	0	nr	nr
Smith, 1978	61	305 in 3 arms		97	97	18	21	nr	nr	3	6	0	0	3	5	nr	nr
Turpie, 1989	31	78	80	78	80	7	7	1	1	na	na	0	0	na	na	nr	nr
Wautrecht, 1996	72	25	10	18	5	0	2	0	1	0	0	0	0	0	0	nr	nr
Footpump vs control																	
Scurr, 1981	62	33	33	33	33	6	15	nr	nr	na	na	0	0	na	na	nr	nr
Wilson, 1992	63	28	32	28	32	5	19	0	6	0	0	0	0	0	0	nr	nr
Footpump combination																	
Fordyce, 1992	73	42	42	39	40	2	16	2	13	na	na	na	na	na	na	nr	nr
Stannard, 1996	64	25	25	25	25	0	5	0	5	na	na	0	0	na	na	nr	nr
Above vs below knee																	
Porteous, 1989	65	60	64	56	58	3	1	nr	nr	na	na	na	na	na	na	nr	nr
Williams, 1988	66	44	44	44	44	6	8	nr	nr	na	na	na	na	na	na	nr	nr

A, active treatment; C, control.

TABLE 6 *Trial events – oral anticoagulants*

Author, year	Ref. No.	Numbers randomised		DVT assessed		DVT		PVT		Non-fatal PE		Fatal PE		All PE		Major bleeds	
		A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C
OAC control/placebo																	
Borgstrom, 1965	74	29	29	23	25	2	13	nr	nr	na	na	0	2	na	na	0	0
Fordyce, 1991	75	74	74	74	74	25	19	6	5	na	na	na	na	na	na	nr	nr
Hamilton, 1970	76	38	38	38	37	10	18	nr	nr	na	na	na	na	na	na	11	9
MacCallum, 1990	77	97	97	40	46	2	5	0	0	na	na	na	na	na	na	4	2
Morris, 1976	78	80	80	75	74	23	50	0	5	0	2	0	6	0	8	9	2
Pinto, 1970	79	25	25	25	25	9	8	nr	nr	na	na	0	0	na	na	1	0
Poller, 1987	80	67	37	67	37	4	11	nr	nr	na	na	na	na	na	na	12	5
Powers, 1989	81	65	63	65	63	13	29	6	19	0	2	0	0	0	2	5	5
Taberner,1978	82	48	48	48	48	3	11	nr	nr	na	na	0	0	na	na	3	0
OAC combination																	
Habersberger, 1973	83	133 total		53	63	5	8	0	0	na	na	0	0	na	na	nr	nr
Hume, 1973	87	17	19	17	19	3	4	nr	nr	na	na	na	na	na	na	1	1
Korvald, 1973	84	99 total		39	43	4	15	1	2	na	na	0	1	na	na	nr	nr
Rokito, 1996	71	35	42	35	42	0	0	nr	nr	na	na	na	na	na	na	2	0
van Geloven, 1977	85	331 total		74	80	13	15	nr	nr	2	5	0	0	2	5	1	0
Woolson 1991	86	69	76	69	76	0	0	6	9	0	0	0	0	0	0	0	0
OAC dose comparison																	
Feller, 1992	88	100	100	98	97	16	30	4	11	0	0	1	0	1	0	0	2
Poller, 1987	80	35	32	35	32	1	3	nr	nr	na	na	0	0	na	na	8	4
OAC vs heparins																	
Hume, 1973	87	17	18	17	18	3	3	nr	nr	na	na	na	na	na	na	1	7
Poller, 1995	97	47	43	31	37	15	8	3	0	na	na	0	0	na	na	3	3
Taberner, 1978	82	48	49	48	49	3	3	nr	nr	na	na	0	0	na	na	3	5
van Geloven, 1977	85	331 total		80	80	20	15	nr	nr	9	5	0	0	9	5	1	0
Friedman, 1994	98	407	800	321	648	87	120	33	41	1	1	0	0	1	1	21	45
Gerhart, 1991	90	145	144	131	132	28	9	7	3	1	0	0	0	1	0	5	8
Hamulyak, 1995	91	342	330	257	260	50	43	15	17	0	0	0	0	0	0	8	5
Heit, 1997	92	279	277	222	232	85	62	15	15	0	1	0	0	0	1	12	22
Hull III, 1993	93	721	715	603	579	231	185	47	36	0	0	0	0	0	0	9	20
Hull IV, 2000	94	501	1000	363	712	81	80	11	6	na	na	na	na	na	na	22	76
Leclerc, 1996	95	334	336	211	206	109	76	22	24	3	1	0	0	3	1	6	7
Francis, 1997	96	292	288	190	192	49	28	16	10	na	na	na	na	na	na	4	6
Fitzgerald, 2001	89	176	173	176	173	80	44	20	23	0	0	0	0	0	0	4	9

A, active treatment; C, control.

TABLE 7 *Trial events – dextran*

Author, year	Ref. No.	Numbers randomised		DVT assessed		DVT		PVT		Non-fatal PE		Fatal PE		All PE		Major bleeds	
		A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C
Dextran vs control																	
Bergqvist I, 1979	100	80 total/3 arms		27	22	13	20	nr	nr	na	na	0	0	na	na	0	0
Bergqvist II, 1980	101	57	58	52	51	15	14	10	8	na	na	0	0	na	na	0	0
Carter, 1973	102	106	101	106	101	1	10	nr	nr	na	na	na	na	na	na	nr	nr
Evarts, 1971	103	18	21	18	21	4	10	nr	nr	na	na	na	na	na	na	nr	nr
Gruber, 1977	104	113	113	92	100	20	36	0	4	na	na	1	4	na	na	nr	nr
Hefley, 1990	105	45	42	45	42	15	14	nr	nr	na	na	na	na	na	na	nr	nr
Hubens, 1976	106	39	41	39	41	5	9	1	2	na	na	na	na	na	na	0	0
Hurson, 1979	107	55	51	55	51	15	9	5	7	8	8	0	1	8	9	nr	nr
Huttunen, 1977	108	150	75	150	75	52	25	nr	nr	na	na	1	0	na	na	nr	nr
Johnsson, 1968	109	27	25	27	25	1	13	nr	nr	na	na	na	na	na	na	0	0
MacIntyre, 1974	110	130	128	128	128	32	47	nr	nr	na	na	0	2	na	na	nr	nr
van Hospenthal, 1977	111	40	49	39	47	3	2	nr	nr	na	na	na	na	na	na	0	0
Welin-Berger, 1982	112	20	20	16	18	4	5	3	2	0	1	0	0	0	1	nr	nr
Dextran combination																	
Andersen, 1986	115	29	31	29	31	5	14	nr	nr	na	na	na	na	na	na	nr	nr
Schondorf, 1980	113	54	55	54	55	9	8	nr	nr	0	1	1	1	1	2	0	0
Smith, 1978	61	12 excl/3 arms		97	95	18	36	nr	nr	3	5	0	0	3	5	14	2
Swierstra, 1984	114	71	81	71	81	21	34	14	23	na	na	na	na	na	na	17	8
van Geloven, 1977	85	331 total 18 exc/4 arms		79	80	9	20	nr	nr	4	9	0	0	4	9	2	1
Dextran vs heparin																	
Bergqvist I, 1979	100	80 total/3 arms		27	28	13	18	nr	nr	na	na	0	1	na	na	0	0
Bergqvist II, 1980	101	57	53	52	46	15	6	10	3	na	na	0	0	na	na	0	2
Gruber, 1977	104	113	119	92	94	20	12	0	1	na	na	1	6	na	na	1	8
Hohl, 1980	116	237 total		117	115	17	2	3	1	na	na	na	na	na	na	nr	nr
Hubens, 1976	106	39	39	39	39	5	4	1	0	na	na	na	na	na	na	0	0
MacIntyre, 1974	110	130	128	128	125	32	15	nr	nr	na	na	0	0	na	na	0	1
Urbanyi, 1982	117	46	43	46	43	2	1	nr	nr	0	0	0	0	0	0	0	0
Van Geloven, 1977	85	331 total, 18 exc/4 arm		79	74	9	13	nr	nr	4	2	0	0	4	2	2	1
Welin-Berger, 1982	112	20	20	16	17	4	8	3	3	0	0	0	0	0	0	nr	nr
Wille-Jorgensen II, 1991	39	98	94	85	79	13	2	nr	nr	1	0	0	1	1	1	1	0
Dan Enox, 1991	99	126	120	111	108	24	7	6	2	na	na	0	0	na	na	nr	nr
Eriksson, 1988	118	51	50	49	49	22	10	3	0	2	2	0	0	2	2	0	0
Matzsch, 1991	119	123	120	108	111	36	22	2	2	4	2	0	0	4	2	0	0
Oertli, 1992	120	103	113	95	103	31	16	1	2	0	1	1	1	1	2	0	0
Wiig, 1995	121	164	165	134	128	38	35	0	3	0	0	0	0	0	0	0	0

A, active treatment; C, control.

TABLE 8 *Trial events – regional and general anaesthesia*

Author, year	Ref. No.	Numbers randomised		DVT assessed		DVT		PVT		Non-fatal PE		Fatal PE		All PE		Major bleeds	
		A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C
Regional vs general anaesthesia trials																	
Brichant, 1995	122	54	52	46	42	14	13	nr	nr	na	na	na	na	na	na	0	0
Davis I, 1981	123	64	68	37	39	17	28	nr	nr	na	na	0	3	na	na	0	5
Davis II, 1989	124	69	68	69	68	9	19	3	8	0	3	0	0	0	3	nr	nr
Fredin, 1986	125	30	30	26	25	11	12	1	2	6	7	0	0	6	7	0	0
Hendolin I, 1981	126	17	21	17	20	2	11	nr	nr	na	na	na	na	na	na	nr	nr
Hendolin II, 1982	127	28	40	28	40	1	2	nr	nr	na	na	na	na	na	na	0	0
Jorgensen, 1991	128	24	24	17	22	3	13	1	3	0	1	0	0	0	1	0	0
McKenzie, 1985	129	20	20	20	20	8	16	nr	nr	na	na	na	na	na	na	0	0
Modig, 1986	17	50	50	48	46	21	38	8	30	5	15	0	0	5	15	nr	nr
Rodrigo, 1994	130	11	11	11	11	5	7	1	4	0	0	0	0	0	0	nr	nr
Williams-Russo, 1996	131	188 total		97	81	39	39	0	0	10	6	0	0	10	6	0	0

A, active treatment; C, control.

Chapter 3
Results

Mechanical compression methods of thromboprophylaxis

Effect of mechanical compression methods on DVT

Information on DVT detected by systematic venography or another systematic method (with or without confirmatory venography) was available for 42 trials[23–64] of compression methods among 5367 patients. A total of 17 trials (2412 patients) assessed graduated compression stockings (GCSs), 22 trials (2779 patients) assessed IPC devices and three trials (176 patients) assessed footpumps (see *Figure 1*).

Among all trials assessing a compression method, 265 patients (9.9%) suffered a DVT among 2685 patients allocated a compression method versus 588 (21.9%) among 2682 allocated control, corresponding to a reduction in the odds of DVT of about two-thirds (odds reduction 63%, 95% CI 57 to 69%, $2p < 0.00001$; *Figure 1c*). Each of the three main compression techniques produced a substantial and highly statistically significant reduction in DVT: GCS [63% (8) reduction; $2p < 0.00001$]; intermittent pneumatic compression [61% (7) reduction; $2p < 0.00001$]; and footpumps [79% (17) reduction; $2p < 0.00001$; *Figure 1c*).

Trials comparing a compression method versus control were subdivided (*Figure 1*) into those that had assessed the effects of compression as the sole method of thromboprophylaxis (monotherapy; *Figure 1a*) and, on the other hand, those that had assessed the separate question of whether adding compression to a 'background' pharmacological method would provide additional protection (adjunctive therapy; *Figure 1b*). Compression methods as monotherapy reduced the risk of DVT by about two-thirds [odds reduction 67% (6), $2p < 0.00001$; *Figure 1a*], whilst there was marginally significant evidence that adding a compression method to a pharmacological agent was slightly less effective than this, producing a reduction of about half in DVT [odds reduction 53% (10), $2p < 0.00001$; heterogeneity χ^2 on 1 degree of freedom (df) = 3.9; $p = 0.05$; *Figure 1b*].

The majority of trials assessing compression methods were conducted in a surgical setting: 14 were orthopaedic,[24,33,34,36,40,48,49,51–53,59,60,63,64] 16 general,[23,25,26,28,29,32,37–39,41,42,44,50,54,61,62] six neurosurgical or after spinal surgery,[31,43,55–58] three gynaecological[30,45,46] and one mixed surgical,[47] with only two trials[27,35] conducted among 257 medical patients at high risk of venous thromboembolism. After subdividing these trials into those assessing monotherapy and those assessing adjunctive therapy, the specific type of surgical or medical setting did not appear to influence the effectiveness of mechanical compression [heterogeneity χ^2 for monotherapy (on 5 df) = 4.6; $p > 0.1$, and heterogeneity χ^2 for adjunctive therapy (on 2 df) = 3.7; $p > 0.1$, not significant (NS); *Figure 2*].

Effects of mechanical compression as monotherapy

Among 30 trials of monotherapy, the effects of each compression method on DVT appeared similar (heterogeneity χ^2 on 2 df = 1.1, NS; *Figure 1a*). *Figures 3a*, *5a*, and *7a* show the results of trials of each mechanical compression method as monotherapy in more detail.

Graduated compression stockings

In nine trials[23–31] among 1292 patients assessing GCS as monotherapy, GCS produced a highly significant 66% (10) reduction in DVT [57/665 (8.6%) GCS vs 133/627 (21.2%) control, $2p < 0.00001$; *Figure 3a*], with no evidence of heterogeneity of effect among the trials (χ^2 on 8 df = 6.6; p = ns). Among these trials of GCS monotherapy, whilst six had assessed above-knee stockings[24–27,29,31] [odds reduction 68% (12)], only one had assessed below-knee stockings[28] [odds reduction 0% (60)], and in two trials the position of the stocking was unspecified[23,30] [odds reduction 69% (18); *Figure 4*]. It was not possible, therefore, given this limited evidence, to assess whether above-knee methods were more effective. Two trials had compared above-knee versus below-knee stockings directly (randomised 'by leg'); the results of these two trials [9/104 (8.7%) above-knee versus 9/108 (8.3%) below-knee; NS] were inconclusive owing to the limited number of recorded events.[65,66]

Intermittent pneumatic compression

In 19 trials[40–58] among 2255 patients assessing IPC as monotherapy, IPC produced a highly significant 66% (7) reduction in DVT [112/1108 (10.1%) IPC vs 268/1147 (23.4%) control, $2p < 0.00001$; *Figure 5a*]. There was marginal evidence of heterogeneity of effect among these trials (χ^2 on 16 df = 28.4; $p = 0.03$), but this was generated chiefly by one trial.[46] Among trials of IPC monotherapy, there was no evidence that sequential compression machines were more protective than single compression machines [sequential compression 65% (12) reduction; single compression 66% (9) reduction; unknown type 100% (91) reduction; χ^2 on 2 df = 0.2; NS; *Figure 6*].

Footpumps

Only two trials[62,63] among a total of 126 patients had assessed footpumps as monotherapy. Nevertheless, footpumps appeared to produce a highly significant 77% (19) reduction in DVT in these trials [11/61 (18.0%) footpumps vs 34/65 (52.3%) control, $2p = 0.00007$; *Figure 7a*].

Effects of combining mechanical compression methods

Eight trials had addressed the question of whether, in the absence of a pharmacological agent, a combination of mechanical methods might be more effective than a single mechanical method.[31,67–73]

All but one trial had compared the combination of GCS and IPC with either method alone. For each of these comparisons, however, only a limited number of patients had been studied [8/132 (6.1%) GCS + IPC versus 13/132 (9.8%) IPC alone and 16/291 (5.5%) GCS + IPC versus 20/286 (7.0%) GCS alone, both comparisons $2p$ = NS]. Given that any additional benefit that might exist would be expected to be small, there was negligible statistical power to address whether a combination of GCS and IPC might be preferable to either one of these methods alone.

Effects of mechanical compression as adjunctive therapy to a pharmacological agent

Twelve trials[32–39,59–61,64] among 1694 patients had assessed the addition of a mechanical compression method to a pharmacological agent (heparin, dextran or aspirin). Mechanical compression as adjunctive therapy produced a highly significant reduction in DVT [53% (10) reduction; $2p < 0.00001$; *Figure 1*]. Although a formal test for heterogeneity suggested that different mechanical compression methods might differ in their effectiveness when used in this way (heterogeneity χ^2 on 2 df = 6.3; $p = 0.04$; *Figure 1b*), this test was only marginally significant, so the existence of such differences remains uncertain. *Figures 3(b)*, *5(b)* and *7(b)* show the results of these trials in more detail.

Graduated compression stockings

Eight trials[32–39] among 1120 patients had assessed adding GCS as adjunctive therapy (with the background agent dextran in three trials, standard heparin in three trials, LMWH in one trial and aspirin in one trial) and among these GCS produced a highly significant 60% (12) reduction in DVT [54/564 (9.6%) GCS + agent versus 108/556 (19.4%) agent alone, $2p < 0.00001$; *Figure 3b*], with no clear evidence of heterogeneity of effect among these trials (χ^2 on 7 df = 13.3; $p = 0.07$).

Intermittent pneumatic compression

Only three trials[59–61] among 524 patients had assessed IPC as adjunctive therapy (where heparin, dextran or aspirin had each been used as background therapy in one trial), with the overall results reflecting the limited amount of data available [31/262 (11.8%) IPC + agent versus 40/262 (15.3%) agent alone, 26% odds reduction, 95% CI 55% reduction to 23% increase, $2p$ = NS; *Figure 5b*].

Footpumps

Only one trial[64] among 50 patients assessed the effectiveness of a footpump as an adjunct to heparin and aspirin, and so there was negligible power to address this question (*Figure 7b*).

Effect of mechanical compression on proximal venous thrombosis

The effect of compression methods on PVT was reported in only 21[24,25,27,28,31,32,34,35,45,46,48,49,51–53,56,57,59,60,63,64] of the 42 trials assessing a compression method (*Figure 8*). The estimates of effect on PVT are susceptible to bias because a decision to report this outcome in trial publications could have been influenced by the direction or the size of the findings. Notwithstanding this potential for bias, however, among 2811 patients in 21 trials, compression methods appeared to reduce PVT by about half [proportional odds reduction 56% (11), $2p < 0.00001$; *Figure 8*], and the benefit appeared similar irrespective of whether compression was used as monotherapy or adjunctive therapy.

Effect of mechanical compression on pulmonary embolism

Information on PE was available from only

18[24,25,27,33,34,38–40,45–48,52,53,55,60,61,63] of the 42 trials which sought DVT systematically. PE data were included only from those trials that confirmed clinical suspicion with ventilation/perfusion scans or pulmonary angiography. Since the diagnosis of PE was not generally performed blind to treatment allocation, the reporting of PE may be subject to bias. This, together with the large number of trials without data on PE, suggests that the marginally statistically significant 40% (21) overall reduction ($2p = 0.05$) in PE observed overall (*Figure 9*) may be inflated by the effects of selection bias, in addition to being statistically uncertain. There were too few patients reporting PE to assess any possible differences between the effects of mechanical compression methods when used alone or as adjunctive therapy. Likewise, there were too few fatal PEs (three compression versus five control) to conduct reliable analyses of this secondary outcome.

Assessment of variation in treatment by trial quality indicators

The effects of compression methods on DVT did not appear to be dependent on any of the four markers of trial quality which were identified (*Figure 10*). Specifically, the odds of DVT were similar irrespective of (i) whether or not the trialist provided confirmation of published trial results (*Figure 10a*); (ii) whether or not we were able to confirm that the randomisation method was robust (*Figure 10b*); (iii) whether or not assessment of DVT had been conducted blind to treatment allocation (*Figure 10c*); and (iv) whether or not a diagnosis was confirmed by a venogram (*Figure 10d*).

Oral anticoagulants

Effect of oral anticoagulants on DVT

Information on DVT detected by systematic venography or another systematic method (with or without confirmatory venography) was available for 15 trials[71,74–87] of oral anticoagulants among 1624 patients. The oral anticoagulant studied was warfarin in 11 trials,[71,75,77–81,83,84,86,87] and phenindione,[76] dicoumarol,[74] nicoumalone[82] and acenocoumarin[85] in one trial each. Nine trials[74–82] (1014 patients) assessed an oral anticoagulant as monotherapy, three trials[83–85] (352 patients) assessed an oral anticoagulant as adjunctive therapy (with heparin or dextran as background therapy) and three trials[71,86,87] (258 patients) assessed adding an oral anticoagulant to a mechanical compression method of thromboprophylaxis (see *Figure 11b*).

Overall 116 patients (14.3%) suffered a DVT among 810 patients allocated an oral anticoagulant versus a total of 206 (25.3%) among 814 allocated control, corresponding to a reduction in DVT of about half [odds reduction 55% (9), 95% CI 42 to 66%, $2p < 0.00001$; *Figure 11*].

Trials comparing an oral anticoagulant versus control were subdivided (*Figure 11*) into those that assessed the effects of an oral anticoagulant as monotherapy (*Figure 11a*) and those that assessed oral anticoagulation as an adjunct to another antithrombotic agent (*Figure 11bi*) or to a mechanical compression method (*Figure 11bii*). The effects of oral anticoagulant regimens in these different circumstances appeared similar (χ^2 on 2 df = 2.0; NS; *Figure 11*), but the numbers included in trials of oral anticoagulation as adjunctive therapy were small, so possible differences could not be excluded.

Effects of different intensities of oral anticoagulation

Although strict division of regimens on the basis of intensity was not possible, a review by a haematologist (O'Shaughnessy D, Consultant Haematologist, Southampton University Hospitals NHS Trust: personal communication, 2003) suggested that three broad categories of oral anticoagulant regimen could be distinguished among the trials under review: **very low-intensity** anticoagulation, with a regimen typically equivalent to an INR target range of <1.5 (e.g. as might be achieved by a fixed mini-dose regimen); **low-intensity** anticoagulation, where it seems likely (based on interpretation of ranges of thrombin times or prothrombin times) that most would be equivalent to an INR <2.5; and **moderate-intensity** anticoagulation where INR was generally allowed to range from 2 to 4, and hence the mean INR (~3) might be expected to exceed that achieved in very low and low intensity regimens. The effects of different oral anticoagulant regimens can be compared indirectly by comparing the size of the protective effect of an oral anticoagulant observed in the trials of a very low-intensity regimen versus control, trials of a low-intensity regimen versus control and trials of moderate-intensity oral anticoagulation versus control (*Figure 12*). Such comparisons need to be interpreted more cautiously than direct comparisons (*Figure 13*) because there is some potential for bias as patients in the trials had different reasons for being at risk of venous thrombosis. Fifteen trials[71,74–87] had compared an oral anticoagulant regimen versus control, with nine[74–82] assessing

oral anticoagulant as monotherapy and six[71,83–87] as adjunctive therapy. Overall, the reduction in DVT appeared similar for moderate and low-intensity regimens, but too few patients had been assessed in trials of very low-intensity regimens for conclusions to be drawn. Only two trials[80,88] involved direct comparisons of low- and moderate-intensity regimens (*Figure 13*), and although moderate-intensity regimens appeared to reduce DVT by 56% (22) compared with low intensity regimens, this comparison involved only 50 events in total, and so needs confirmation in larger studies.

Effects of oral anticoagulation in different types of surgery

There appeared to be substantial heterogeneity of effect on DVT among the different categories of surgery (χ^2 on 4 df = 21.4; $p = 0.0003$; *Figure 14*). This was attributable to an apparent absence of benefit in three trials of oral anticoagulation in elective hip surgery and one small trial of elective hip surgery (EH) or hip fracture surgery (HF) patients, but whether this reflected a real difference, confounding by differences in regimen intensity, or the play of chance, could not be established reliably with the limited number of trials available.

Effect of oral anticoagulants on proximal venous thrombosis

The effect of oral anticoagulants on PVT was reported in only seven[75,77,78,81,83,84,86] of the 15 trials assessing oral anticoagulants (*Figure 15*). Overall, PVT occurred in 19 of 477 (4.0%) patients allocated to oral anticoagulants versus 40 of 496 (81%) allocated control, corresponding to a reduction of 55% (19%) in the odds of PVT ($2p = 0.004$), which was similar to the effect observed in DVT at any site in the leg.

