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

P Roderick, G Ferris, K Wilson, H Halls, D Jackson, R Collins and C Baigent



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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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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.



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List of abbreviations

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

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

X

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 lowdose 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 I 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 platelets¹⁸ 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 illdefined 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 Antithrombotic 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 postrandomisation 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 2*P*.

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, anticoagulants, 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.

GCS vs control Allan, 1983	ŝ	randomi- sation	background agent (all patients)	Ireatment I Ireatment regimen I	Ireatment regimen I	Ireatment / Ireatment regimen 2		speciality	DVI method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
	23	٩	None	ĸ	l d preop- d7 postop	None	None	S	ΕŢ	z	~	d 1,2,3,5,7 postop	None	None	z	Rand nk
Barnes, 1978	24	۹.	None	Thigh-length	Duration of hospn (inc surgery)	None	None	표	DUS	≻	z	Preop- discharge (alternate days)	Scan	z	≻	Seq
Holford, 1976	25	۹.	None	Thigh-length	I d preop- 1 full ambulation (d 4-5 postop)	None p)	None	S	FUT	z	ระ	Preop, then d 1–6 postop (daily)	Scan	None	z	Env nk
Inada, 1983	26	_	None	Thigh-length	l d preop– d 8 postop	None	None	S	FUT	≻	su	I h preop- N d I,3,5 postop	None P	None	z	Rand ns
Muir, 2000	27	д.	None	Thigh-length	Adm-d 7	None	None	MED	DUS	z	≻	d I, d 7	Scan	z	z	Env nk
Rosengarten, 1970) 28	L	None	Knee-length	Preop- discharge or d 14 postop	None	None	S	FUT	z	ะ	d 1–14 postop/ discharge (daily)	None	None	z	Rand ns
Shirai, 1985	29	_	None	Thigh-length	l d preop – mobile	None	None	S	FUT	z	su	No details	None	None	z	Rand ns
Turner, 1984	30	۵.	None	รม	Admission– discharge	None	None	Ъ	FUT	z	≻	d I postop discharge (daily)	None	None	z	Rand c
Turpie, 1989	m	۹	None	Thigh-length	Admission- discharge or d 14 postop	None	None	R	FUT/IPG Y	≻	≻	Study entry- discharge/ d 14 postop (daily)	Fatal pm	≻	≻	Seq
GCS combination Bergqvist, 1984	32	_	Dex	Thigh-length	l d preop- d 7 postop (total 7 d)	None	None	ß	FUT	z	≻	Preop then d 1,3,5,7 postop (daily if FUT+); obs 30 d	Ропе	е N	≻	Rand c
Fredin, 1989	33	۵.	Dex	Thigh-length	l d preop- d 14 postop	None	None	Ξ	FUT	≻	≻	Preop, d 1,3,5,7; veno d 10	Scan/ pm	≻	≻	Seq

TABLE 1 Trial characteristics – compression methods

	Author, year	Ref. No.	Unit of randomi- sation	Background agent (all patients)	Treatment	Treatment regimen	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
35 L Agina Tughtength Admiss Note Note Note Note Note Note Note 2 pactor. Note Note Note Note Note Note Note Note	Kalodiki, 1996	34	۵.	ГММН	Thigh-length	preop- discharge (8–12 d)	None	None	Ŧ	Veno	z	~	d 8–12 post-op (once)	Scan sys	~	~	Pharm
67 1 FC Tigh-leght Prop. Note 57 FU N Respective function of the second of	Kierkegaard, 195	33 35	-	Aspirin	Thigh-length	Adm− discharge (≥8 d)	None	None	MED	FUT	≻	۲ ۲	d 2 postop– adm–dischar _{ (alternate; daily if FUT+)	None	None	≻	Seq
37 P Dev Kneelength rs None EH EUT Y N di-10 None None None 37 P Hep Kneelength Id prop- None No	Mellbring, 1986	67	-	D	Thigh-length	Preop- mobile	None	None	S	FUT	z	S	Preop then d 1,3,5,7,9 postop (daily if FUT+)	None	None	≻	Env
37 P Hep Knee-length Id prop. None G2 Tr N N No	Ohlund, 1983	36	۵.	Dex	Knee-length	sı	None	None	Ŧ	FUT	≻	z	d 1–10 postop (4–5×/patient		None	≻	Rand c
68 L PC Trigh-length Freep None None GS FUT Y rs Udpreep None None G3 FUT Y rs Udpreep None None G4mb-1 and	Rasmussen, 1986		۵.	Нер	Knee-length	I d preop– mobile (or ≥d 5 postop)	None	None	ß	Tc Plasmin		SU	d 4–5 postop (once)	None	None	z	Rand ns
38 P Hep Trigh-length preop- discharge/ discharge/ discharge/ discharge/ discharge/ discharge/ discharge/ discharge/ discharge/ discharge/ discharge/ discharge/ mobile mobile tength, PC tength, PC teng teng tength, PC tength, PC tength, PC teng tength, PC	Scurr, 1987	68	_	R	Thigh-length	Preop (adm)– full ambulation	Чоле	Лопе	S	FUT	~	รน	I d preop (DUS/IPG), d I ,3,5,7 post-op (FUT), d 5-7 (DUS/IPG)	None	None	Z	Rand ns
P Hep Thigh-length Prop- None GS FUT Y d 1,3,5,7 Scarl None Y nobile mobile mobile mobile postop Xray None Y P None ns, Prop (nol)- None EH/EK FUT Y ns Scanl None Y rype ns, Prop (nol)- None EH/EK FUT Y ns Scan Y Y	Wille-Jorgensen 1985		٩	Hep	Thigh-length	preop– discharge/ d 7 postop	None	None	S	FUT	≻		Preop, immediately postop, d 1,3,5,7 postop	Scan if FUT+	≻	≻	Seq
40 P None ns, Preop (nol)- None None EH/EK FUT Υ Υ ns Scan Υ Υ single postop (ol)- not specified	Wille-Jorgensen 1991 PC vs control	II, 39	۵ ـ		Thigh-length Length, type	Preop- mobile <i>IPC</i>	None	None	ß	FUT	≻	≻	d I,3,5,7 postop	Scan/ Xray	None	≻	Seq
	3achmann, 1976		۹	None		Preop (nol)– postop (ol)– not specified			EH/EK	FUT	≻	≻	٤	Scan	≻	≻	Rand nk