Effect of oral anticoagulants on pulmonary embolism

Information on PE was available from only four[78,81,85,86] of the 15 trials of oral anticoagulants that sought DVT systematically and confirmed clinical suspicion of PE with ventilation/perfusion scans or pulmonary angiography. Since the diagnosis of PE was not generally performed blind to treatment allocation, the reporting of PE may be subject to bias. This, together with the large number of trials without data on PE, suggests that the statistically significant 79% (25) overall reduction ($2p = 0.002$) in PE (*Figure 16*) may be inflated by the effects of selection bias. There were too few patients reporting PE to assess any possible differences between the effects of fixed and adjusted intensity oral anticoagulant regimens, or between trials testing an oral anticoagulant as monotherapy or as adjunctive therapy. Likewise, there were too few (just nine) fatal PEs to provide reliable estimates of any possible effect on such events.

Effect of oral anticoagulants on major bleeding

The effects on the risk of major bleeding of an oral anticoagulant were assessed in 12 trials[71,74,76–82,85–87] (1278 patients; *Figure 17*). Major bleeding occurred in 49/644 (7.6%) allocated to an oral anticoagulant and 24/634 (3.9%) in those allocated control. This corresponded to an odds ratio of 1.92 (95% CI 1.17 to 3.15). Most of the evidence on bleeding came from trials of oral anticoagulants as monotherapy and too few bleeds had occurred in trials of adjunctive therapy to estimate the effects on bleeding of oral anticoagulants when used in this way. Among trials assessing monotherapy, there were too few bleeds to assess whether there was a trend towards a higher risk of bleeding with more intense regimens.

Assessment of variation in treatment by trial quality indicators

The effects of compression methods on DVT did not appear to be dependent on any of the four markers of trial quality which were identified (*Figure 18*). Specifically, the odds of DVT were similar irrespective of (i) whether or not the trialist provided confirmation of published trial results (*Figure 18a*); (ii) whether or not we were able to confirm that the randomisation method was robust (*Figure 18b*); (iii) whether or not assessment of DVT had been conducted blind to treatment allocation (*Figure 18c*); and (iv) whether or not a diagnosis was confirmed by a venogram (*Figure 18d*).

Direct comparison of oral anticoagulants with a heparin regimen

Thirteen[82,85,87,89–98] trials had compared an oral anticoagulant with a heparin regimen. The majority of trials had compared oral anticoagulation with LMWH (nine trials,[89–96,99] 7260 patients), whereas the comparator was low-dose unfractionated heparin in four trials[82,85,87,97] among 382 patients (*Figure 19*). Overall, an oral anticoagulant regimen appeared less effective than either an unfractionated or LMWH regimen for the prevention of DVT. Oral anticoagulation was associated with a 64% (8) greater risk of DVT ($2p < 0.00001$) than the heparin regimens studied in these trials (*Figure 19*).

There were too few PEs to assess reliably possible differences between these two methods of anticoagulation in the prevention of PE (*Figure 20*).

Oral anticoagulant regimens, however, were associated with a lower risk of major bleeding than heparins [99/3389 (2.9%) oral anticoagulant versus 213/4253 (5.0%) heparin regimen; odds reduction 35% (10); $2p = 0.0003$] (*Figure 21*).

Dextran

Effect of dextran on DVT

Information on DVT detected by systematic venography or another systematic method (with or without confirmatory venography) was available for 18 trials[61,85,100–115] of dextran among 2245 patients (*Figure 22*). Thirteen trials[100–112] (1573 patients) assessed dextran as monotherapy, three trials[85,113,114] (420 patients) assessed dextran as adjunctive therapy (with heparin or an oral anticoagulant as background therapy) and two trials[61,115] (252 patients) assessed adding dextran to a mechanical compression method (*Figure 22*).

Overall, 242 patients (20.9%) suffered a DVT among 1157 patients allocated dextran versus a total of 326 (30.0%) among 1088 allocated control, corresponding to a reduction in the odds of DVT of about half [odds reduction 43% (8), 95% CI 30 to 53%, $2p < 0.00001$; *Figure 22*].

Trials comparing dextran versus control were subdivided into those that had assessed the effects of dextran as monotherapy (*Figure 22a*) or as adjunctive therapy to a pharmacological agent (*Figure 22bi*) or to a mechanical method (*Figure 22bii*). There was no clear evidence that the effects of dextran differed when given as monotherapy or as adjunctive therapy (χ^2 on 2 df = 3.4; NS), but the numbers included in trials of adjunctive therapy were small, so such a difference could not be excluded.

Effects of different intensities of dextran

Two types of dextran (dextran 40 and dextran 70) had been assessed among the trials under review. Among 13 trials comparing dextran as monotherapy versus control, four had tested dextran 40 and nine had tested dextran 70 (or a dextran of unspecified molecular weight). The proportional reduction in risk of DVT produced by different dextran regimens appeared similar (χ^2 heterogeneity on 2 df = 2.6; NS; *Figure 23*).

Effects of dextran in different types of surgery

There appeared to be moderate heterogeneity of effect on DVT among the different categories of surgery (χ^2 on 2 df = 7.4; $p = 0.02$; *Figure 24*), but the reasons for this apparent heterogeneity could not be established reliably owing to the small number of trials available.

Effect of dextran on proximal venous thrombosis

The effect of dextran on PVT was reported in only six[101,104,106,107,112,114] of the 18 trials assessing dextran (*Figure 25*). Overall, PVT occurred in 33 of 355 (9.3%) patients allocated to dextran versus 46 of 364 (12.6%) allocated control, corresponding to a reduction of 28% (21) in the odds of PVT ($2p$ = NS).

Effect of dextran on pulmonary embolism

Information on PE was available from only five[61,85,107,112,113] of the 18 trials of dextran that sought DVT systematically and confirmed clinical suspicion of PE with ventilation/perfusion scans or pulmonary angiography. Overall, there was a 43% (25) reduction ($2p = 0.09$) in PE (*Figure 26*), which, although being statistically uncertain, was compatible with a moderate protective effect. There were too few patients reporting PE to assess any possible differences between the effects of different dextran regimens (e.g. dextran 40 versus dextran 70), or between trials testing dextran as monotherapy or as adjunctive therapy. Likewise, there were too few (just 11) fatal PEs to provide reliable estimates of any possible effect on such events.

Effect of dextran on major bleeding

Overall, dextran was associated with an approximately 3-fold increased risk of major bleeding {33/491 (6.7%) dextran versus 11/506 (2.2%) control; odds ratio 3.37 [standard error (SE) 0.63]; *Figure 27*}, with all of this evidence coming from trials of dextran as adjunctive therapy.

Assessment of variation in treatment by trial quality indicators

The effects of dextran on DVT did not appear to be dependent on any of the four markers of trial quality which were identified (*Figure 28*). Specifically, the odds of DVT were similar irrespective of (i) whether or not the trialist provided confirmation of published trial results (*Figure 28a*); (ii) whether or not we were able to confirm that the randomisation method was robust

(*Figure 28b*); (iii) whether or not assessment of DVT had been conducted blind to treatment allocation (*Figure 28c*); and (iv) whether or not a diagnosis was confirmed by a venogram (*Figure 28d*).

Direct comparison of dextran with a heparin regimen

Fifteen trials had compared dextran with a heparin regimen[39,85,99–101,104,106,110,112,116–121] (*Figure 29*). Of these, 10 trials[39,85,100,101,104,106,110,112,116,117] (1439 patients) had compared dextran with low-dose heparin and five trials[99,118–121] (1135 patients) had compared dextran with LMWH (*Figure 29*). Overall, dextran was less effective than either an unfractionated or an LMWH regimen for the prevention of DVT. Dextran was associated with an 86% (15) greater risk of DVT ($2p < 0.00001$) than the heparin regimens studied in these trials (*Figure 29*). Dextran, however, was associated with a lower risk of major bleeding than heparins [4/1030 (0.4%) dextran versus 12/1206 (1.2%) heparin regimen; risk reduction 64% (32); $2p = 0.04$ (*Figure 30*)]. Only eight[39,85,112,117–121] of the 15 trials reported data on PE, and owing to the small numbers of patients included in such trials and the low event rate there was limited power to assess the relative effectiveness of the regimens for preventing PE [12/684 (1.8%) dextran versus 9/679 (1.3%) heparin; odds increase 31% (51), NS (*Figure 31*)].

Regional anaesthesia compared with standard general anaesthesia

Effect of RA on DVT

Information on DVT detected by systematic venography or another systematic method (with or without confirmatory venography) was available for 11 trials[18,122–131] comparing RA versus GA among 929 patients (*Figure 32*). Overall 130 patients (28.0%) suffered a DVT among 464 patients allocated RA versus a total of 198 (42.6%) among 465 allocated GA, corresponding to a reduction in the odds of DVT of about half [odds reduction 53% (10), 95% CI 37 to 64%, $2p < 0.00001$; *Figure 32*). RA is particularly suitable for elective orthopaedic surgery, so most trials had been conducted during such operations. The protective effects appeared similar irrespective of the particular surgical procedure (*Figure 33*), however, suggesting that any benefits might well be present in other surgical situations where regional anaesthesia is feasible.

Effect of RA on proximal venous thrombosis

The effect of RA as compared to GA on PVT was reported in only six[18,124,125,128,130,131] of the 11 trials assessing this comparison (*Figure 34*). Overall, PVT occurred in 14 of 281 (5.0%) patients allocated to RA versus 47 of 264 (17.8%) allocated GA, corresponding to a reduction of 77% (16) ($2p < 0.00001$) in the odds of PVT. This result was determined chiefly by the results in one trial,[18] however, so it remains unclear whether RA is particularly effective for the prevention of PVT (as opposed to more distal thrombosis).

Effect of RA on pulmonary embolism

Information on PE was available from only six[18,124,125,128,130,131] of the 11 trials of RA vs GA that sought DVT systematically. Overall, there was a 43% (23) reduction ($2p = 0.06$) in PE (*Figure 35*), which, although being statistically uncertain, was compatible with a moderate protective effect. There were too few fatal PEs to assess any possible effects on such events [0/345 (0%) RA versus 3/332 (1.0%) GA; odds reduction 86% (51), NS].

Effect of RA on major bleeding

Major bleeding was not reported in any of 317 patients randomised to RA compared with 5/315 (1.6%) in those having GA (odds ratio 0.14; 95% CI 0.02 to 0.80; $2p = 0.03$; *Figure 36*), suggesting that RA may reduce the risk of bleeding in association with surgical procedures. However, it should be noted that only one trial recorded any such bleeds, and data were not available from four trials. This result must therefore be regarded as potentially unreliable, and in need of confirmation by larger studies.

Assessment of variation in treatment by trial quality indicators

The effects of RA on DVT did not appear to be dependent on any of the four markers of trial quality which were identified (*Figure 37*). Specifically, the odds of DVT were similar irrespective of (i) whether or not the trialist provided confirmation of published trial results (*Figure 37a*); (ii) whether or not we were able to confirm that the randomisation method was robust (*Figure 37b*); (iii) whether or not assessment of DVT had been conducted blind to treatment allocation (*Figure 37c*); and (iv) whether or not a diagnosis was confirmed by a venogram (*Figure 37d*).

Figures showing the main results for each comparison

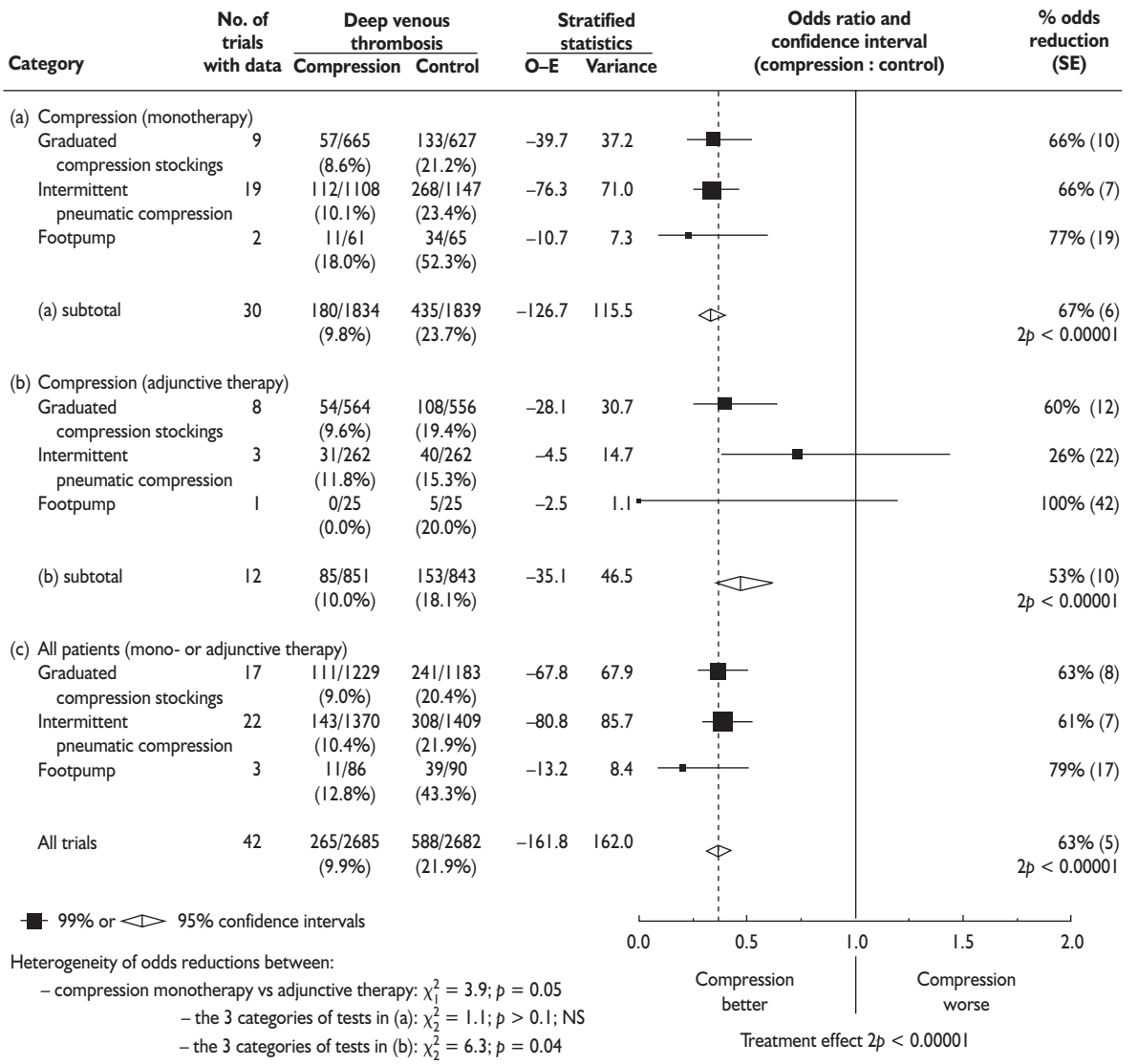

FIGURE 1 *Effects of compression methods of thromboprophylaxis on deep venous thrombosis*

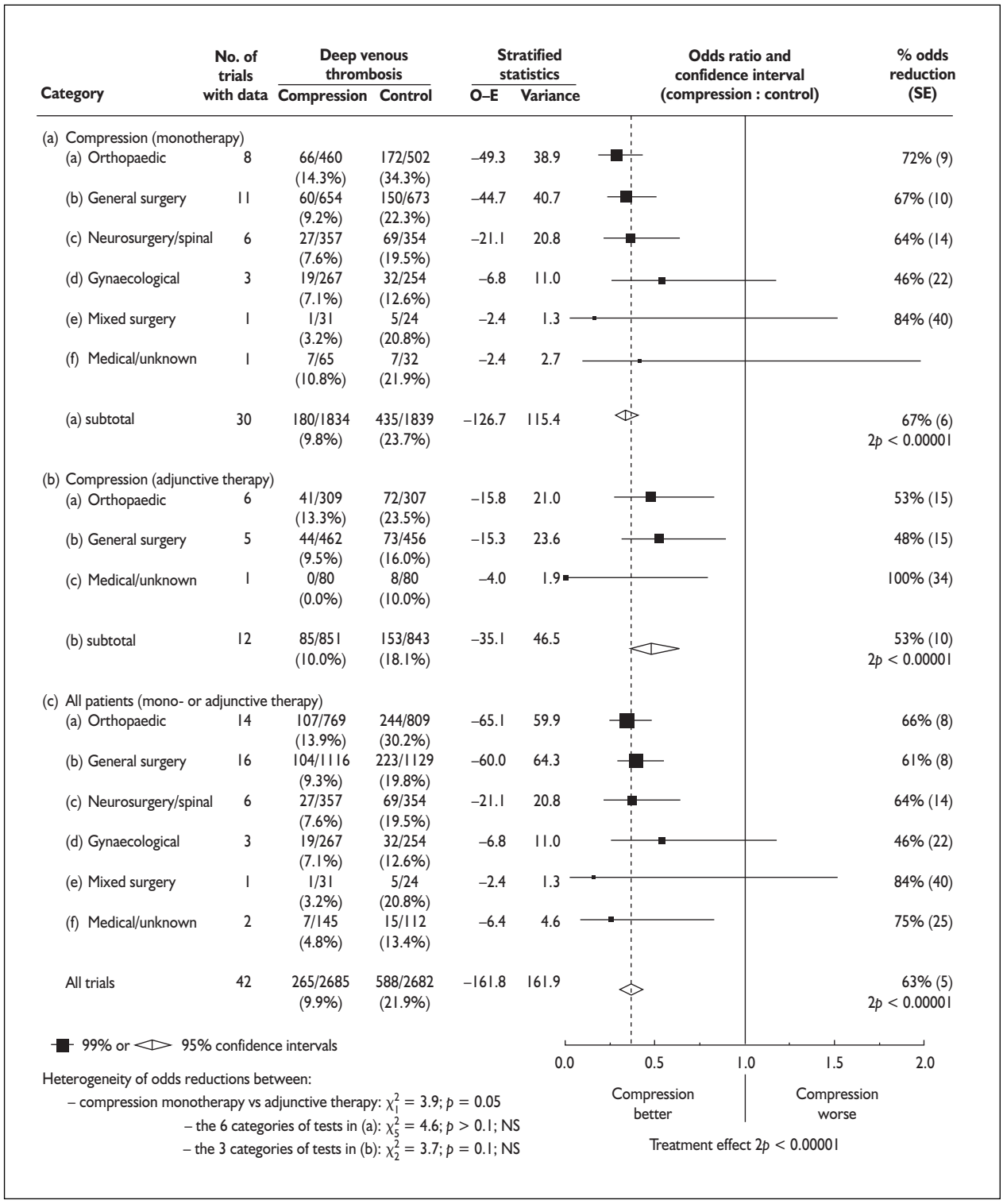

FIGURE 2 *Effects of compression methods on deep venous thrombosis among different types of patients*

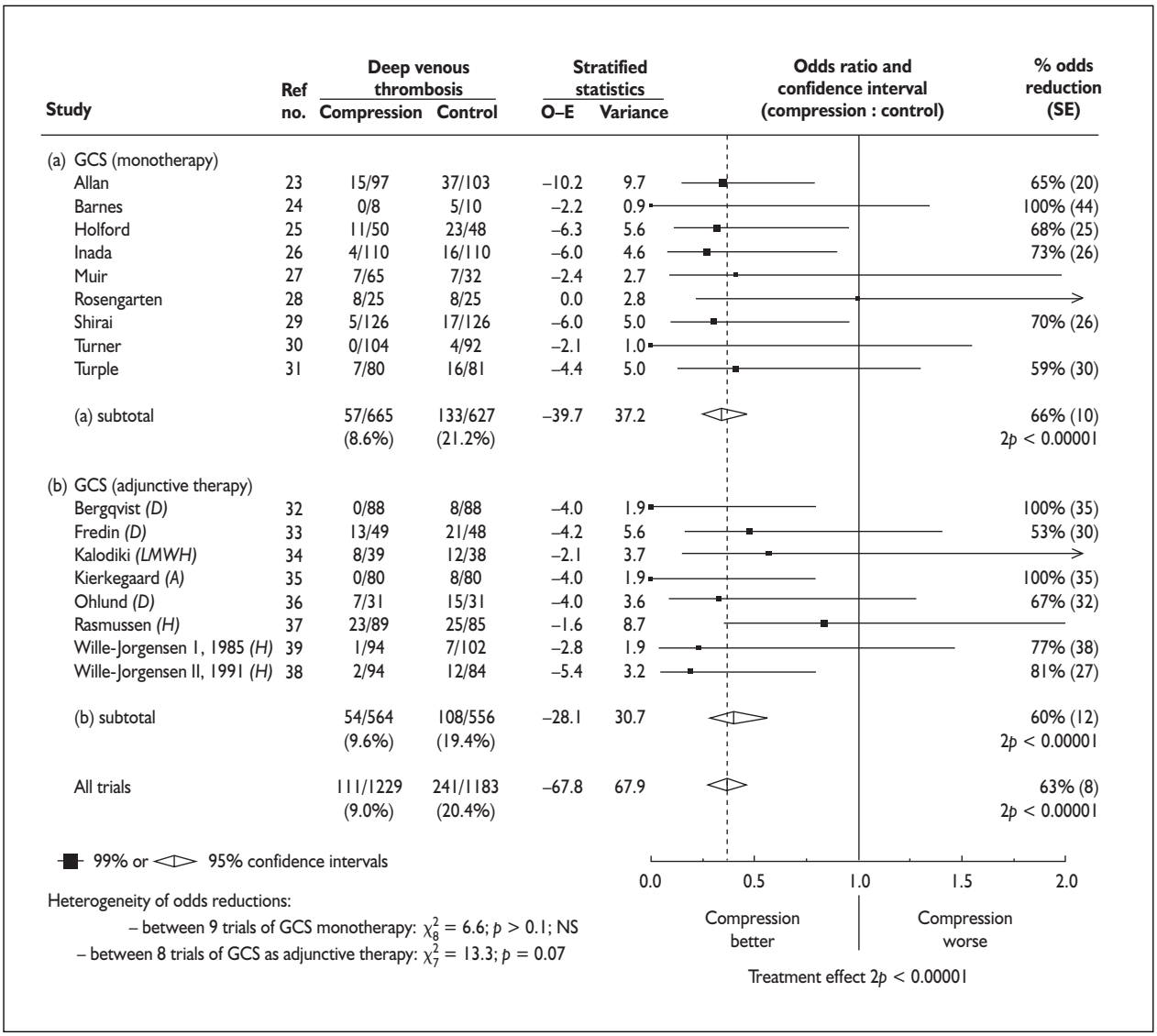

FIGURE 3 *Effects of graduated compression stockings (GCS) on deep venous thrombosis. Abbreviations: A, aspirin; D, dextran; GCS, graduated compression stockings; H, unfractionated heparin; LMWH, low molecular weight heparin.*

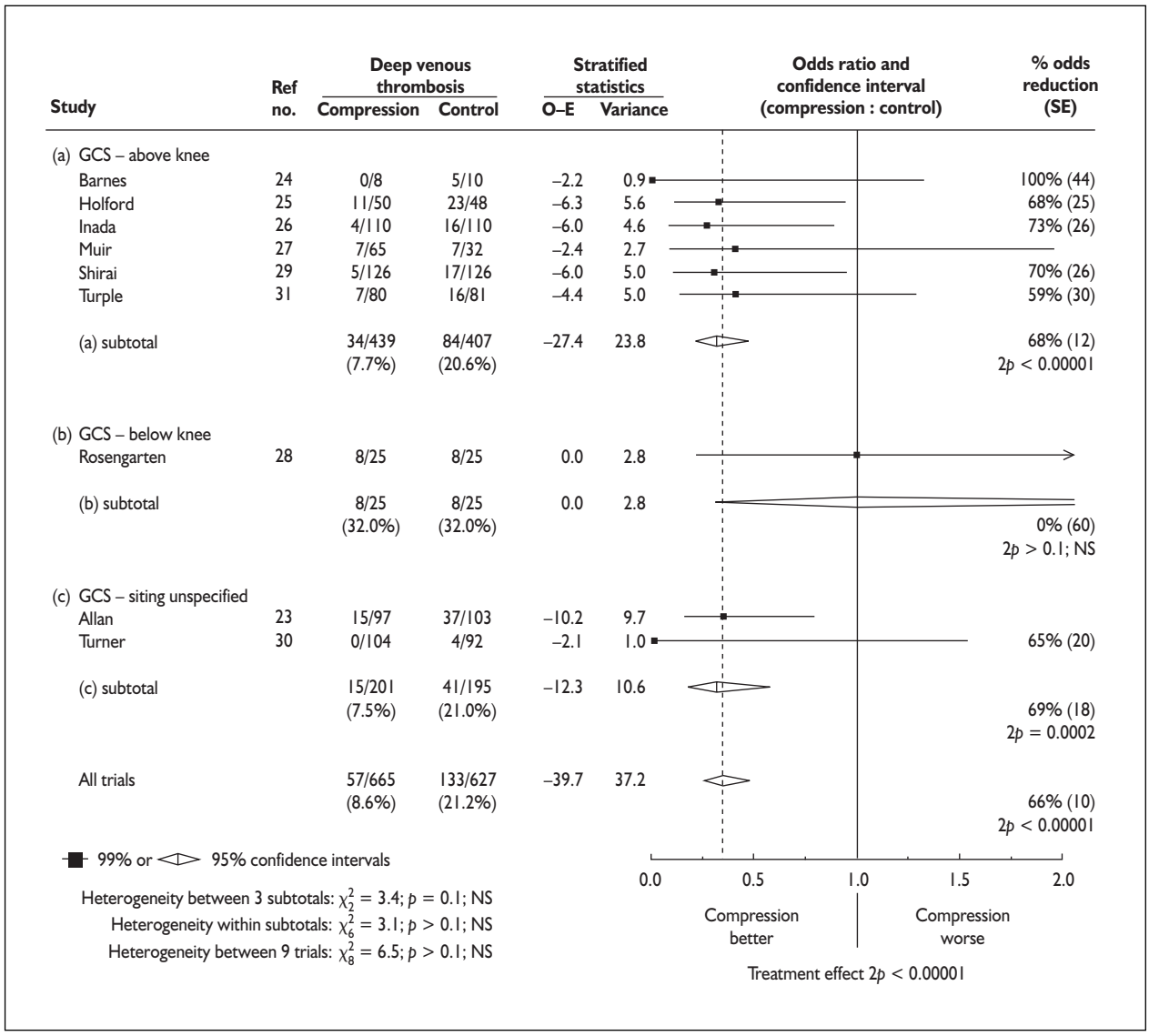

FIGURE 4 *Effects of type of graduated compression stocking (GCS) on deep venous thrombosis when used as monotherapy*

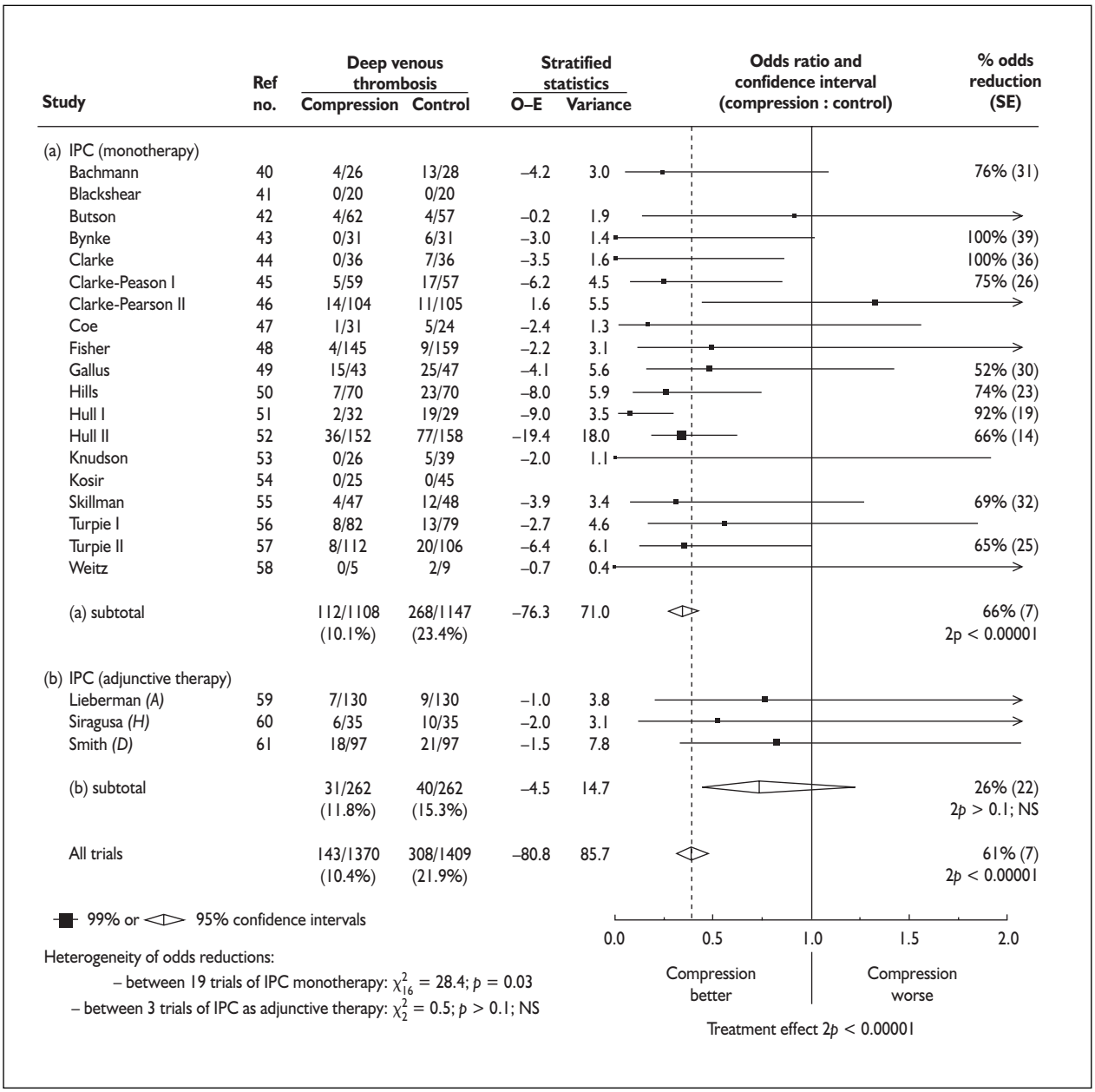

FIGURE 5 *Effects of intermittent pneumatic compression (IPC) on deep venous thrombosis. Abbreviations: A, aspirin; D, dextran; H, unfractionated heparin; IPC, intermittent pneumatic compression.*

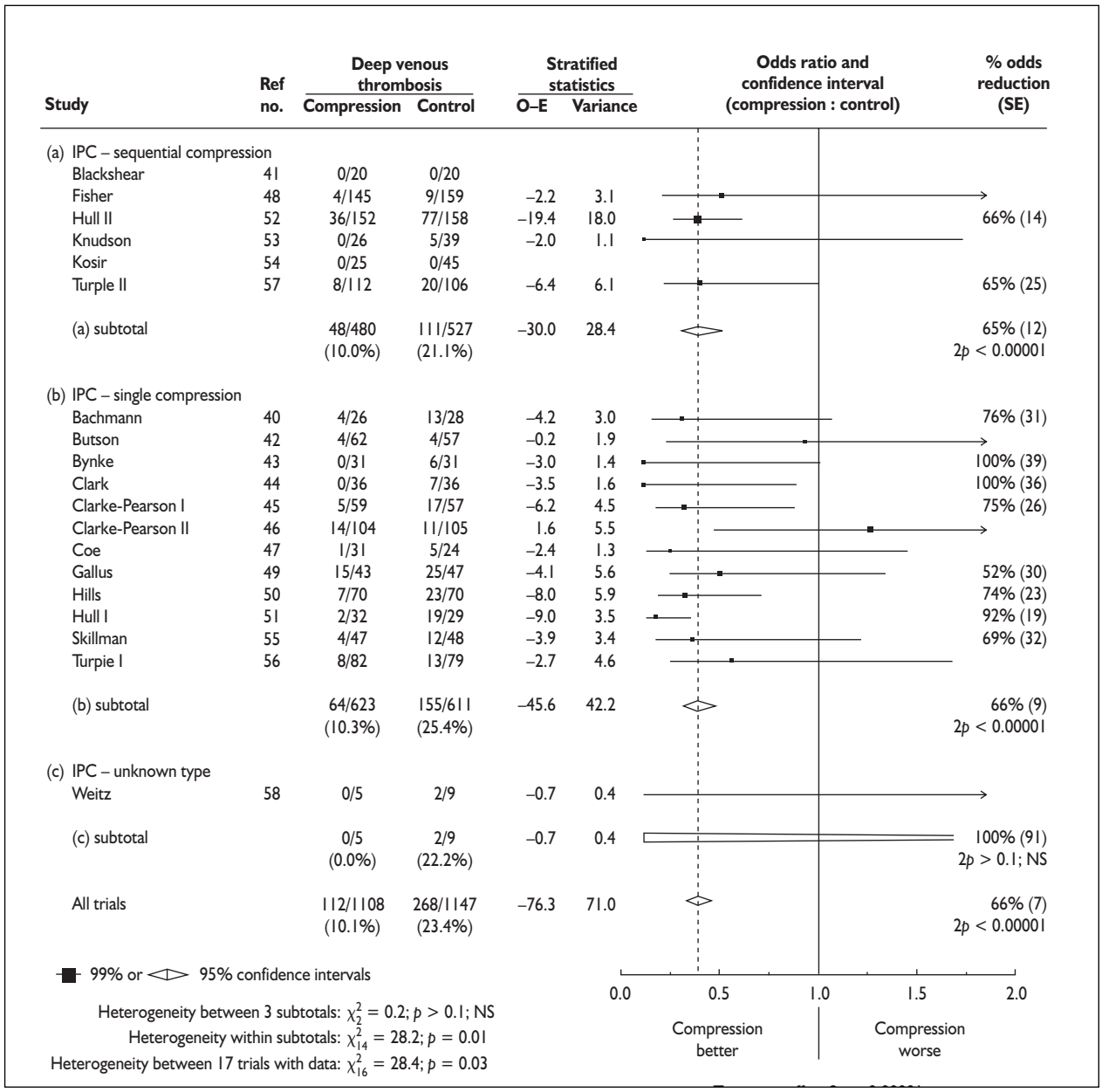

FIGURE 6 *Effects of type of intermittent pneumatic compression (IPC) on deep venous thrombosis*

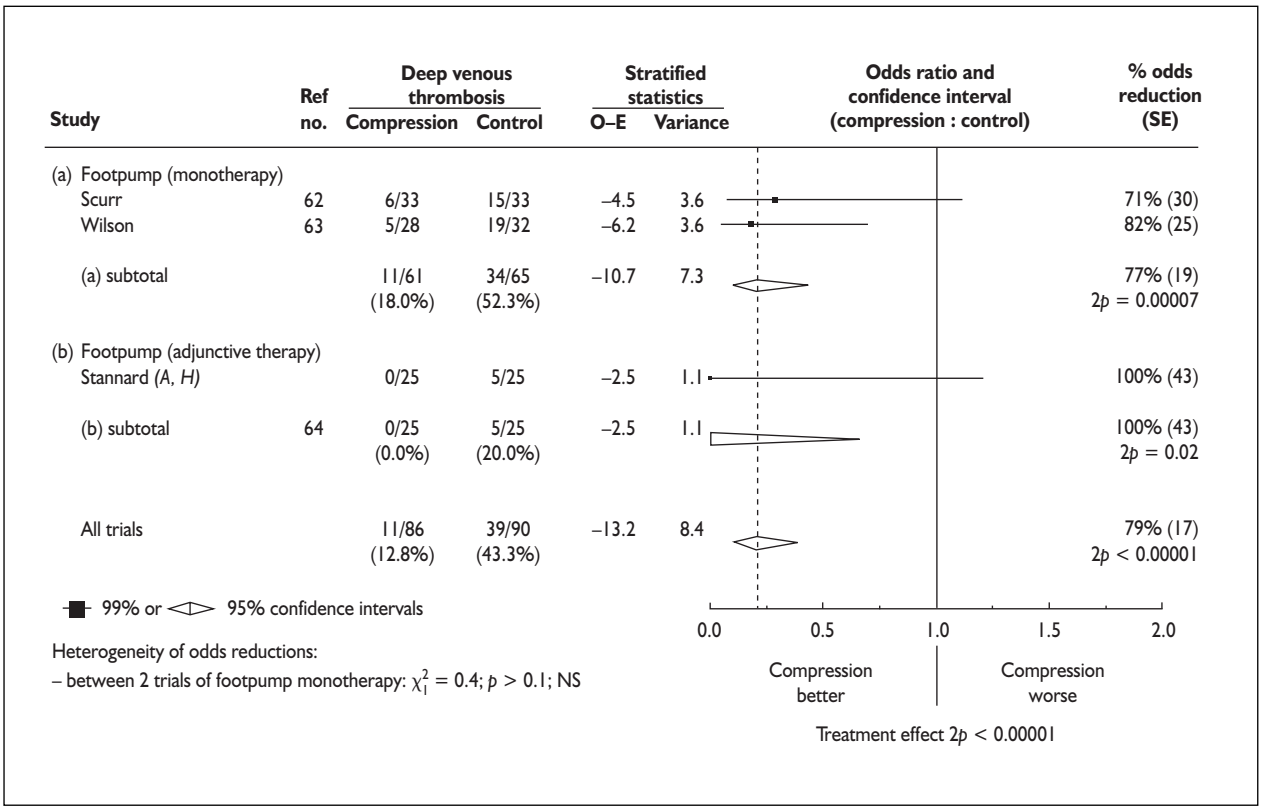

FIGURE 7 *Effects of footpumps on deep venous thrombosis. Abbreviations: A, aspirin; H, unfractionated heparin.*

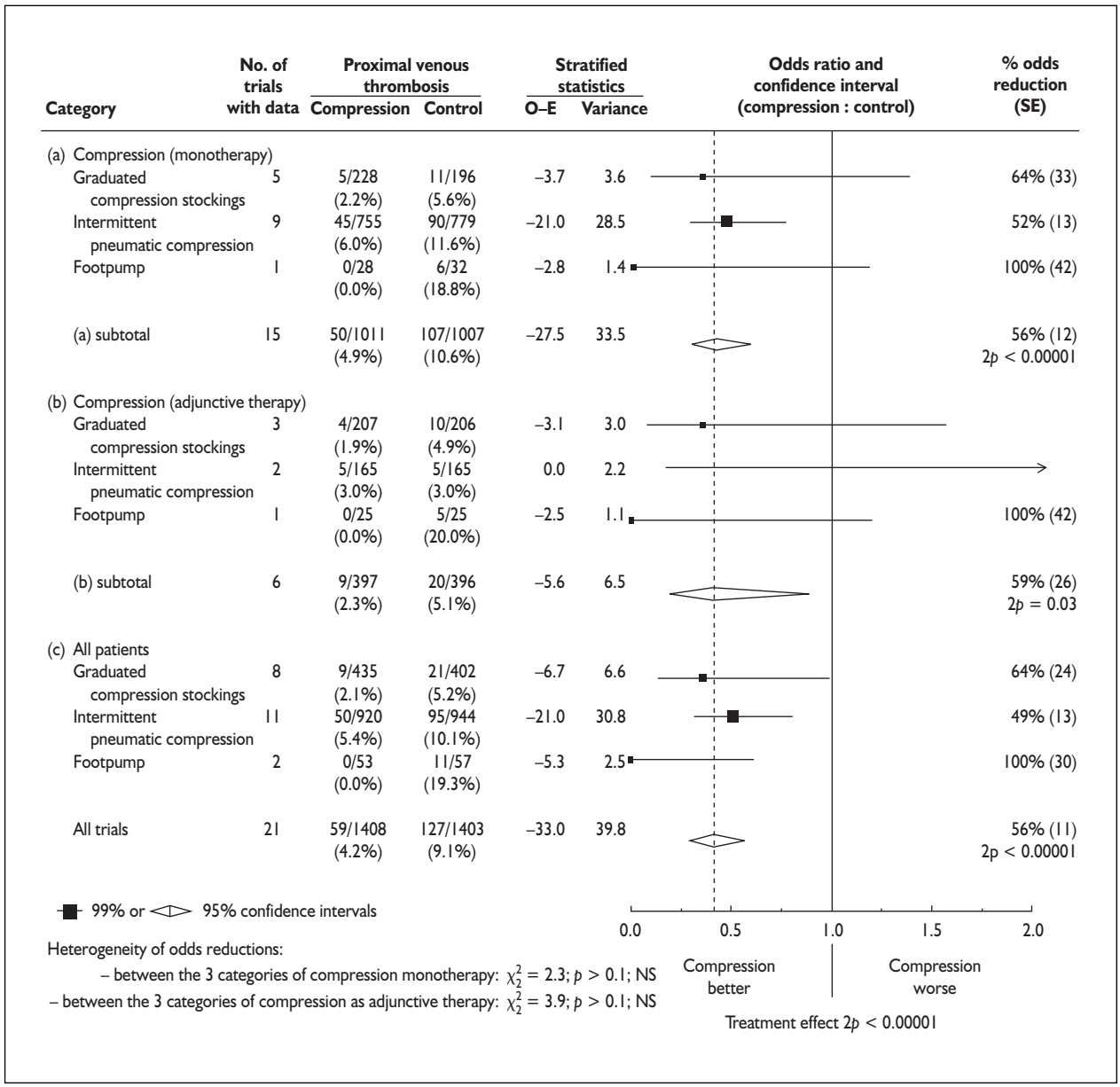

FIGURE 8 *Effects of compression methods of thromboprophylaxis on proximal venous thrombosis*

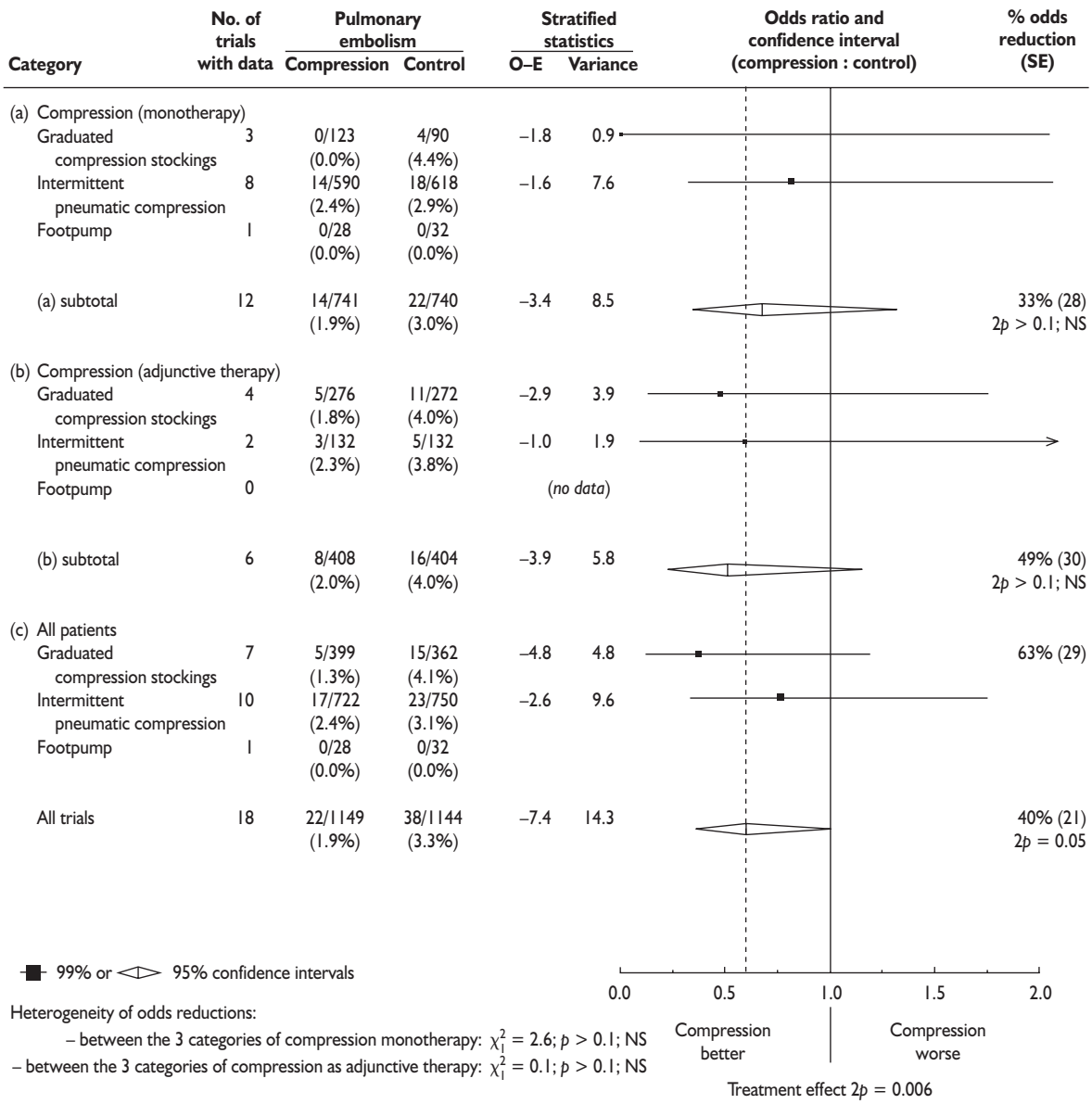

FIGURE 9 *Effects of compression methods of thromboprophylaxis on pulmonary embolism*

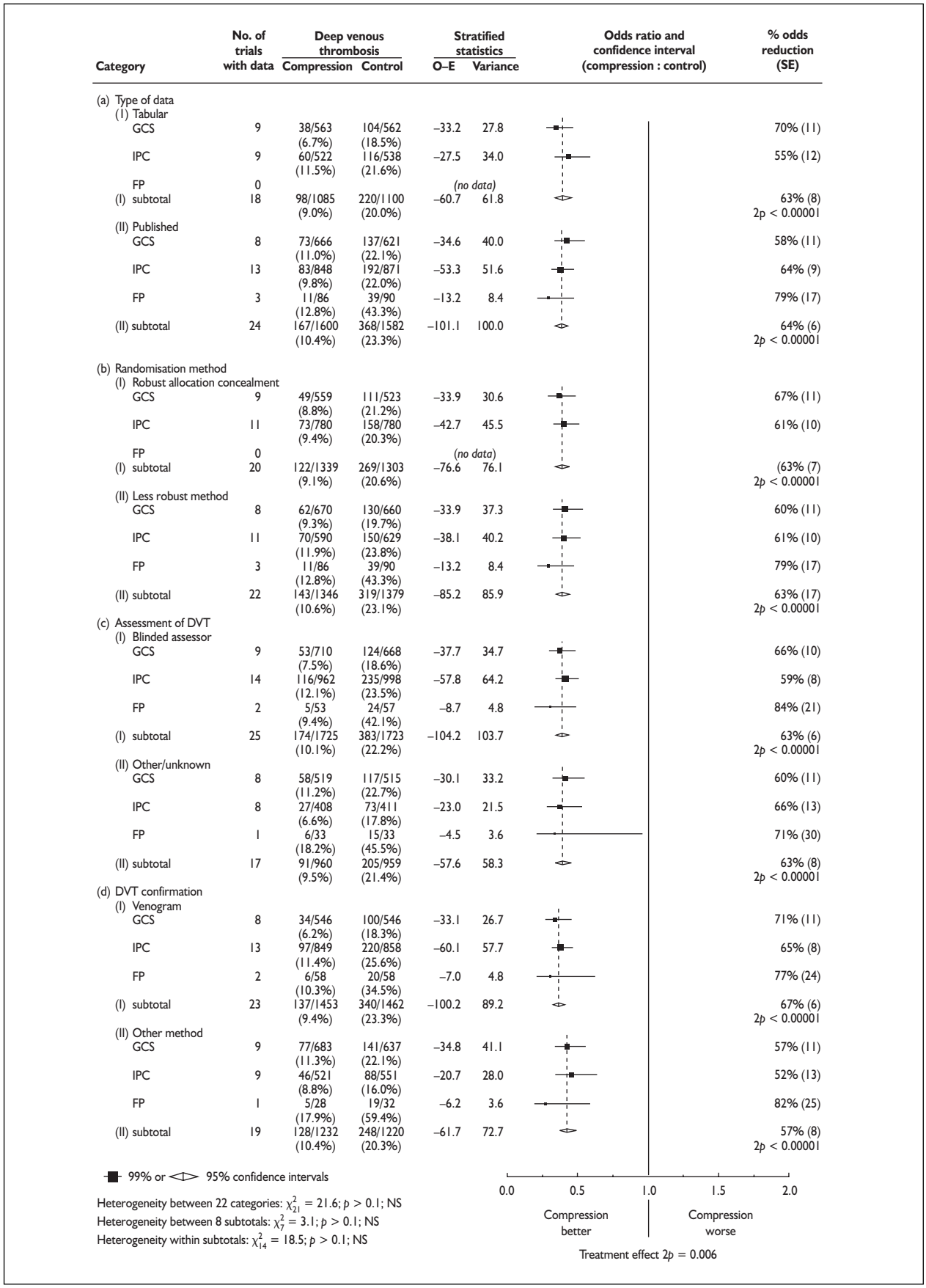

FIGURE 10 *Effects of methodological factors of compression on deep venous thrombosis. Abbreviations: FP, footpumps; GCS, graduated compression stockings; IPC, intermittent pneumatic compression.*

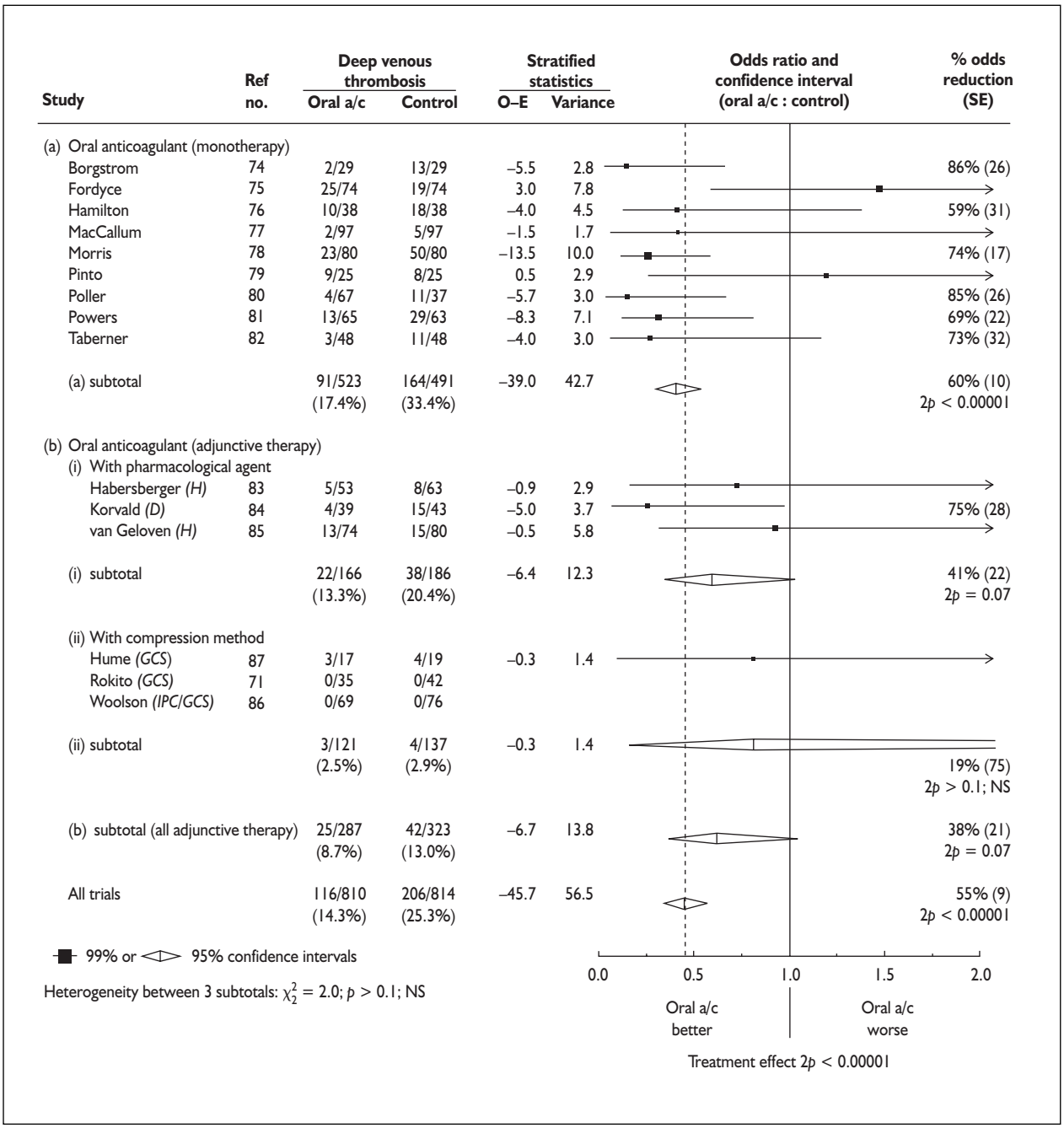

FIGURE 11 *Effects of oral anticoagulants on deep venous thrombosis. Abbreviations: a/c, anticoagulant; D, dextran; GCS, graduated compression stockings; H, unfractionated heparin; IPC, intermittent pneumatic compression.*

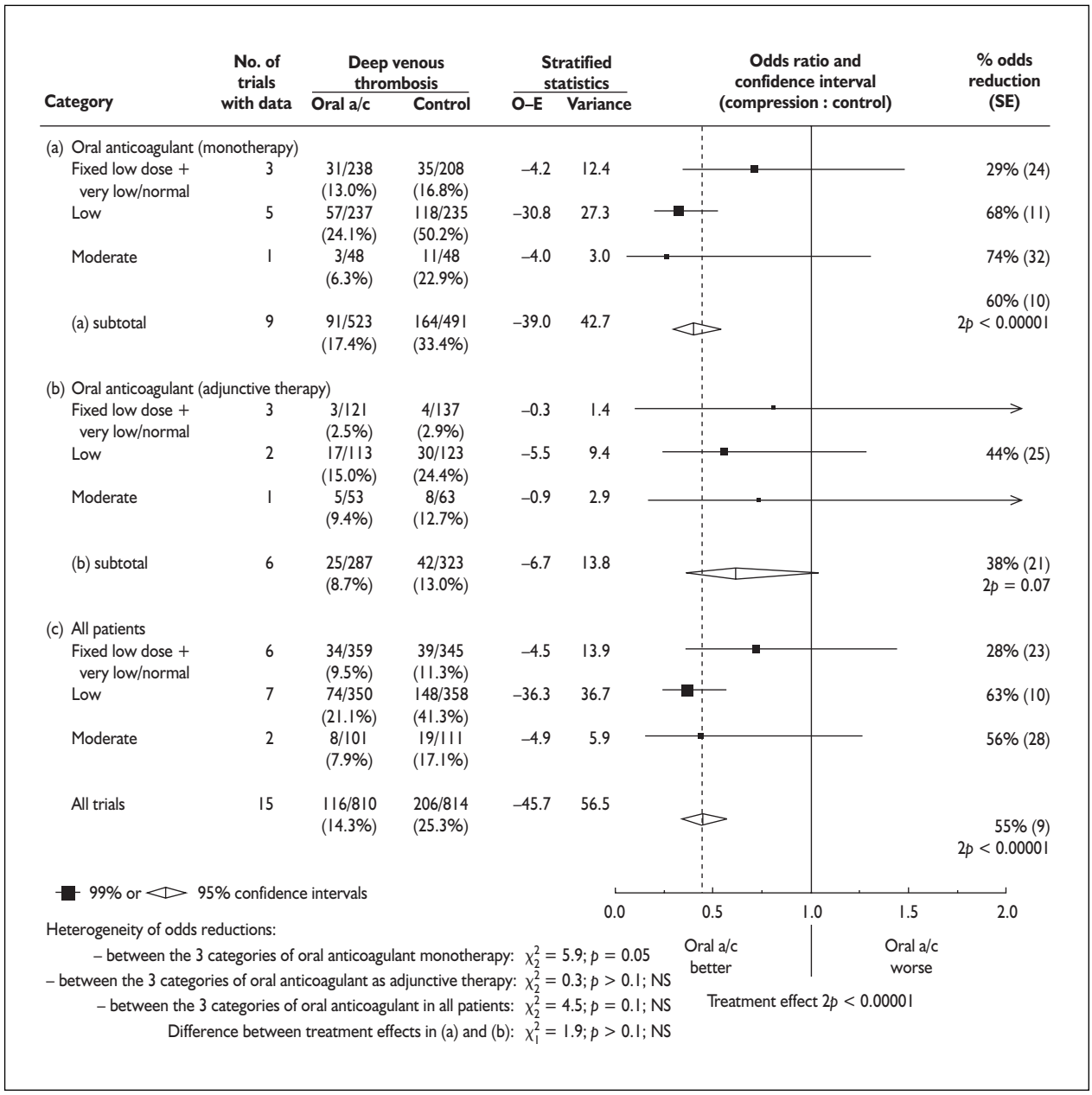

FIGURE 12 *Effects of oral anticoagulant intensity on deep venous thrombosis*

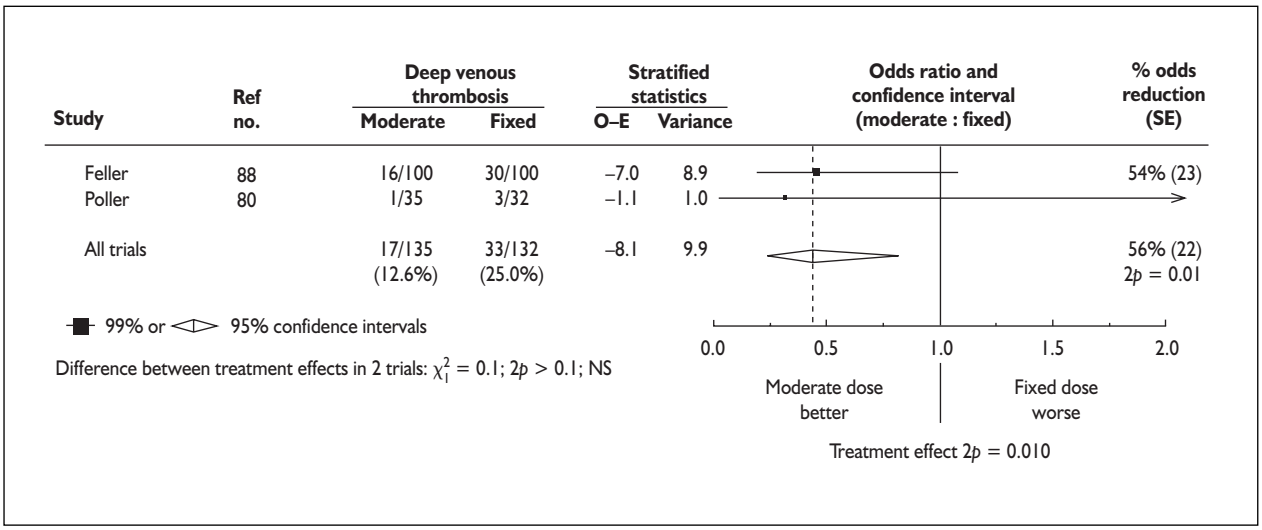

FIGURE 13 *Direct comparison of moderate and fixed low-dose oral anticoagulant regimens on deep venous thrombosis*

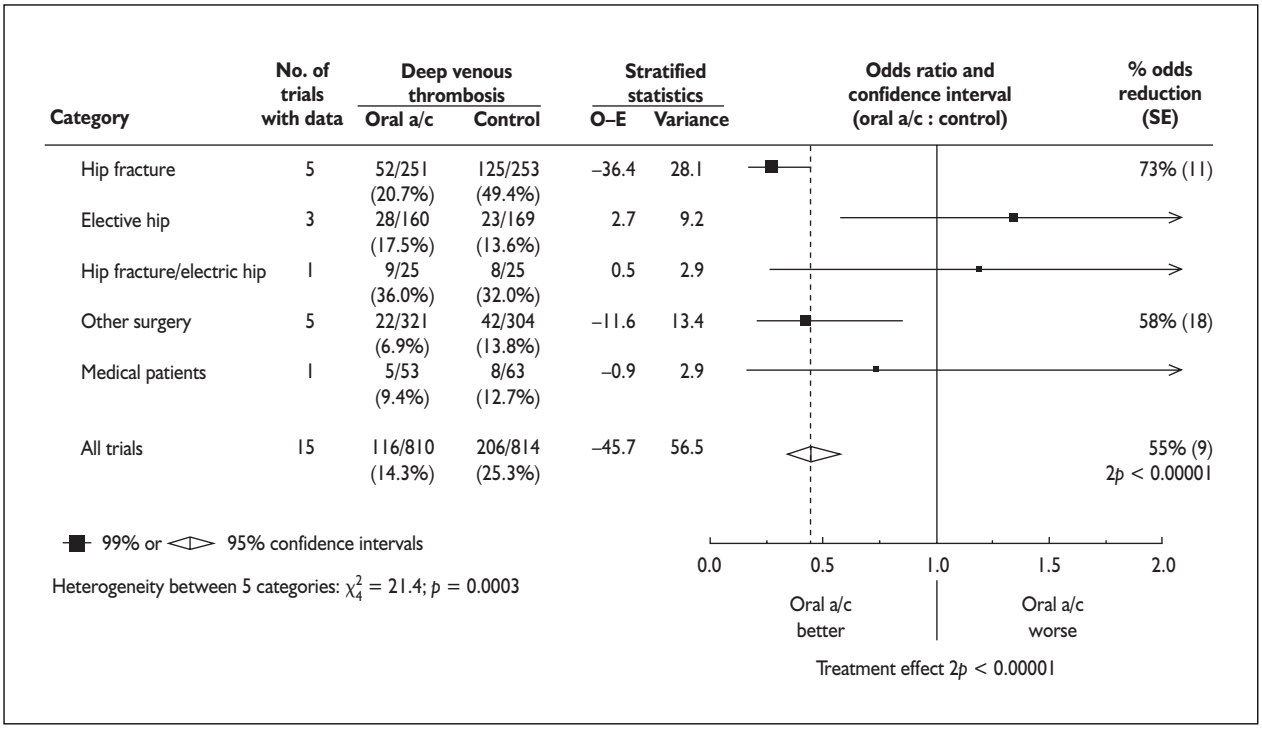

FIGURE 14 *Effects of oral anticoagulants on deep venous thrombosis among different types of patients*

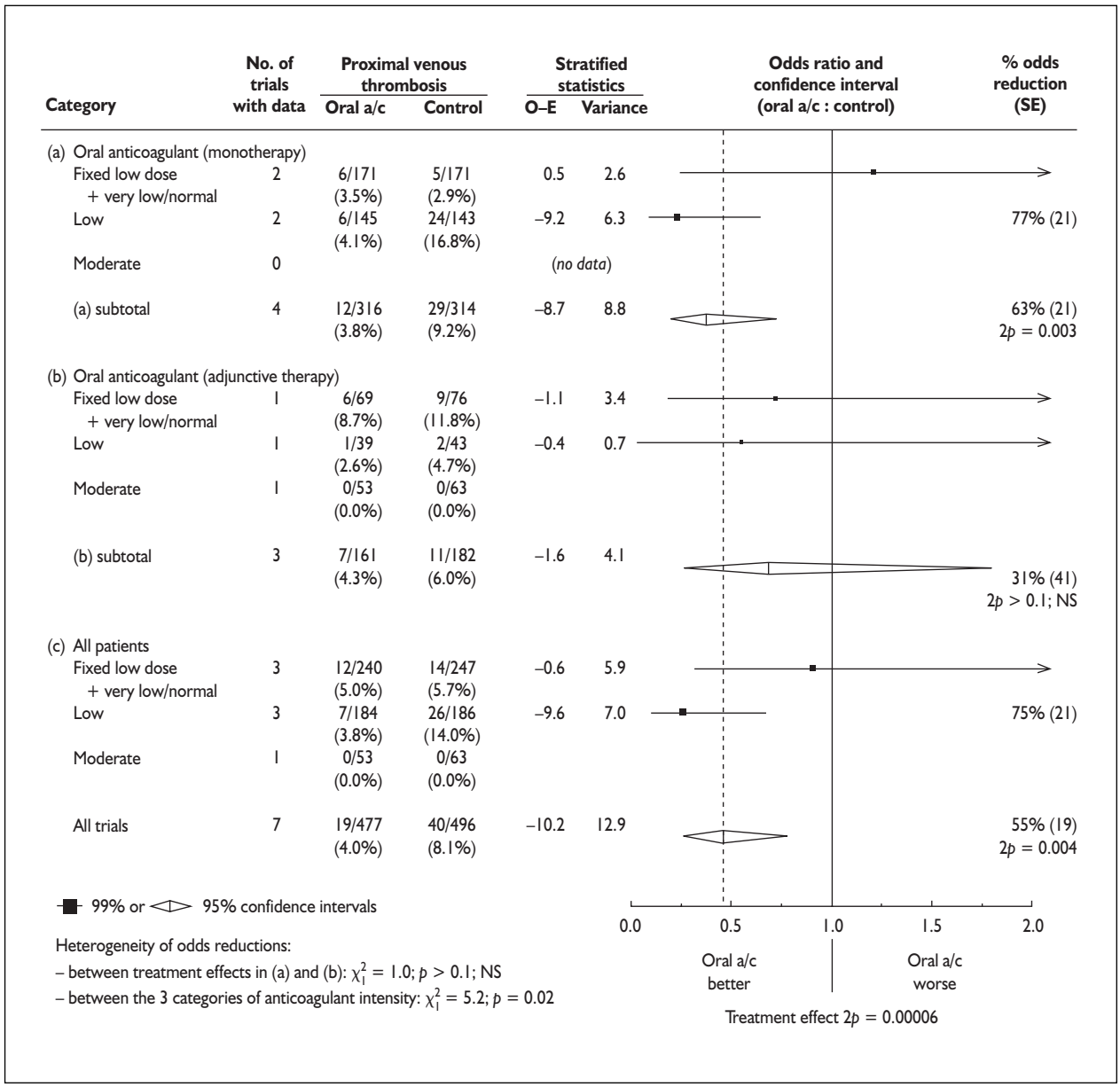

FIGURE 15 *Effects of oral anticoagulant intensity on proximal venous thrombosis*

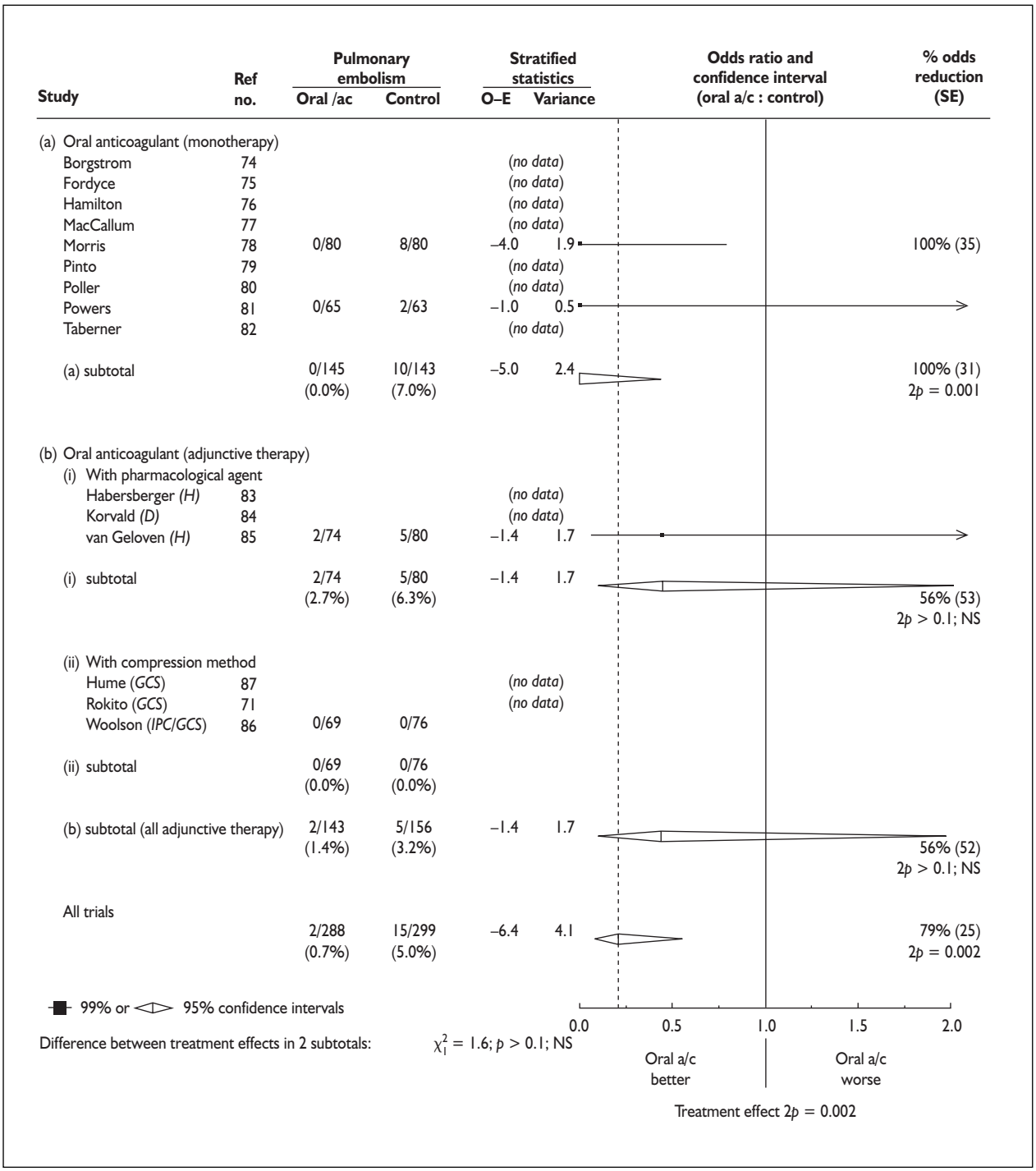

FIGURE 16 *Effects of oral anticoagulants on pulmonary embolism in trials assessing deep venous thrombosis systematically. Abbreviations: D, dextran; GCS, graduated compression stockings; H, unfractionated heparin; IPC, intermittent pneumatic compression.*

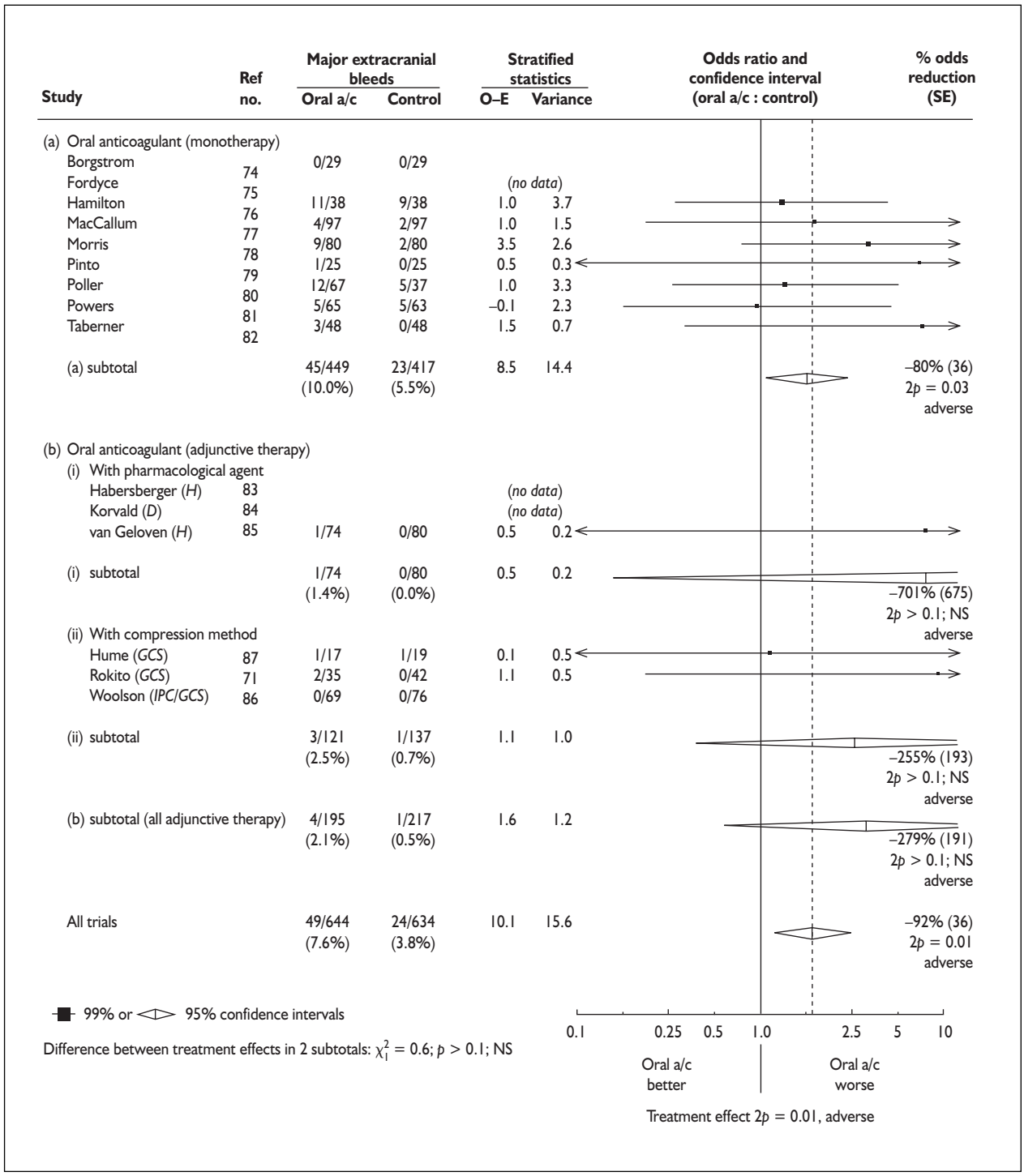

FIGURE 17 *Effects of oral anticoagulants on major extracranial bleeding. Abbreviations: D, dextran; GCS, graduated compression stockings; H, unfractionated heparin; IPC, intermittent pneumatic compression.*

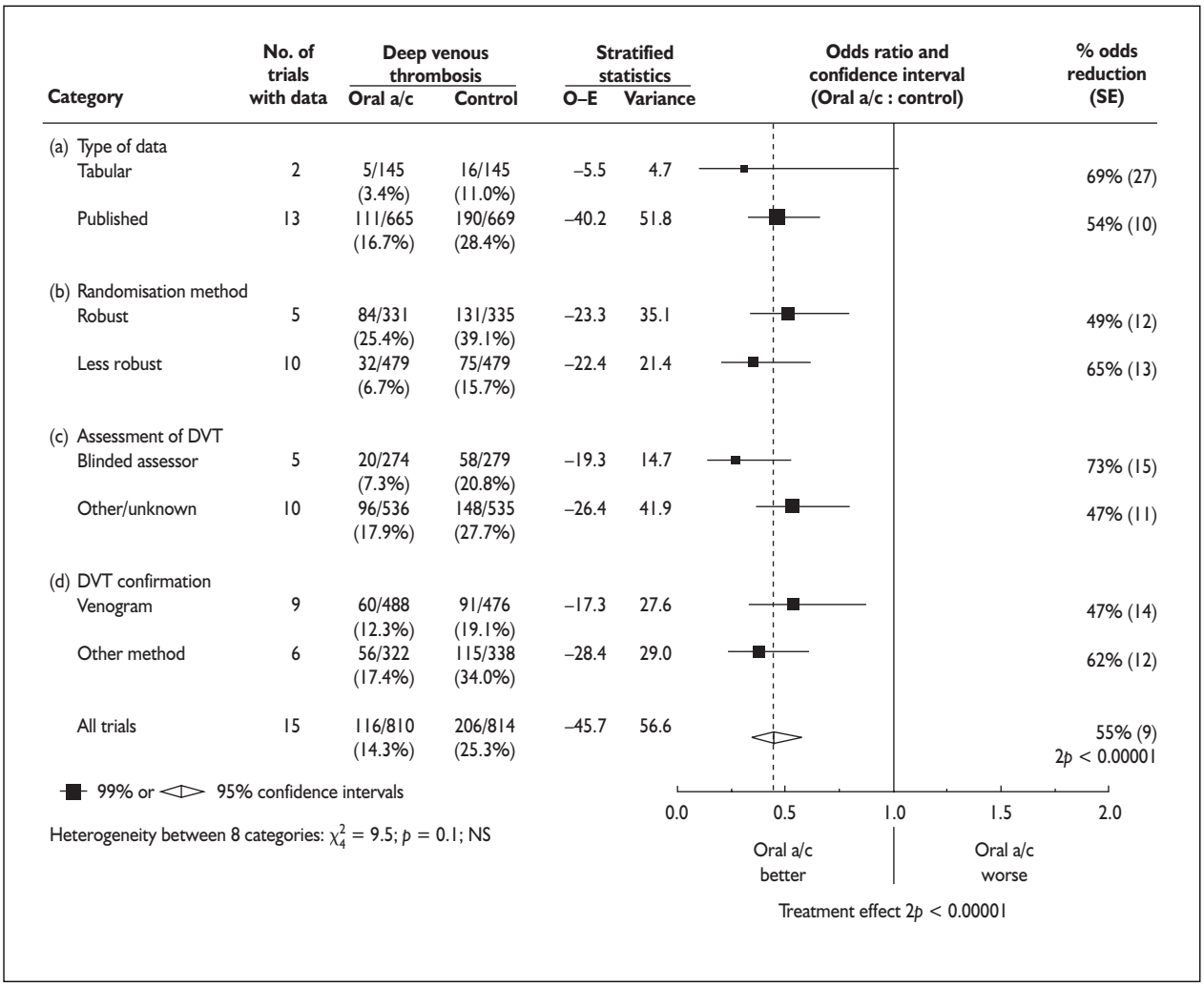

FIGURE 18 *Effects of methodological factors of oral anticoagulants on deep venous thrombosis*

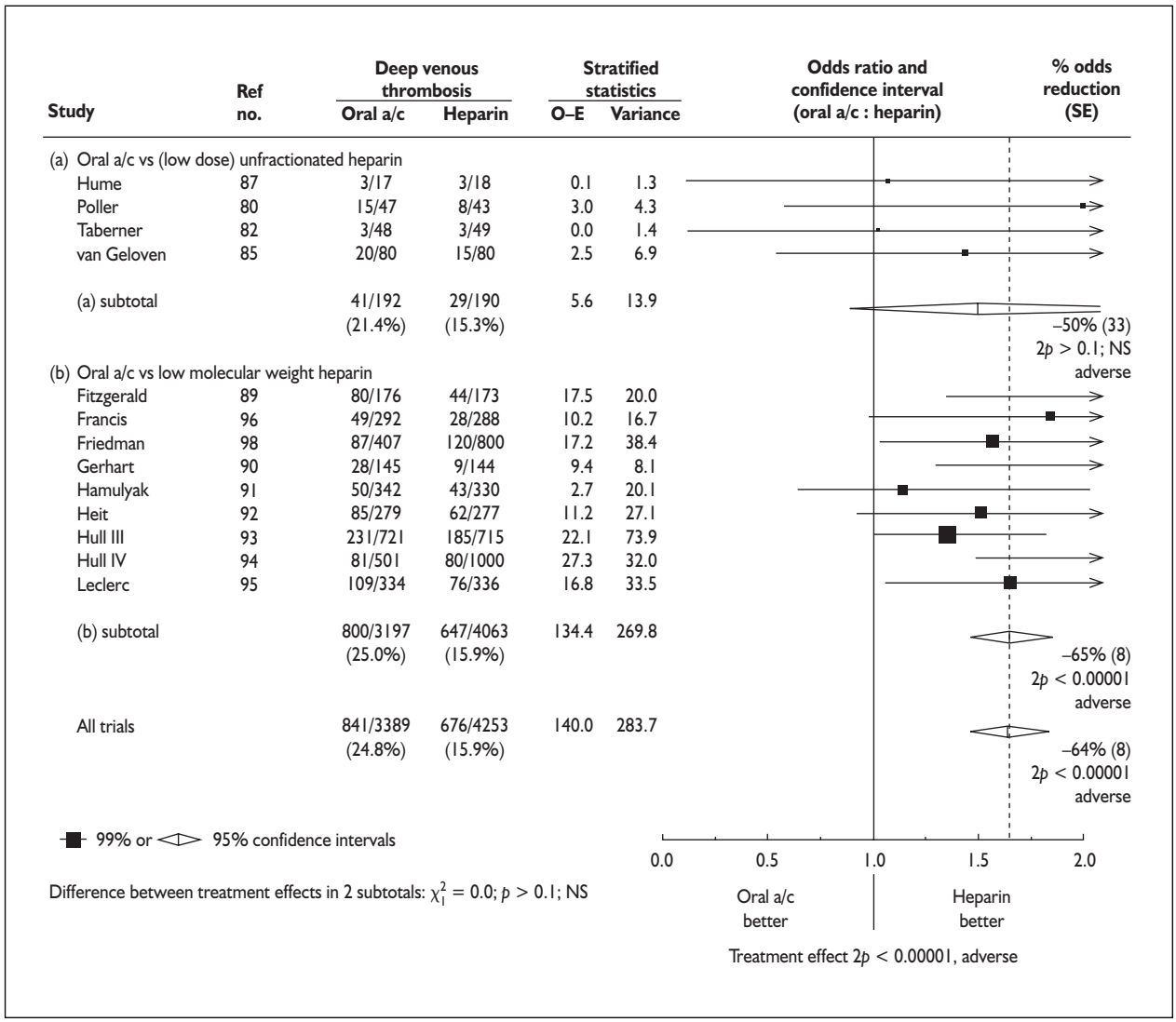

FIGURE 19 *Direct comparison of effects of oral anticoagulants and heparin on deep venous thrombosis*

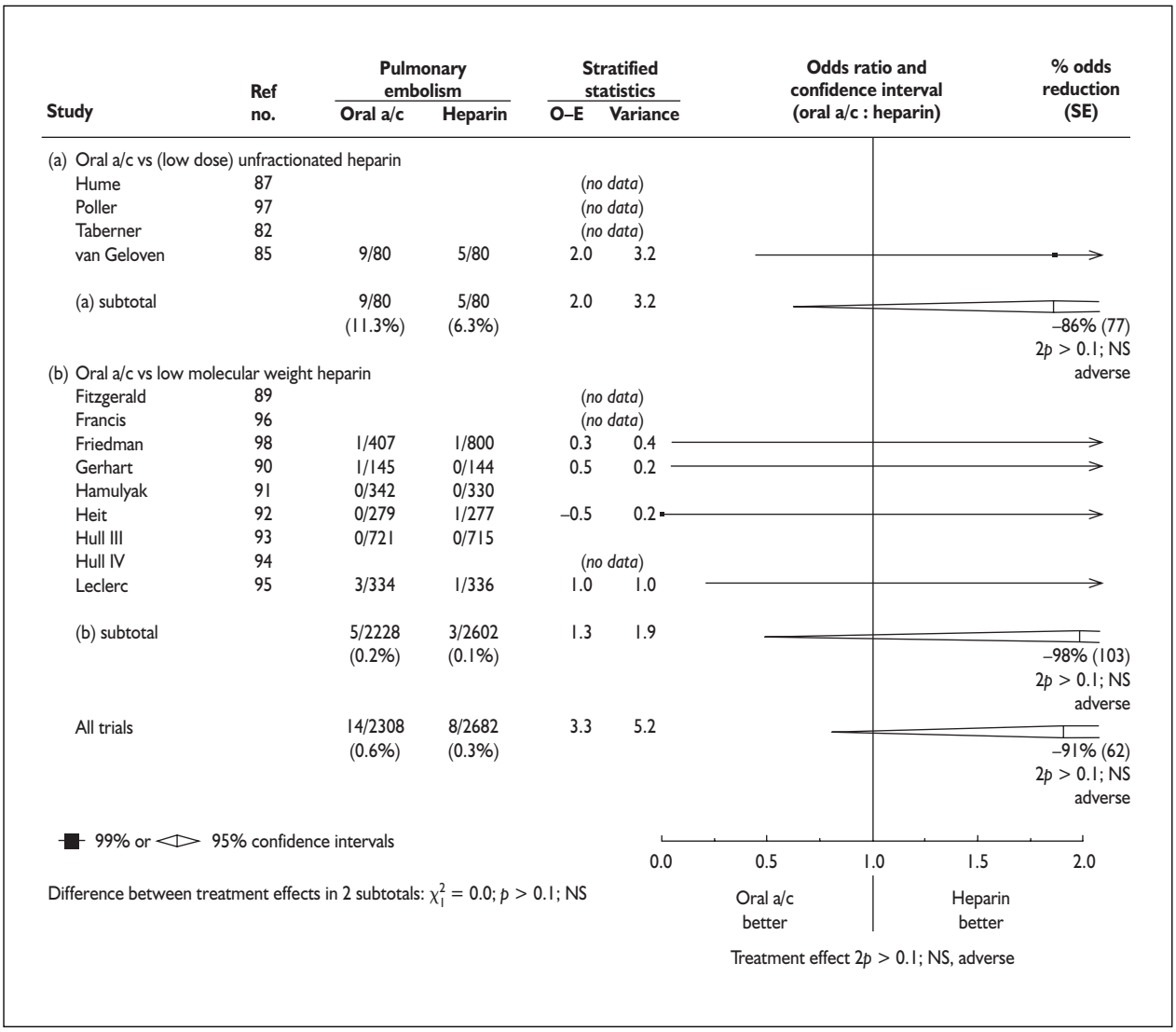

FIGURE 20 *Direct comparison of effects of oral anticoagulants and heparin on pulmonary embolism*

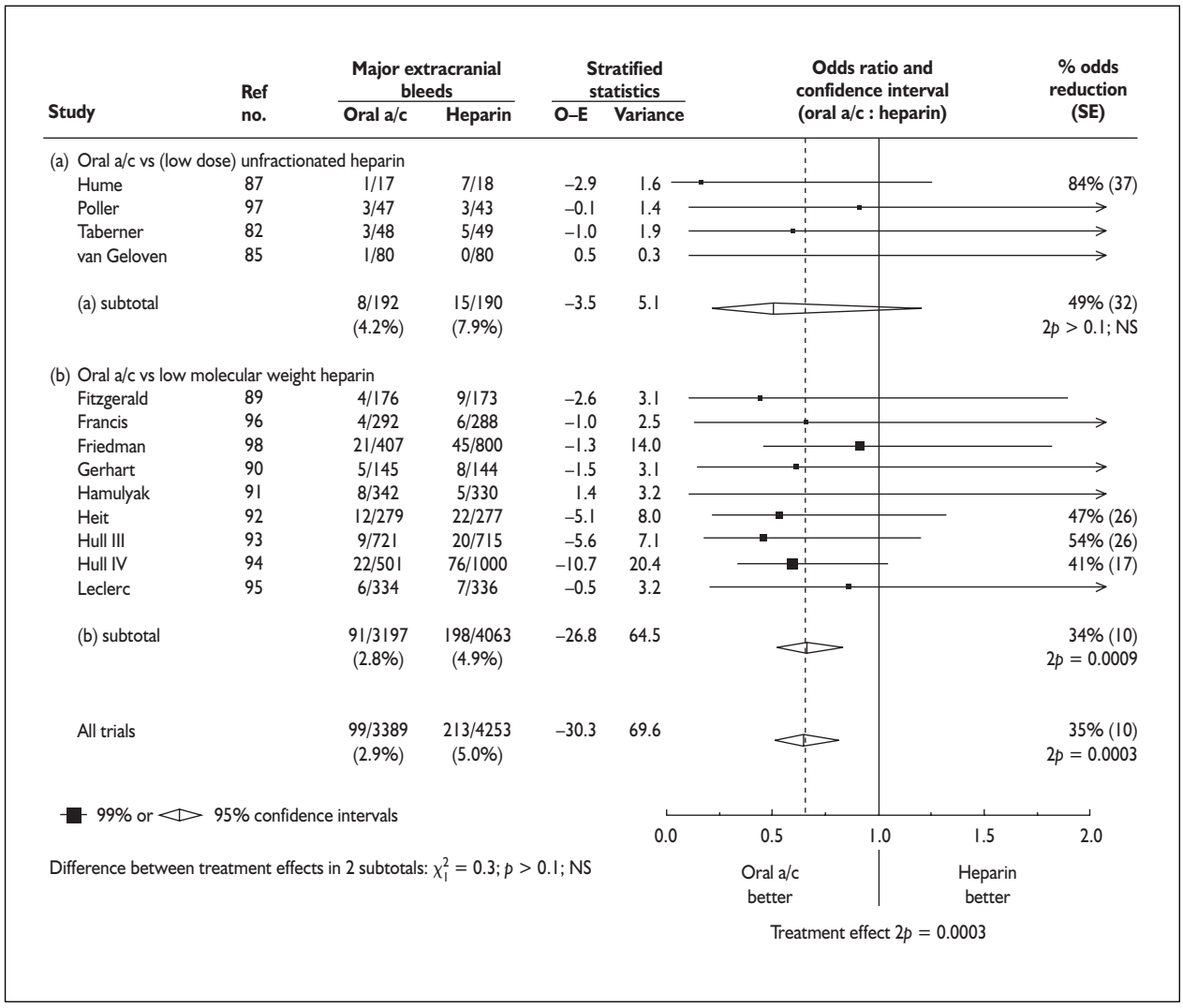

FIGURE 21 *Direct comparison of effects of oral anticoagulants and heparin on major extracranial bleeding*

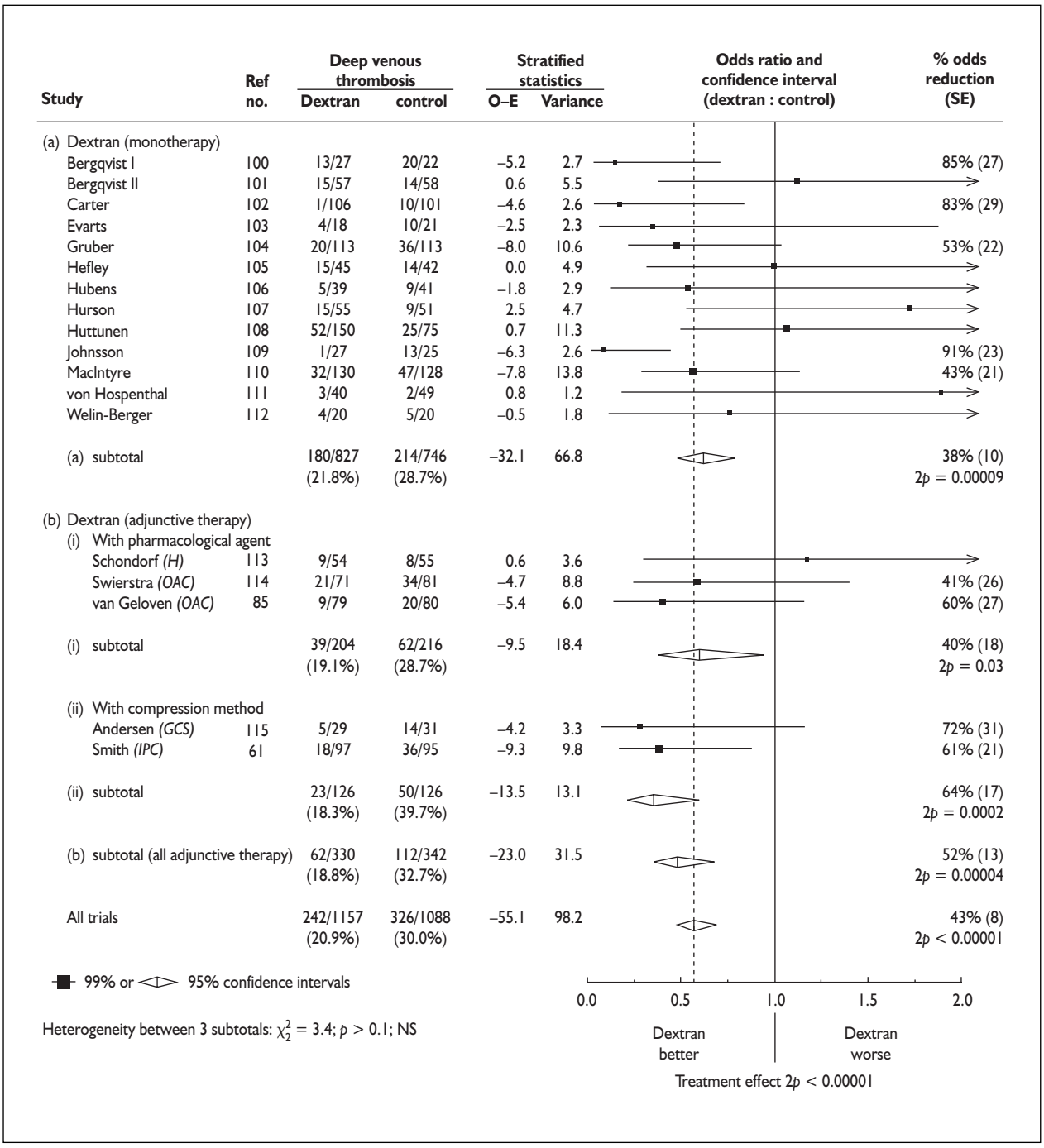

FIGURE 22 *Effects of dextran on deep venous thrombosis. Abbreviations: GCS, graduated compression stockings; H, unfractionated heparin; IPC, intermittent pneumatic compression; OAC, oral anticoagulant.*

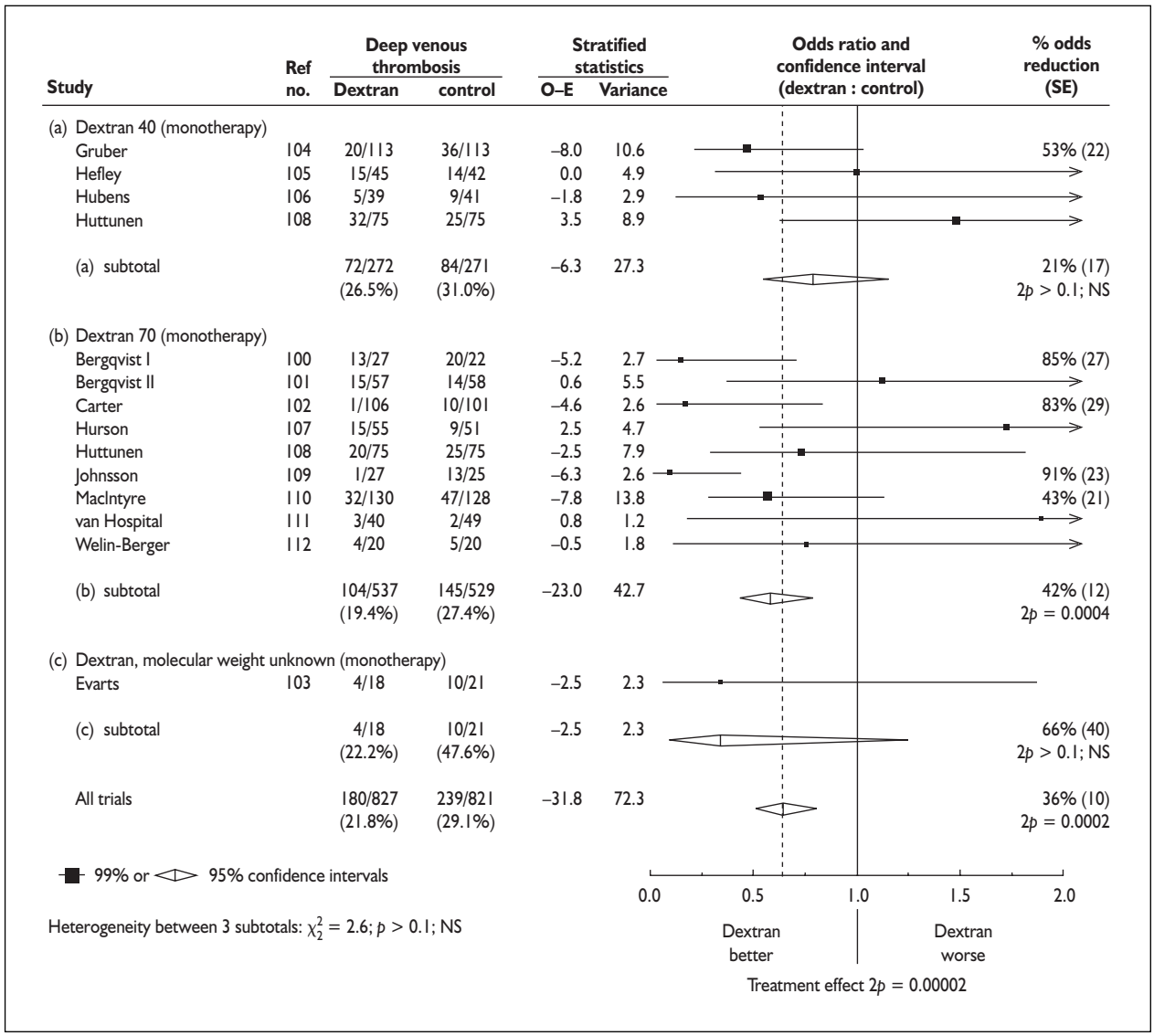

FIGURE 23 *Proportional effects of dextran on deep venous thrombosis, subdivided by molecular weight*

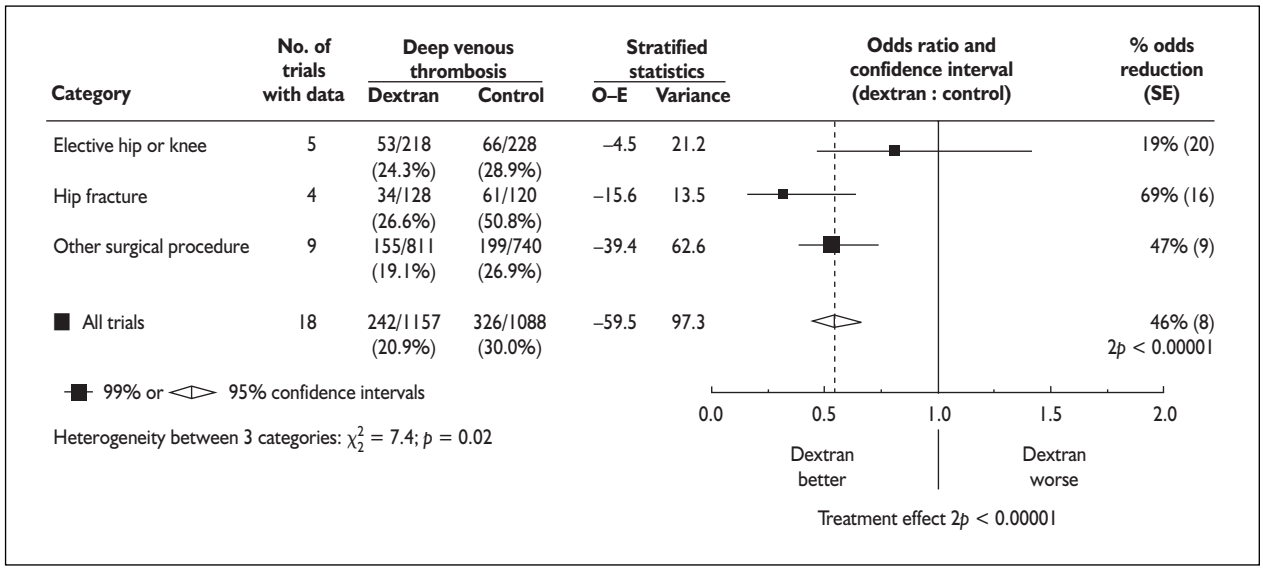

FIGURE 24 *Effects of dextran on deep venous thrombosis among different types of patients*

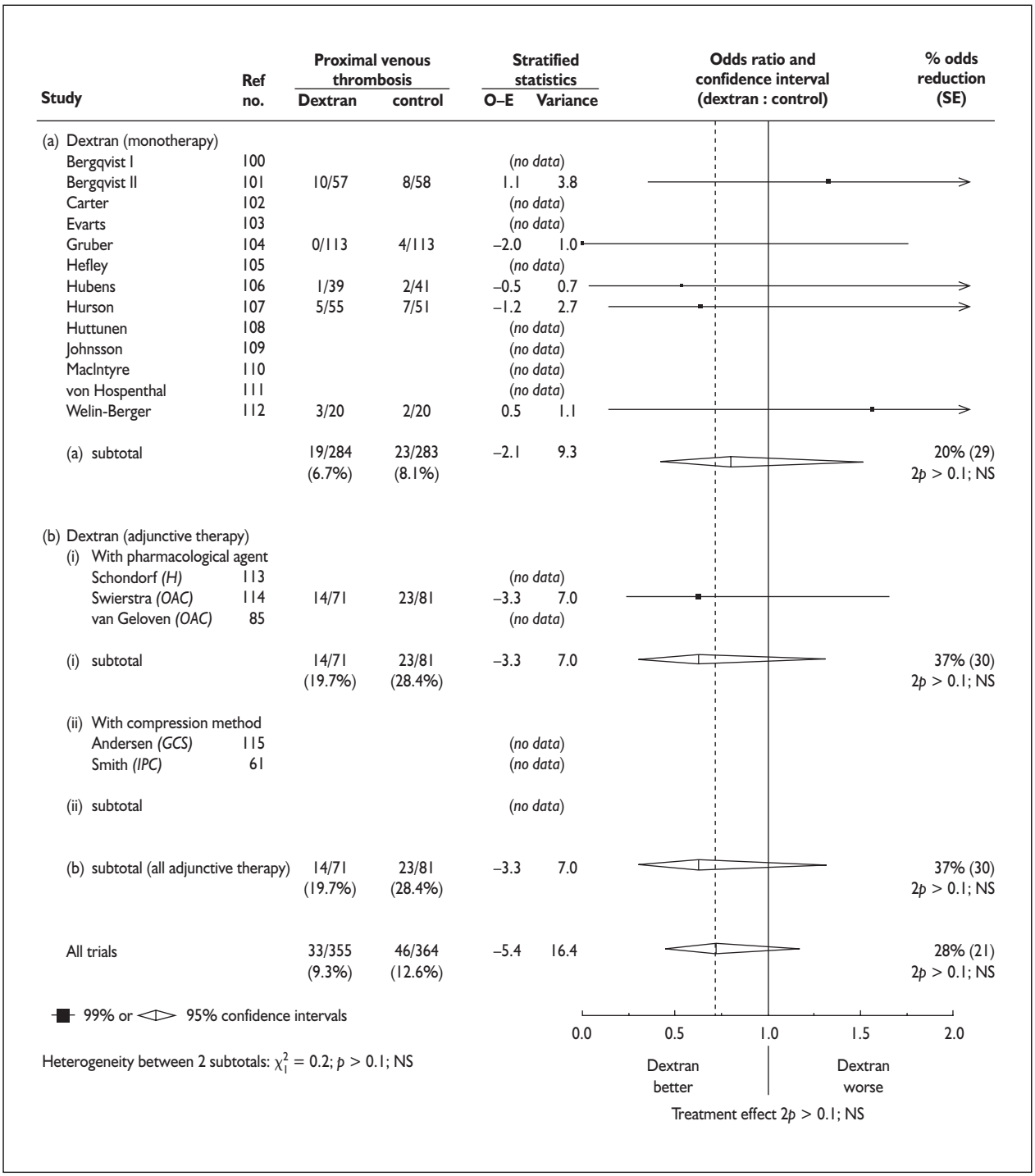

FIGURE 25 *Effects of dextran on proximal venous thrombosis. Abbreviations: GCS, graduated compression stockings; H, unfractionated heparin; IPC, intermittent pneumatic compression; OAC, oral anticoagulant.*

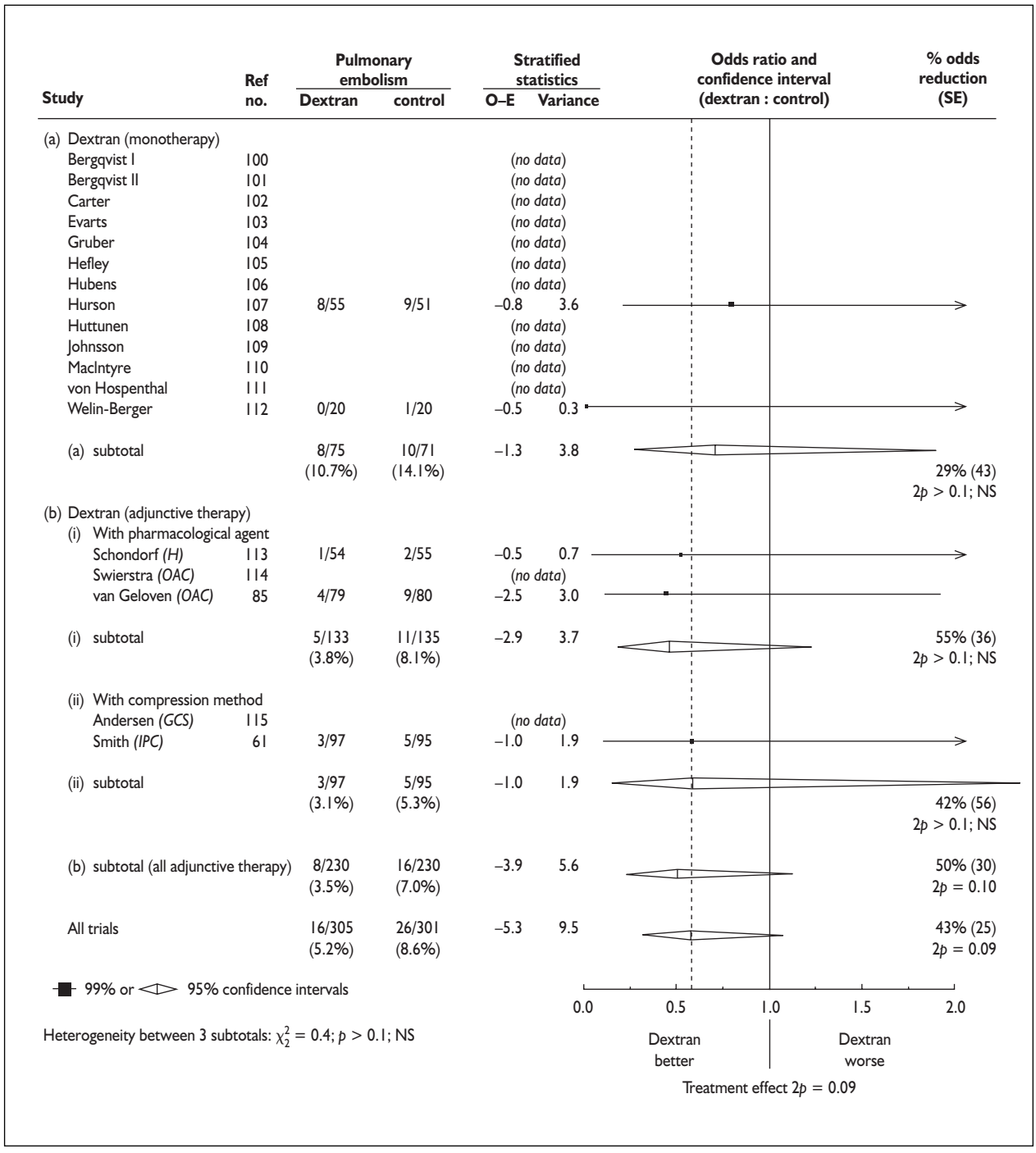

FIGURE 26 *Effects of dextran on pulmonary embolism in trials assessing deep venous thrombosis systematically. Abbreviations: GCS, graduated compression stockings; H, unfractionated heparin; IPC, intermittent pneumatic compression; OAC, oral anticoagulant.*

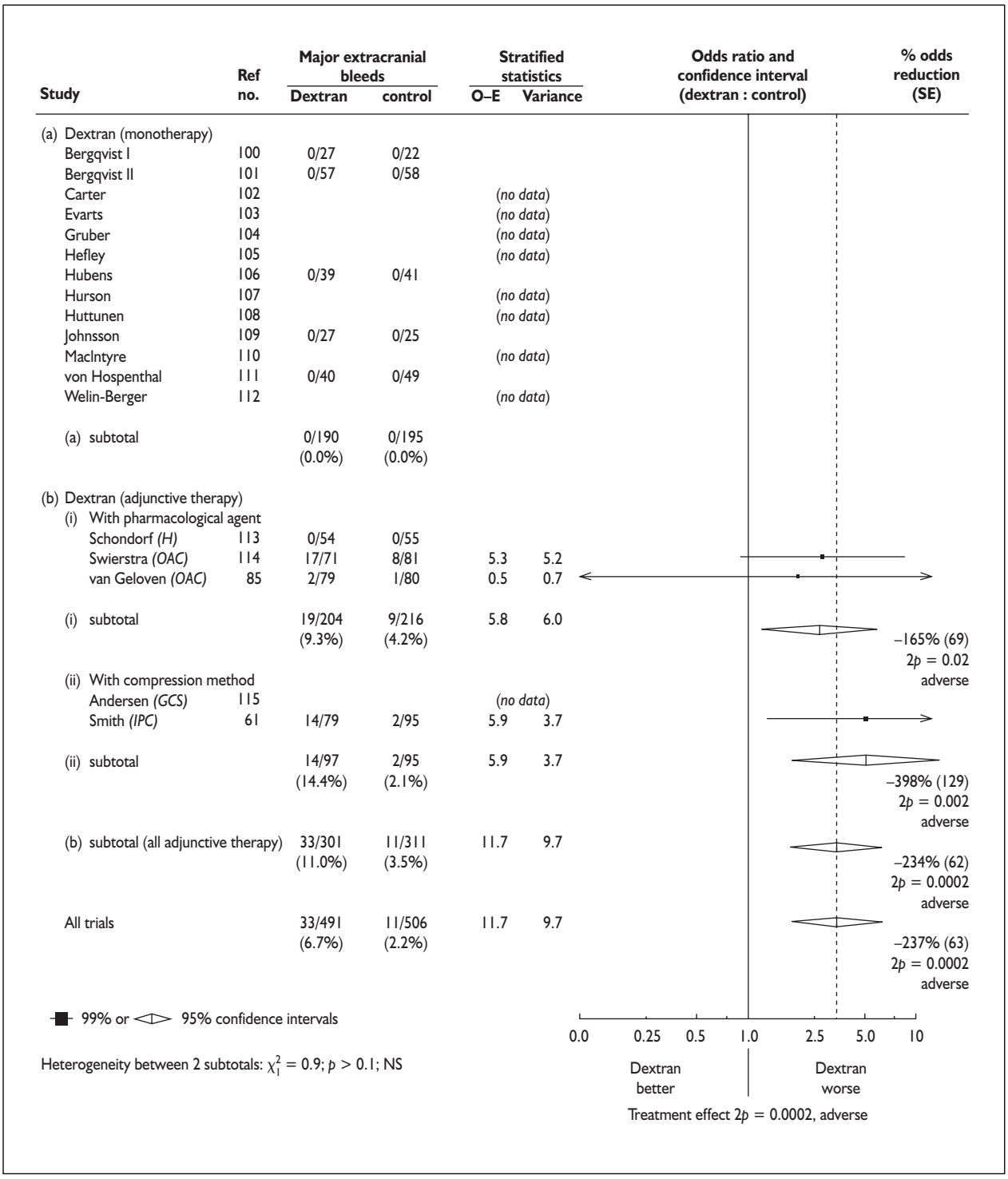

FIGURE 27 *Effects of dextran on major extracranial bleeding. Abbreviations: GCS, graduated compression stockings; H, unfractionated heparin; IPC, intermittent pneumatic compression; OAC, oral anticoagulant.*

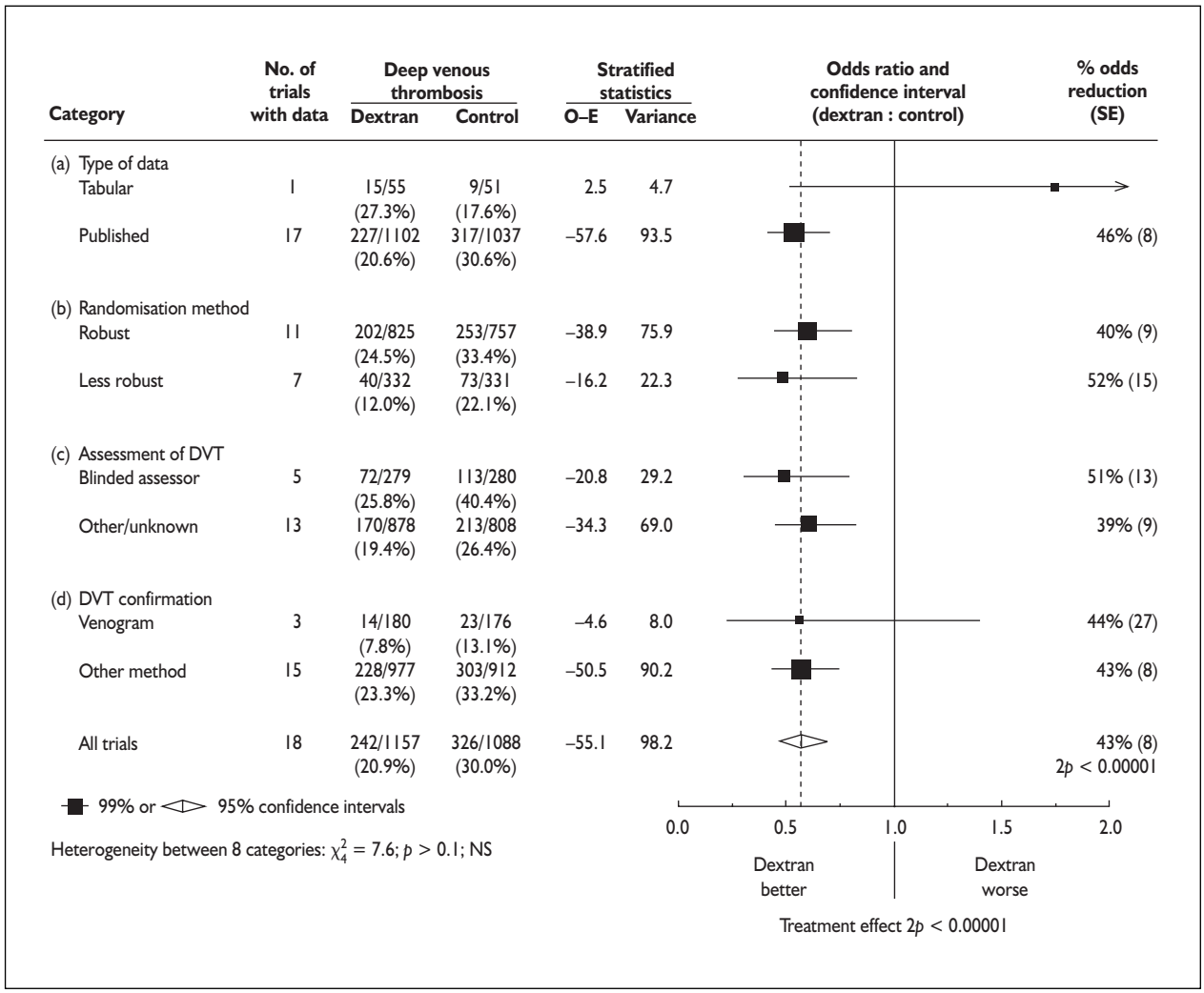

FIGURE 28 *Effects of methodological factors of dextran on deep venous thrombosis*

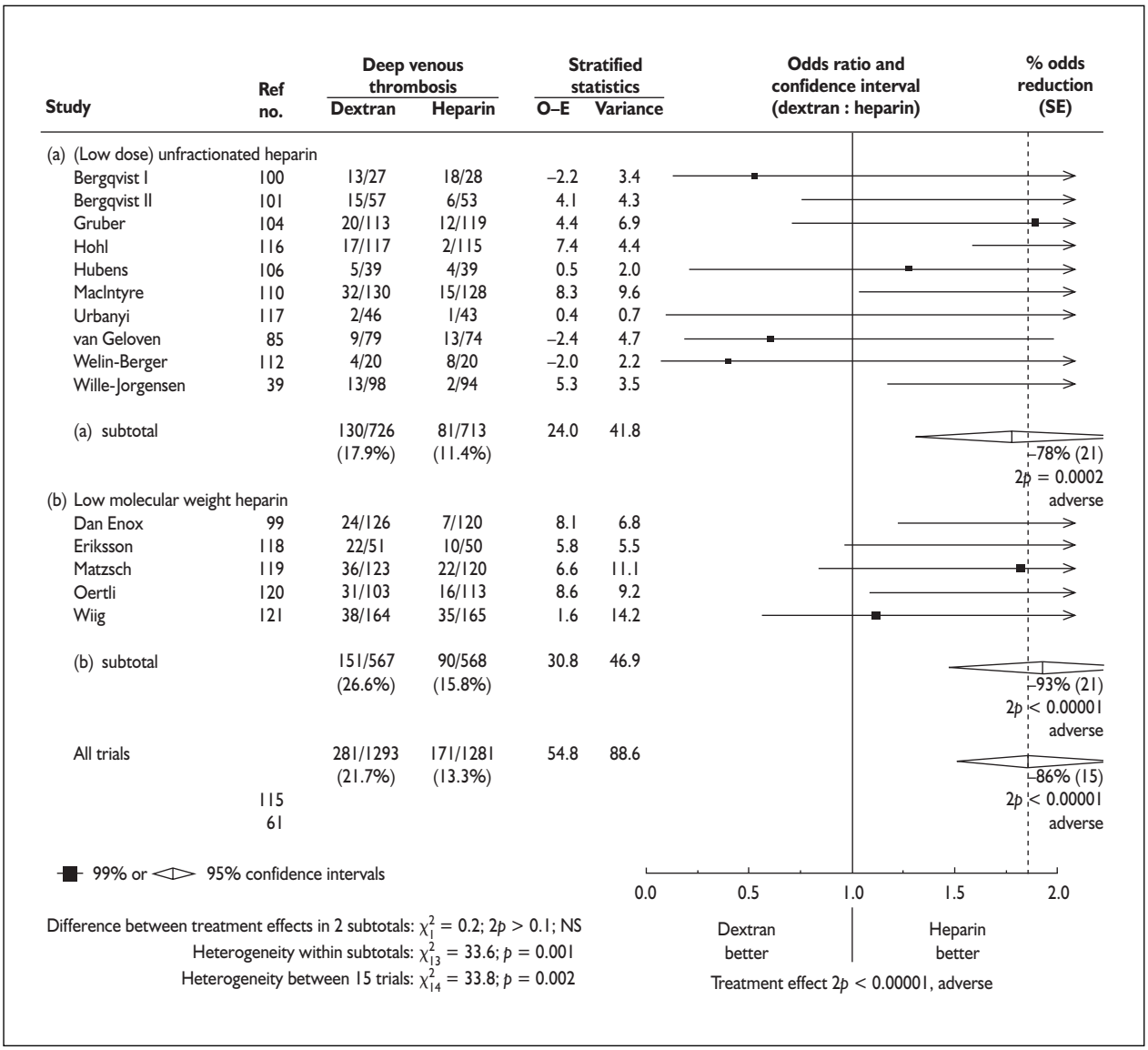

FIGURE 29 *Direct comparison of effects of dextran and heparin on deep venous thrombosis*

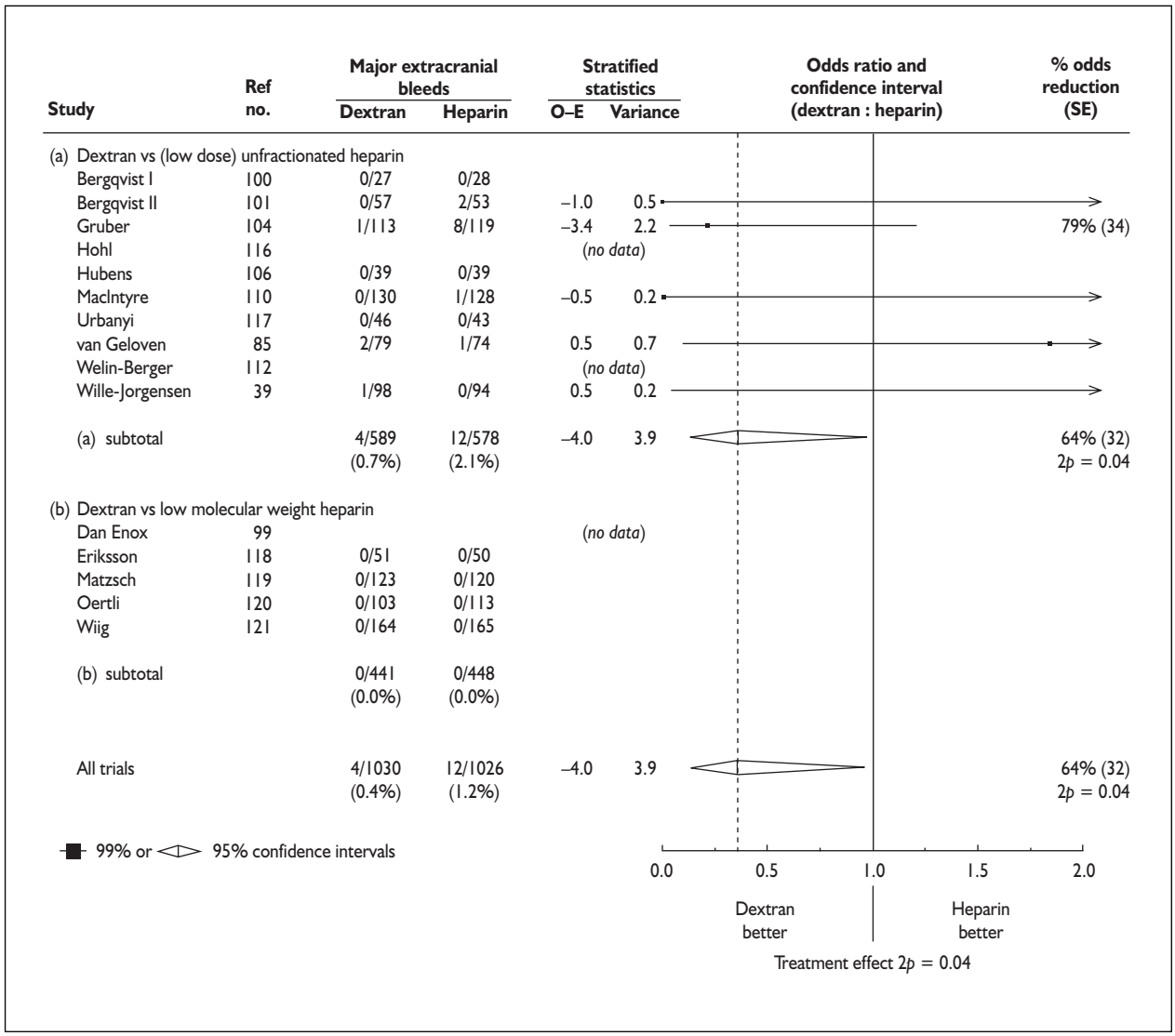

FIGURE 30 *Direct comparison of effects of dextran and heparin on major extracranial bleeding*

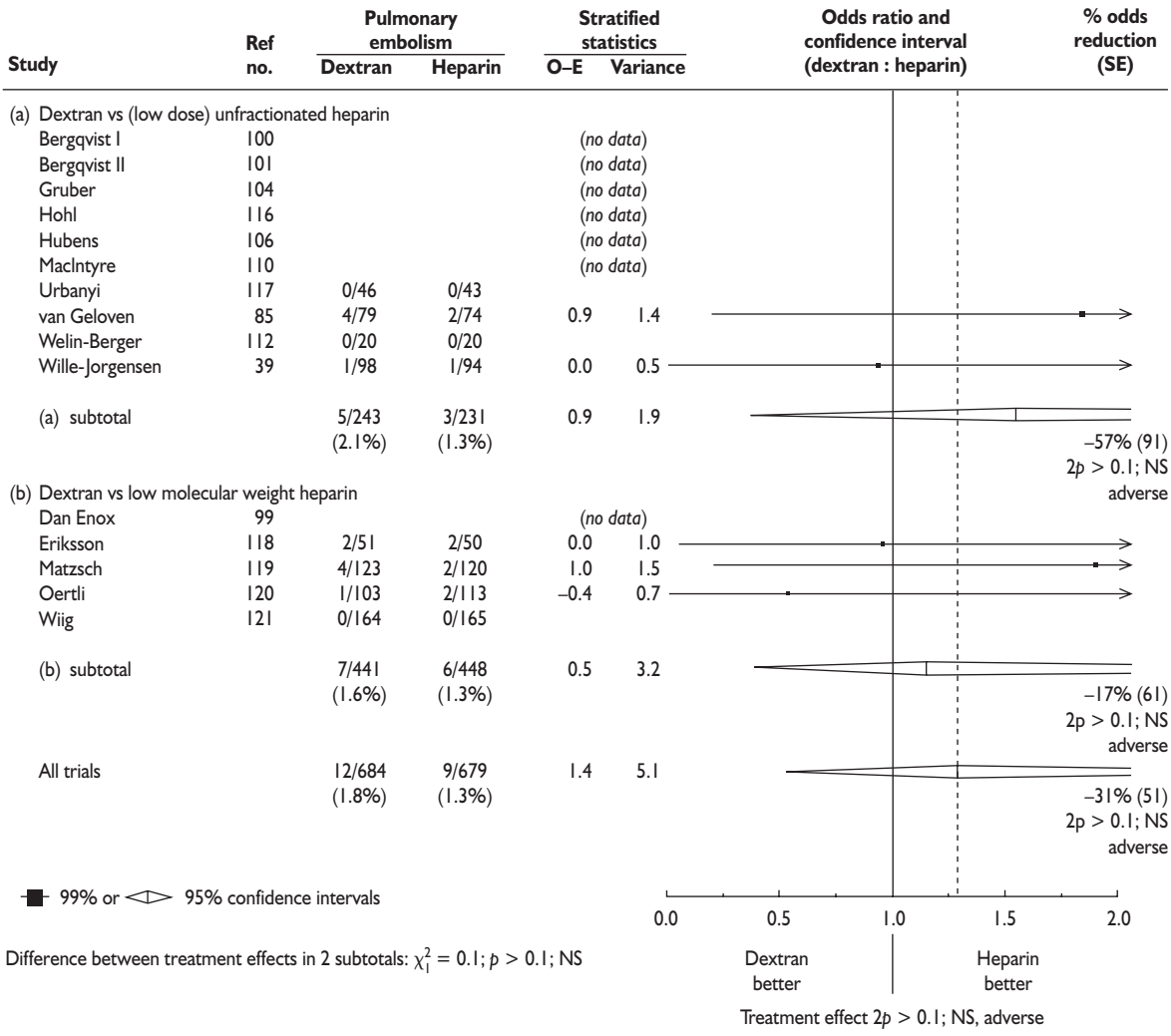

FIGURE 31 *Direct comparison of effects of dextran and heparin on pulmonary embolism*

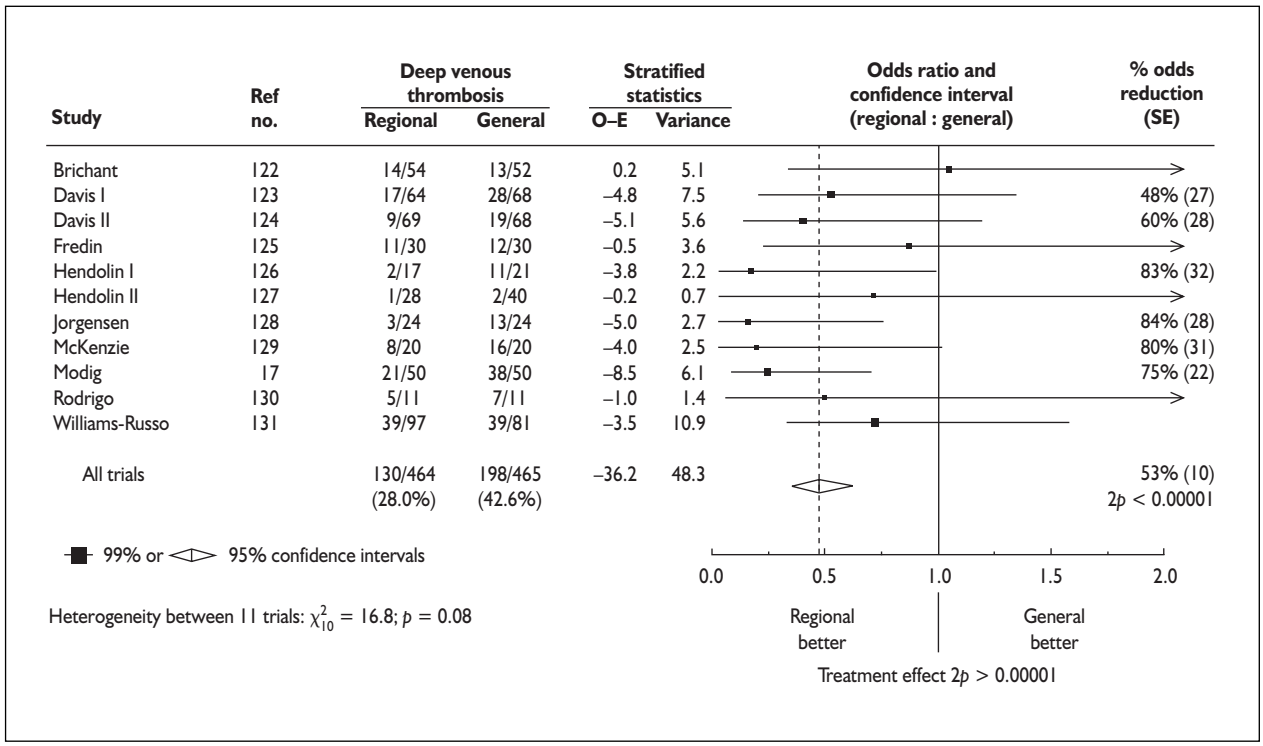

FIGURE 32 *Effects of regional or general anaesthesia on deep venous thrombosis*

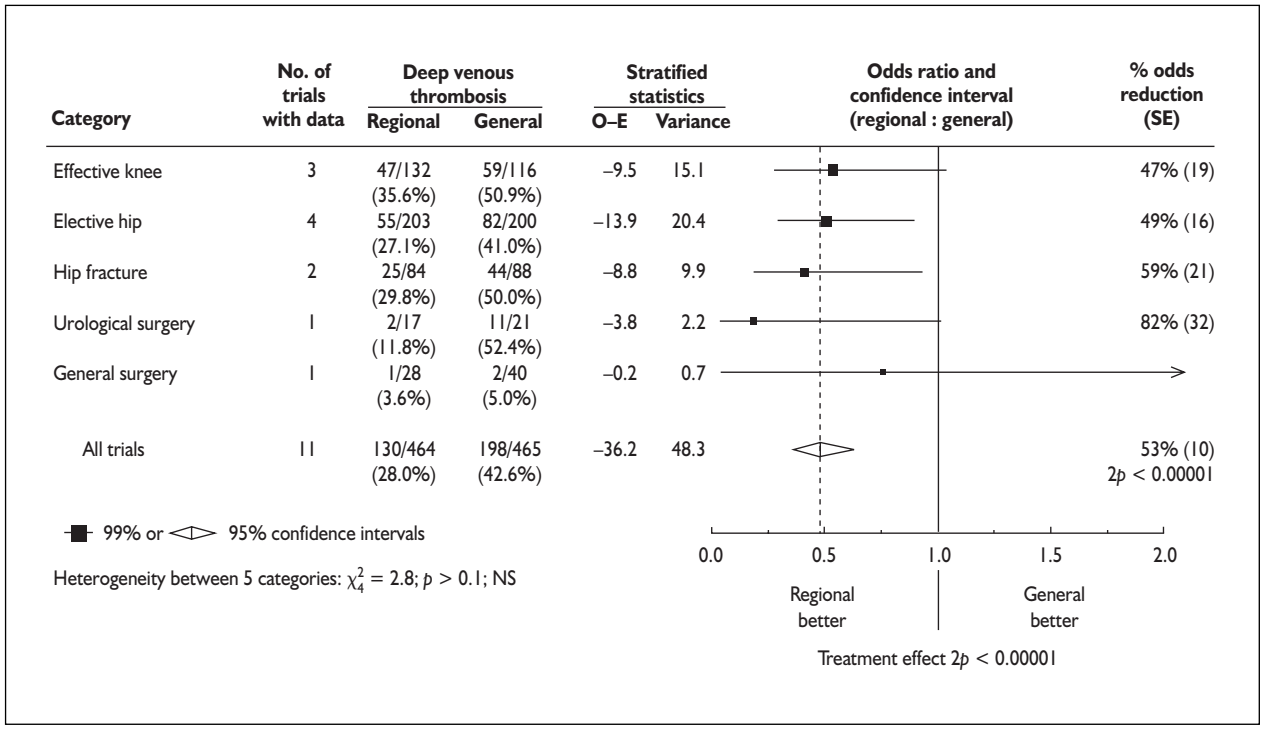

FIGURE 33 *Comparison of the effects of regional anaesthesia and general anaesthesia on deep venous thrombosis among different types of patients*

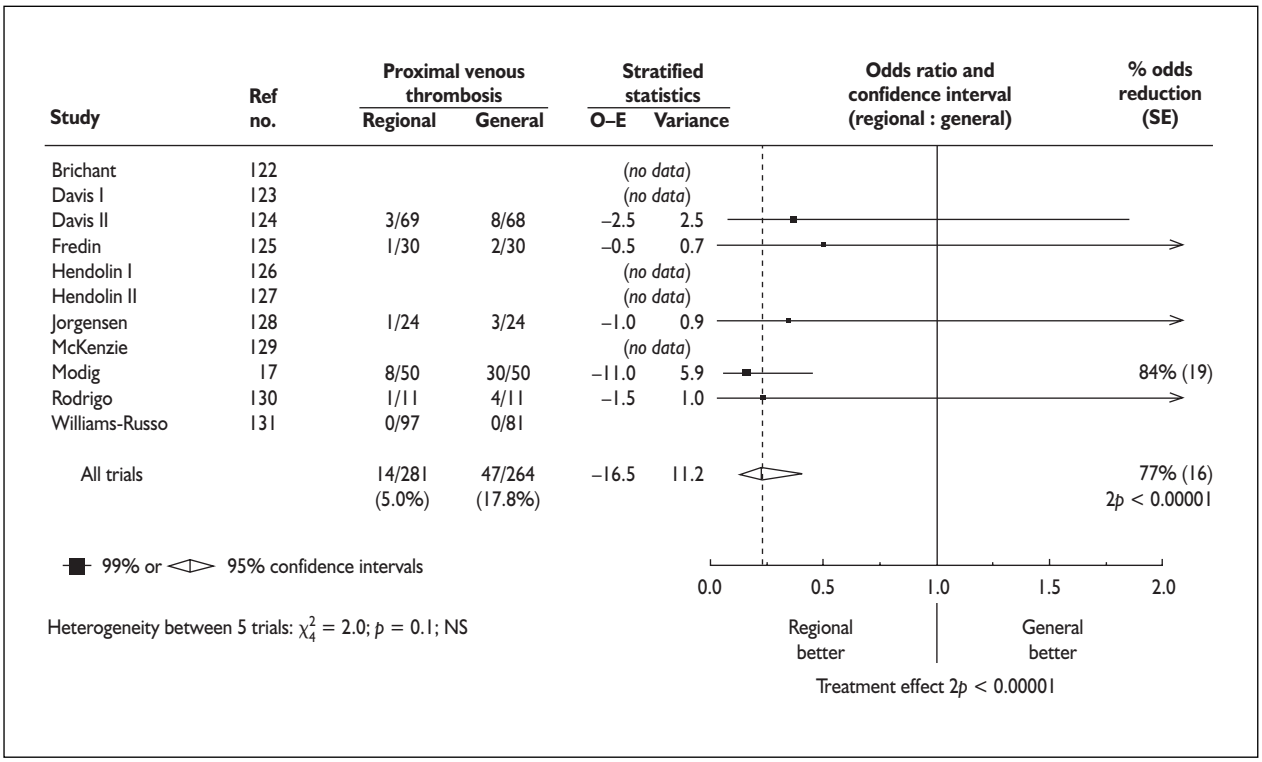

FIGURE 34 *Effects of regional or general anaesthesia on proximal venous thrombosis*

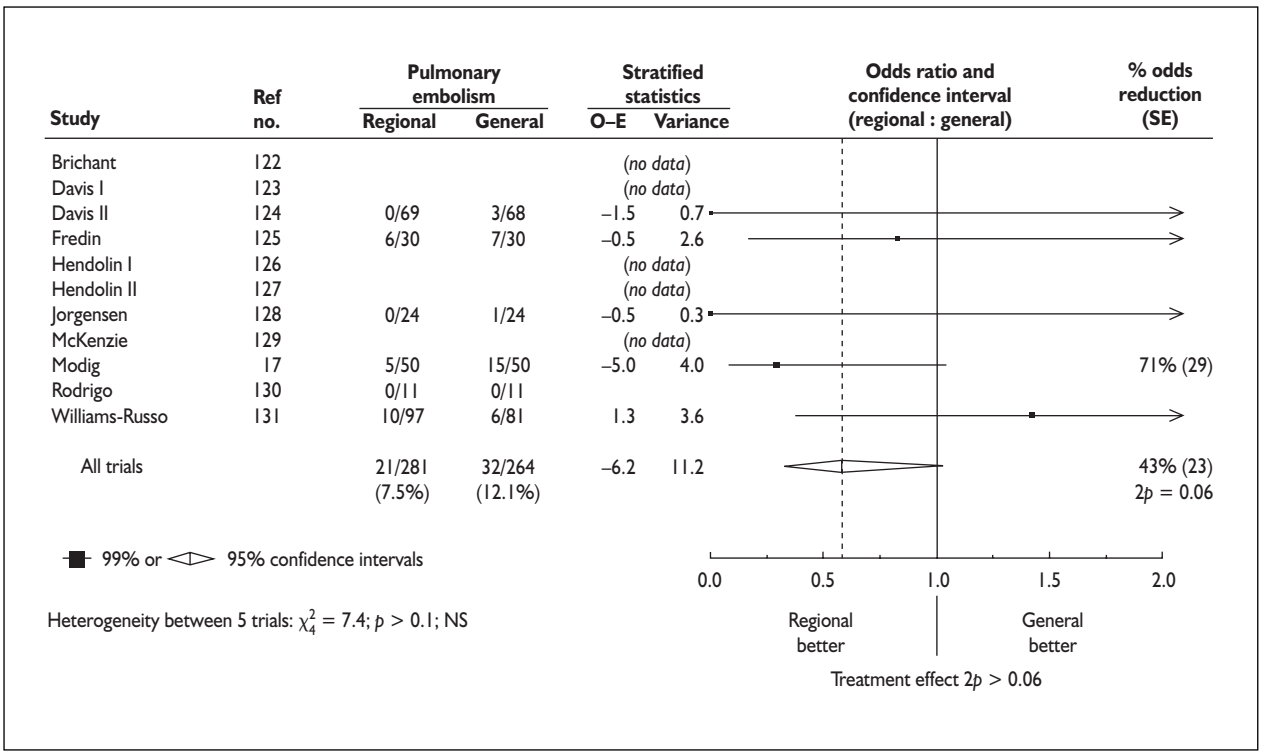

FIGURE 35 *Effects of regional or general anaesthesia on pulmonary embolism in trials assessing deep venous thrombosis systematically*

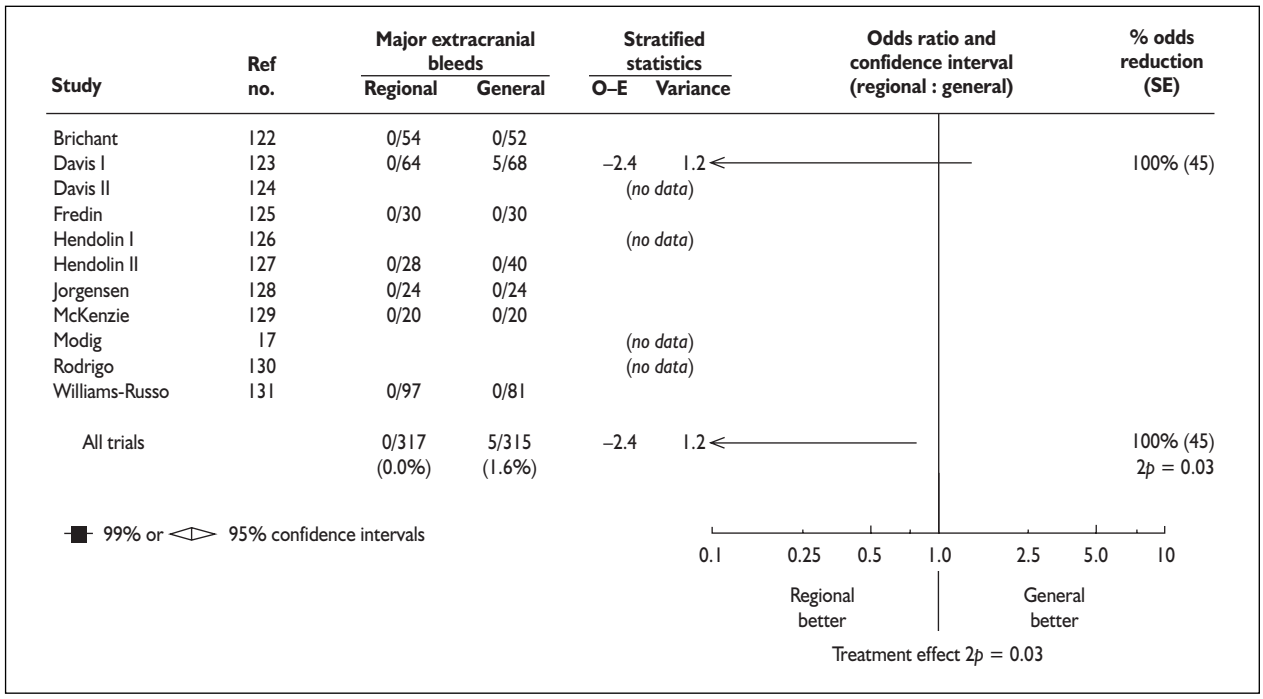

FIGURE 36 *Effects of regional or general anaesthesia on major extracranial bleeding*

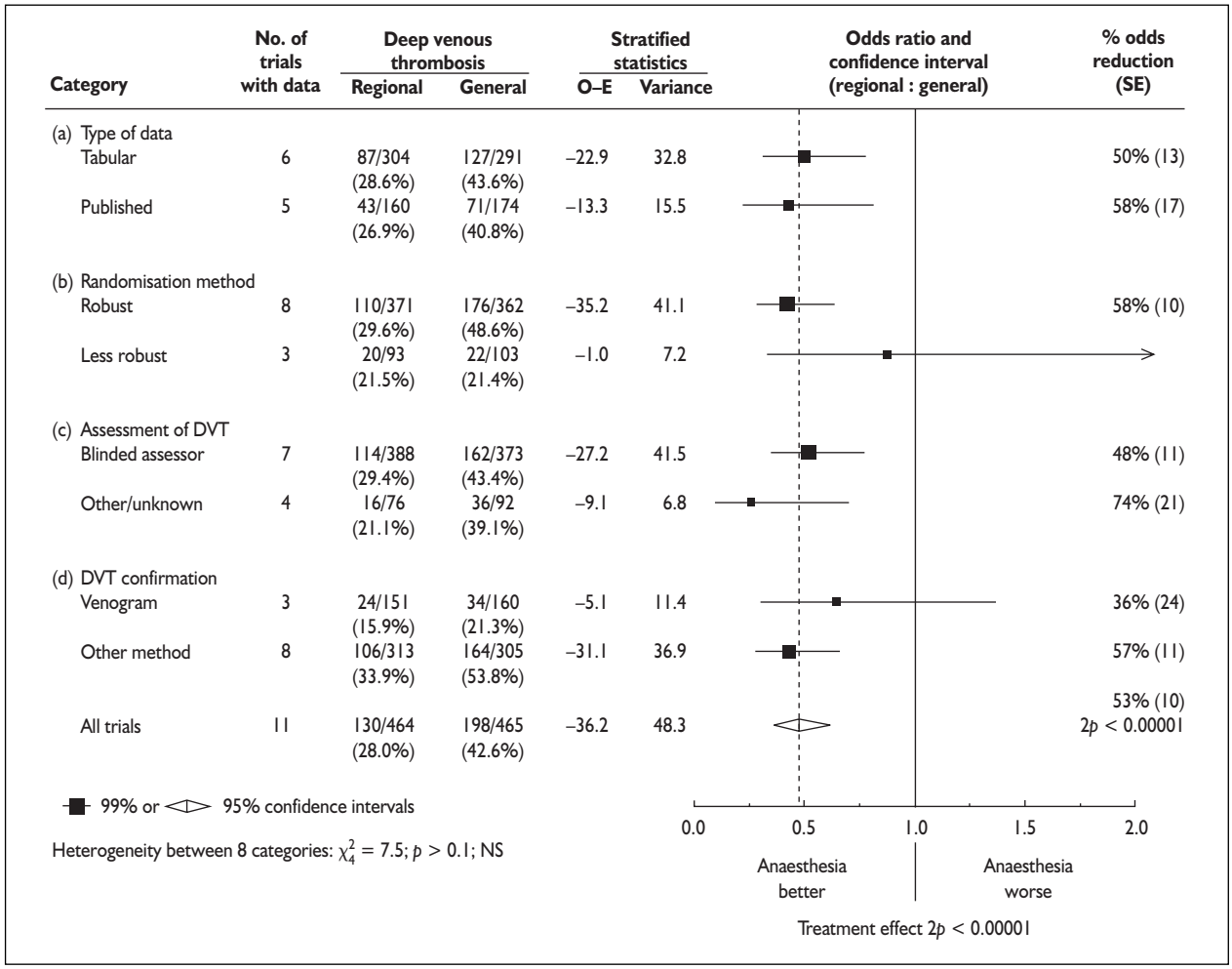

FIGURE 37 *Effects of methodological factors of anaesthesia on deep venous thrombosis*

Chapter 4
Discussion

The aim of this review was to assess three separate modes of thromboprophylaxis: mechanical, pharmacological and anaesthetic. Our reason for choosing to examine these methods together was that meta-analyses of the effectiveness and safety of these methods either did not exist or did not present data in a way which would allow the results to be generalised to a wide range of high-risk patients. We therefore sought to conduct meta-analyses of all proper RCTs assessing one (or more) of these methods among patients undergoing surgery, or among patients who had a medical condition conferring an increased risk of venous thrombosis. Our aim was to identify all such trials reported prior to December 2001. We reviewed three types of mechanical compression methods (graduated compression stockings, intermittent pneumatic compression and footpumps), two pharmacological methods (oral anticoagulants and dextrans) and RA (as compared with GA).

Mechanical compression methods

Mechanical compression methods reduced the risk of DVT by about two-thirds when used as the only form of thromboprophylaxis, and by about half when added to a pharmacological method such as low-dose heparin. These benefits were similar irrespective of the particular mechanical method used, and similar in each of the surgical groups studied. Since PVT is more likely to fragment and cause PE, we were particularly interested in assessing effects on PVT. Mechanical methods appeared to reduce the risk of PVT by about half, although this result may be subject to reporting bias since only a minority of trials reported PVT as a specific outcome. There was also an apparent reduction of about two-fifths in the risk of PE, suggesting that mechanical compression methods do not merely prevent the local consequences of leg thrombosis, but might also protect against more severe systemic embolic sequelae.

Our meta-analysis differs from systematic reviews conducted previously because we sought to include only properly randomised trials, and we included trials involving all of the main types of mechanical thromboprophylaxis (GCS, IPC, footpumps). Previous reviews examining specific parts of this randomised evidence[132–136] have, however, reached broadly similar conclusions concerning the effects of mechanical compression methods on DVT, but, because of their more limited scope, did not identify clear benefits on PVT or PE.

Hence this more comprehensive set of meta-analyses of the effects of all compression methods in all high-risk conditions – surgical and medical – is important. They demonstrate that such methods are also likely to protect against the more serious thrombotic outcomes of PVT and PE. Our review also demonstrated clearly that mechanical methods are effective even among patients who are already receiving a pharmacological method of thromboprophylaxis, such as low-dose heparin or aspirin, reducing the risk of DVT by about half in these circumstances. The THRIFT guidelines currently state that compression and pharmacological methods do not have additive effects, so these may need to be updated in the light of our review.[4]

The benefits of mechanical compression appeared similar among the different surgical patients studied, most of whom were undergoing general surgery, elective hip replacement or, in the case of IPC, neurosurgery. There were few trials among patients undergoing knee surgery or surgery for hip fracture, nor were there many trials among patients with major trauma or spinal cord damage, or among seriously ill patients requiring intensive care, or among medical patients with high-risk conditions such as stroke or cancer.[137]

The striking consistency of the two-thirds reduction in the risk of DVT among the categories that were studied suggests that these benefits would be likely to translate to other contexts. Indeed, contrary to the claims of other authors,[138] since the size of the absolute reduction in the risk of DVT is likely to be directly proportional to the baseline risk of DVT, the benefits may be particularly valuable in some ultra-high-risk categories.

The protective effects of each of the three methods appeared similar in indirect comparisons (*Figure 1*), and hence the choice of compression method for a particular patient may be best

decided on practical grounds. We did not assess any specific hazards of mechanical methods, but the main adverse effect of compression is patient discomfort, which occurs most often with IPC. Since GCSs are widely available and inexpensive, they may well be the most widely practicable method. Very few patients have a contraindication to mechanical compression. Poor tissue viability, most commonly due to peripheral arterial disease, may be aggravated by mechanical compression.[139] The presence of such arterial disease may be a relative contraindication (that is, the risks of ulceration would need to be weighed against the risks of DVT and PE in an individual patient prior to treatment). Similar considerations would apply in patients with fragile skin secondary to diabetes or thrombophlebitis. However, whether above-knee devices are more effective than below-knee devices is currently unknown, and large-scale trials are needed to address this question reliably. Once again, therefore, the choice may be made on practical grounds. It seems likely that below-knee devices will be the usual choice because they are cheaper and more practicable, with no evidence (as yet) that they are less effective.

Pharmacological methods

Oral anticoagulants

Oral anticoagulants reduced the risk of DVT by about half, while the risk of major bleeding was approximately doubled. There did appear to be some variation in effectiveness of oral anticoagulants in different surgical procedures, but it was unclear whether this reflected true differences, confounding by the anticoagulant intensity or the play of chance. Since mechanical thromboprophylaxis is likely to be appropriate in most patients at risk of venous thromboembolism, whether an oral anticoagulant is effective as monotherapy is of less relevance than whether an oral anticoagulant can add to the effects of a mechanical compression method. However, since only three trials among a total of 258 patients had assessed this question, the results were inconclusive. Since oral anticoagulants were highly effective when used as monotherapy, however, and the protective effects of oral anticoagulants as adjunctive therapy to either a pharmacological or mechanical method were statistically compatible to those observed when used as monotherapy, it seems likely that oral anticoagulants would add to any protective effects of mechanical compression methods.

Oral anticoagulants also appeared to reduce the risk of PVT by about half, but, as was the case for mechanical compression methods, this result may be subject to selection bias since only a minority of trials reported this outcome. Likewise, the apparently large protective effect on PE [odds reduction 79% (25)] may be somewhat unreliable. Our results update and extend the findings of a previous meta-analysis of trials of oral anticoagulant therapy, which was limited to trials among patients undergoing hip surgery.[140] This meta-analysis included nine trials, three of which were not included in our own review because they did not systematically record VTE. The estimate of effect on PE was broadly similar to that reported in the present meta-analysis.

Direct and indirect randomised comparisons between anticoagulant regimens of differing intensity were inconclusive, but did raise the possibility that moderate intensity regimens (mean INR $\approx$ 3) might be more effective for preventing DVT than fixed low-intensity regimens (INR $<$ 2.5). However, there were too few bleeds recorded to assess possible differences in bleeding risk. Only a few trials had assessed the effects of fixed 'mini-dose' (that is, very low-intensity) regimens, where the INR is generally around 1.5, so the efficacy and safety of such regimens could not be established reliably.

As compared with the low-dose heparin or LWMH regimens studied (that is, the currently recommended pharmacological thromboprophylatic treatment among surgical patients), the oral anticoagulant regimens appeared somewhat less effective at preventing DVT, but they also caused less major bleeding. Oral anticoagulant regimens are inconvenient because they require regular laboratory monitoring of INR and dosage adjustments, and aspirin, which does not require such monitoring, may also be given orally. The current place of oral anticoagulant regimens for venous thromboprophylaxis remains substantially uncertain. It is possible, however, that fixed 'mini-dose' warfarin may add to the protective effects of other oral pharmacological agents, such as aspirin, when there is a persisting risk of VTE requiring longer term treatment, and RCTs addressing this question would be helpful.

Dextran

The effects of dextran regimens appeared similar to those observed for oral anticoagulant regimens, reducing the risk of DVT by about half, irrespective of the molecular weight of the dextran regimen used and increasing the risk of major bleeding around 3-fold. As for oral anticoagulant regimens, there was some evidence that the effectiveness of

dextrans might vary according to the type of surgical procedure, but the reasons for this heterogeneity could not be established reliably. Too few studies had reported data on PVT or PE to provide reliable estimates of effect on these outcomes.

As was the case for oral anticoagulants, therefore, although dextran appears moderately protective, it is associated with an excess risk of bleeding (and, in addition, dextran may also cause fluid overload and, rarely, anaphylaxis). The protective effects of dextran on DVT were about half those of low-dose heparin or LMWH regimens, but heparin regimens were associated with a greater risk of major bleeding. It remains unclear, therefore, whether there are particular clinical circumstances when, for a patient receiving a mechanical compression method, dextran would be considered as an adjunctive therapy ahead of a heparin-based regimen or aspirin.

Regional anaesthesia

RA reduced the risk of DVT by about half as compared with GA, and these benefits appeared similar in each of the surgical settings studied.

These results are consistent with those previously reported among patients undergoing hip fracture surgery.[141,142] In one previous review, 15 trials were identified, of which three systematically reported DVT outcomes. DVT incidence was reduced by 60%, but there was no significant effect on PE. Major bleeding was not reported, although there was no difference in the odds of receiving a blood transfusion. Mortality at 1 month was reduced among those allocated to regional anaesthesia, but there was no benefit remaining after 1 year. A Cochrane Review included three trials of RA versus GA which measured DVT, and found a significant risk reduction of 36%.[142] Ten trials reported PE as a cause of death, and among these trials there was no evidence of any difference between these two methods.

Since the initiation of our review, a more comprehensive meta-analysis, not only of the effects of RA on VTE, but also of effects on mortality and other important outcomes, has been published.[143] Our estimates of effects on DVT and on bleeding risks were broadly similar to those reported in this study, but the authors of the latter also demonstrated that RA conferred a reduced risk of other postoperative complications, such as myocardial infarction.

RA has most often been assessed as an alternative to GA among patients undergoing orthopaedic surgery, but for some types of general surgery where RA is possible it might be expected that similar benefits might accrue. This might be a useful topic for future RCTs.

Methodological considerations

We sought to identify trials through a sensitive electronic search strategy (including non-English language articles), and we also requested information from manufacturers and trialists. Among the trialists' responses to our requests for clarification or additional trial data, a high proportion resulted in material changes to numbers of events reported in publications. For example, this was sometimes because numbers originally reported had not been 'intention-to-treat', or investigators had counted total numbers of legs affected by thrombosis rather than the numbers of patients with at least one thrombosis. Since we were able to obtain responses from only about one-third of trialists, it might be inferred that the data presented here may only be approximately correct. Those trialists who we were unable to contact might have provided important material which would have excluded some trials and altered results for others. This potential for bias was explored by assessing effects among trials where published data only were available, and those where we received clarification from trialists, and we were unable to demonstrate any statistical heterogeneity between the two groups. However, the inherent uncertainty that is inevitable when results from a published paper are incorporated into a meta-analysis without corroboration by the trialist remains a potential source of bias, and needs to be taken into account when interpreting results.

Our review sought to include only properly randomised and unconfounded trials with systematic radiological assessment of DVT, and this should have helped to reduce the potential for bias in assessment of treatment effects. Other sources of bias also need to be considered, however, and we therefore conducted sensitivity analyses based on particular design features of the available trials. For example, trials of mechanical compression methods were not placebo controlled and, in principle, this might bias ascertainment or reporting of outcomes. Sensitivity analyses showed, however, that the results among trials using blinded assessment of DVT were similar to those using open assessment, suggesting that the bias resulting from a lack of blinding of assessment is likely to be small. We

found no significant effects on the results in relation to the clarity of randomisation method, or use of venography to assess outcomes or whether data were confirmed by trialists.

A more serious potential bias, and one which is difficult to quantify, might result if only the more promising studies were to be published, resulting in an overestimation of the treatment effect. We have not conducted formal analyses using so-called 'funnel plots', because such analyses have limited value when there is no large trial to provide an indication of the true treatment effect, and hence of the line about which symmetry of smaller trials might be expected. However, although doubts remain about the size of any benefits, it is clear that each of the methods tested – mechanical, pharmacological and anaesthesia – confers at least moderate benefit and so they are each of potential value. For example, since mechanical methods have few hazards against which benefits need to be weighed, mechanical compression is likely to produce a clinically worthwhile net benefit in the majority of patients at risk of venous thrombosis, even if its true effectiveness is somewhat less than that estimated here.

There was some evidence, albeit indirect, that our estimates of the size of the protective effects of oral anticoagulants and dextrans might be biased, although we cannot quantify this bias. Previous meta-analyses have suggested that both low-dose heparin and LMWH reduce the risk of DVT by about two-thirds.[5] This meta-analysis suggested that oral anticoagulants reduced the risk of DVT by about half, so it might be expected that an oral anticoagulant regimen would be about 25% less effective (relative risk = 0.5/0.67 = 0.75) than a heparin regimen. However, when we assessed trials involving a head-to-head randomised comparison of an oral anticoagulant and a heparin regimen, we found that oral anticoagulant regimens were only about half as effective as heparin regimens. These conflicting findings suggest either that oral anticoagulants reduce DVT by less than half, or that direct comparisons of oral anticoagulant and heparin regimens have overestimated the efficacy of the heparin regimens studied (or that some more complicated combination of these alternatives explains the findings). It is perhaps wise, therefore, to allow for the possibility that hidden biases in this meta-analysis may have inflated (or reduced) effect sizes, and that the qualitative findings will be more reliable than any precise quantitative formulation.

Trials using clinical assessment as the sole method of identifying DVT were excluded, as this method is insensitive and may be subject to observer bias. DVT is difficult to assess reliably, and although a range of diagnostic techniques have been included in this review, they are of generally low sensitivity compared with the gold standard of venography. We assessed whether this might have introduced bias in assessment by conducting sensitivity analyses among those trials that used venography only as confirmation of a diagnosis and those that used it systematically. The results were similar in the two groups of trials, suggesting that differences in the method of DVT assessment are unlikely to have substantially biased our results.

PE is also difficult to assess reliably, and most trials relied on initial clinical suspicion as the ascertainment method rather than systematic scanning. Such clinical assessment is insensitive and a decision whether to scan may have been influenced by knowledge of treatment allocation. Since most trials were not placebo controlled, we cannot exclude such bias, and this adds to the statistical uncertainty engendered by the small numbers of such events (and hence wide CIs) around estimates of effects on such emboli.

Balancing absolute risks and benefits

The results presented in this report are remarkably consistent in showing that, for particular approaches, the relative reductions in thromboembolic events and the relative increases in bleeding risks are broadly comparable for a wide range of different clinical circumstances. We have avoided calculating absolute benefits and risks directly from the available data, because such estimates might well prove unreliable in view of a decline in the risk of venous thrombosis that has occurred since the 1970s and 1980s, when many trials were conducted. Moreover, the risks may vary substantially between different surgical procedures, so estimates of absolute benefits and risk from the trial data would be determined by the particular patients who were studied. However, given that the proportional benefits and risks are consistent, the absolute benefits and risks resulting from a particular thromboprophylatic treatment studied in this report can be simply estimated by applying the relevant risk ratios (extrapolated from the odds ratios presented here) to the baseline risks that are currently observed in association with a given operation (or medical condition). This report has not reviewed risk factors for VTE; categorisation of patients into low, medium and high risk can be found in a recent International Consensus Statement and THRIFT group publications.[3,4]

Chapter 5
Conclusion

Implications for policy and practice

The risk of VTE in hospitalised patients has declined owing to changing surgical and anaesthetic practice, but it is still an avoidable cause of mortality and morbidity. Despite the evidence available from numerous trials of thromboprophylactic methods, there is still debate about how to apply this evidence. There are three main conclusions from this review:

1. In the absence of a clear contraindication (such as severe peripheral arterial disease), patients undergoing a surgical procedure would be expected to derive net benefit from a mechanical compression method of thromboprophylaxis (such as GCSs), irrespective of their absolute risk of VTE.
2. Patients who are considered to be at particularly high risk of VTE may also benefit from a pharmacological thromboprophylactic agent, but since oral anticoagulant and dextran regimens are substantially less effective at preventing DVT than standard low-dose unfractionated heparin or LMWH regimens, they may be less suitable for patients at high risk of VTE, even though they are associated with less bleeding.
3. Whenever feasible, the use of RA as an alternative to GA may also provide additional protection against VTE.
4. There is little information on the prevention of VTE among high-risk medical patients (such as those with stroke), so further RCTs in this area would be helpful.

Implications for future randomised trials

The review has defined four key areas where further randomised trials would be helpful:

1. prevention of VTE with mechanical methods among high-risk medical patients (such as those with stroke)
2. comparison of above-knee versus below-knee stockings
3. addition of a pharmacological method of thromboprophylaxis to a compression method among moderate-risk patients
4. intensification of pharmacological thromboprophylaxis (for example, with mini-dose warfarin) among high-risk patients already receiving combined mechanical and pharmacological thromboprophylaxis.

Assessment of patient compliance should be undertaken in such studies, and further research into patient preferences for the different modalities undertaken.

Implications for consumers

VTE is an important complication of surgery (except minor procedures) and of most medical illnesses requiring hospitalisation. It can prove fatal in some cases. However, there is good evidence that the risk of VTE can be reduced substantially by simple application of agents that compress the lower limbs, such as GCSs. These may not be sufficient to reduce the risk in people who have conditions that make them more susceptible to VTE. In such cases, agents to thin the blood can be used, the most effective being heparin-type drugs (which have to be administered by injection) or aspirin (which can be taken orally).

Wherever possible, patients should have RA rather than a GA, as this reduces the risk of VTE occurring.

Patients admitted to hospital should expect assessment for their risk of VTE and use of these agents as indicated.

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Contribution of authors

Paul Roderick (Reader in Public Health), Colin Baigent (Reader in Clinical Epidemiology), and Rory Collins (Professor of Medicine and Epidemiology) designed the study, supervised the collection and analysis of the data, and wrote the manuscript. Gill Ferris (Research Assistant) was responsible for the initial data collection, whilst Heather Halls (Research Assistant) and Kate Wilson (Research Assistant) organised the data extraction. Deborah Jackson (Research Assistant) provided general administrative assistance during the project.

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Appendix 1

Literature search strategies for electronic databases

MEDLINE search strategy

1. RANDOMIZED-CONTROLLED-TRIAL
2. CONTROLLED-CLINICAL-TRIAL
3. RANDOMIZED-CONTROLLED-TRIALS#
4. RANDOM-ALLOCATION#
5. DOUBLE-BLIND-METHOD#
6. SINGLE-BLIND-METHOD#
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. ANIMAL.DE. NOT (HUMAN.DE. AND ANIMAL.DE.)
9. 7 NOT 8
10. CLINICAL-TRIAL
11. CLINICAL-TRIALS#
12. CLIN$4 ADJ TRIAL$1.TI.
13. CLIN$4 ADJ TRIAL$1.AB.
14. (SINGL$ OR DOUBL$ OR TREBL$ OR TRIPL$) ADJ (BLIND$ OR MASK$).TI.
15. (SINGL$ OR DOUBL$ OR TREBL$ OR TRIPL$) ADJ (BLIND$ OR MASK$).AB.
16. PLACEBO$1
17. RANDOM$7.TI.
18. RANDOM$7.AB.
19. RESEARCH-DESIGN#
20. 10 OR 11 OR 12 OR 13 OR 14 OR 16 OR 17 OR 18 OR 19
21. ANIMAL.DE. NOT (HUMAN.DE. AND ANIMAL.DE.)
22. 20 NOT 21
23. 22 NOT 9
24. COMPARATIVE-STUDY
25. EVALUATION-STUDIES#
26. FOLLOW-UP-STUDIES#
27. PROSPECTIVE-STUDIES#
28. (CONTROL$ OR PROSPECTIV$ OR VOLUNTEER$).TI.
29. (CONTROL$ OR PROSPECTIV$ OR VOLUNTEER$).AB.
30. 24 OR 25 OR 26 OR 27 OR 28 OR 29
31. ANIMAL.DE. NOT (HUMAN.DE. AND ANIMAL.DE.)
32. 30 NOT 31
33. 32 NOT (9 or 23)
34. 9 or 23 or 33
35. deep adj vein adj thrombosis
36. venous adj thrombosis
37. thrombophlebitis#
38. thromboprophylaxis
39. pulmonary-embolism#
40. 34 or 35 or 36 or 37 or 38 or 39
41. dextrans#
42. warfarin#
43. dihydroergotamine#
44. compression
45. bandages#
46. compression not (compression adj ultrasound)
47. foot adj pump$1
48. av adj impulse$1
49. greenfield adj filter$1
50. regional anesthesia or (regional anaesthesia)
51. anethesia-conduction#
52. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 34 and 40 and 52
54. ANIMAL.DE. NOT (HUMAN.DE. AND ANIMAL.DE.)
55. 53 not 54

EMBASE search strategy

1. RANDOMIZED-CONTROLLED-TRIAL
2. CONTROLLED-STUDY#
3. RANDOMIZATION#
4. DOUBLE-BLIND-PROCEDURE#
5. SINGLE-BLIND-PROCEDURE#
6. CLINICAL-TRIAL#
7. CLINICAL-TRIAL
8. CLIN$4 ADJ TRIAL$1.TI
9. CLIN$4 ADJ TRIAL$1.AB
10. (SINGL$ OR DOUBL$ OR TREBL$ OR TRIPL$) ADJ (BLIND$ OR MASK$).TI.
11. (SINGL$ OR DOUBL$ OR TREBL$ OR TRIPL$) ADJ (BLIND$ OR MASK$). AB
12. PLACEBO$
13. PLACEBO#
14. RANDOM$7.TI.
15. RANDOM$7.AB.
16. RESEARCH ADJ DESIGN
17. COMPARISON#
18. EVALUATION-AND-FOLLOW-UP#
19. PROSPECTIVE ADJ STUD$3
20. PROSPECTIVE-STUDY#
21. (CONTROL$ OR PROSPECTIV$ OR VOLUNTEER$).TI.
22. (CONTROL$ OR PROSPECTIV$ OR VOLUNTEER$).AB
23. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22

24. DEEP ADJ VEIN ADJ THROMBOS$2
25. VENOUS ADJ THROMBOS$2
26. THROMBOPHLEBITIS#
27. THROMBOPROPHYLAXIS
28. LUNG-EMBOLISM#
29. PULMONARY ADJ EMBOLISM$1
30. 24 or 25 or 26 or 27 or 28 or 29
31. COMPRESSION NOT (COMPRESSION ADJ ULTRASOUND)
32. BANDAGES-AND-DRESSINGS#
33. BANDAG$3.TI
34. BANDAG$3.AB.
35. FOOT ADJ PUMP$
36. AV ADJ IMPULS$
37. GREENFIELD ADJ FILTER$
38. REGIONAL-ANESTHESIA#
39. REGIONAL ADJ ANESTHESIA OR (REGIONAL ADJ ANAESTHESIA)
40. DEXTRAN#
41. WARFARIN#
42. DIHYDROERGOTAMINE
43. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44. 23 and 30 and 43
45. ANIMAL# NOT (ANIMAL# AND HUMAN#)
46. 44 not 45

Derwent search strategy

1. clin$4 adj trial$1
2. random$7
3. (singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)
4. placebo$
5. research adj design
6. comparative adj stud$3
7. evaluation adj stud$3
8. follow adj up adj stud$3
9. control$ or prospective$ or volunteer$
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. deep adj vein adj thrombos$2
12. venous adj thrombos$2
13. thrombophlebitis or thromboprophylaxis
14. pulmonary adj embolism$1
15. lung adj embolism$1
16. 11 or 12 or 13 or 14 or 15
17. dextran$
18. warfarin$1 or coumarin$1
19. dihydroergotamine$1
20. compression or bandage$1
21. foot adj pump$1
22. greenfield adj filter$1
23. (regional adj anesthesia) or (regional adj anaesthesia)
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 10 and 16 and 24

BIOSIS search strategy

1. randomised controlled trial*
2. randomized controlled trial*
3. controlled-clinical trial*
4. random allocation
5. random* allocation*
6. double blind*
7. single blind*
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. clinical trial*
10. (singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)
11. placebo*
12. random*
13. research design
14. 9 or 10 or 11 or 12 or 13
15. (comparative study) or (comparative studies)
16. (evaluation stud*) or (evaluation study)
17. (follow-up stud*) or (follow up study)
18. prospective stud*
19. control* or prospectiv* or volunteer*
20. 15 or 16 or 17 or 18 or 19
21. 8 or 14 or 20
22. deep adj vein adj thrombos$2
23. venous adj thrombos$2
24. thrombophlebitis or thromboprophylaxis
25. pulmonary adj embolism$1
26. lung adj embolism$1
27. 22 or 23 or 24 or 25 or 26
28. dextran$
29. warfarin$1 or coumarin$1
30. dihydroergotamine$1
31. compression or bandage$1
32. foot adj pump$1
33. greenfield adj filter$1
34. (regional adj anesthesia) or (regional adj anaesthesia)
35. 24 or 25 or 26 or 27 or 28 or 29 or 30
36. 21 and 27 and 35

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The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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