Author, year	Ref. No.	Unit of randomi- sation	Background agent (all patients)	Treatment I	Treatment regimen l	Treatment 2 Treatment regimen 2		Speciality	DVT method	Venogram confirmed?	DVT Timing of assessment DVT blinded assessmen	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
Blackshear, 1987	4	_	None	ns, sequen	Periop– 24 h postop	None	None	ß	SND	z	su	Preop + postop	None	None	z	Rand nk
Butson, 1981*	42	٩	None	Knee-length, single	Anaesthesia– 2–4 d postop/ ambulation	None	None	S	FUT	≻	S	d I-d 14 postop	Fatal only pm	None	z	Env nk
Bynke, 1987	43	_	None	Thigh-length, single	Periop	None	None	NR	FUT	≻	su	Preop, d 3, d 7 postop	None	None	z	Rand c
Clark, 1974	4	_	None	Knee-length, single	Anaesthesia for 17–23 h	None	None	S	FUT	z	~	Preop, d I, d 3 postop	None	None	≻	Seq
Clarke-Pearson A, 1984	, 45	۵.	None	Knee-length, single	Anaesthesia– 5 d postop	None	None	Ъ	FUT/IPG Y	~	~	FUT: d I postop– discharge (alternate), IPG: preop, d 5 postop	Scan angio	≻	≻	Seq
Clarke-Pearson B, 1984	, 46	٩	None	Knee-length, single	Periop	None	None	Ğ	FUT/IPG Y	≻	~	IPG preop- disch (alternate), FUT preop- disch (daily)	Scan angio	≻	~	Seq
Coe, 1978	47	۹.	None	Knee-length, single	Anaesthesia– discharge	None	None	Я	FUT	≻	≻	d l postop– discharge (daily)	Scan or angio	None	z	Rand nk
Fisher, 1995	48	۵.	None	Thigh-length, sequen	Postop- ambulation	None	None	HF/PF	Dopp	≻	~	Dopp: adm, every 5 d postop to ambulation, Scan: d 3–d 5 postop	Scan sys	≻	z	Seq
Gallus, 1983	49	۹.	None	Knee-length, single	Intraop–d 7 postop	None	None	Ш	IPG/FUT Y	≻	~	FUT daily postop, IPG d 7 postop, Veno d 7 postop	None	None	~	Seq
Hills, 1972	50	<u>م</u>	None	Knee-length, single	Periop– ambulation (I d postop)	None	None	GS	FUT	z	su	d I-d 7 postop	None	None	z	Env nk
																continued

	Author, year	Ref. No.	Unit of randomi- sation	Background agent (all patients)	Treatment	Treatment regimen I	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT Timing of assessment DVT blinded assessmen	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
3 P Nue Tigh-tert, hore, h	1ull I, 1979	5	<u>م</u>	None	Knee-length, single	Postop– discharge/ 17 d	None	None	出	FUT	~	~	Veno d 7-d 10 or d 14-17 postop	None	None	z	Seq
31 P None Tigh-Leght, Wrthn 3/1, None None Y Tigh-Leght, Wrth 3/1, None None Y Y Y Tigh-Leght, Wrth 3/1, None None Y </td <td>Jull II, 1990</td> <td>52</td> <td>٩</td> <td>e Z</td> <td>Thigh-length, sequen</td> <td>Postop– discharge/ 14 d</td> <td>e Z</td> <td>None</td> <td>Ш</td> <td>FUT/IPG</td> <td>~</td> <td>~</td> <td>FUT d I-d 14 postop, PGG d 5 postop then alt d until disch, veno d 14 postop or disch</td> <td>Scan</td> <td>></td> <td>z</td> <td>Rand ns</td>	Jull II, 1990	52	٩	e Z	Thigh-length, sequen	Postop– discharge/ 14 d	e Z	None	Ш	FUT/IPG	~	~	FUT d I-d 14 postop, PGG d 5 postop then alt d until disch, veno d 14 postop or disch	Scan	>	z	Rand ns
74 P Note ns sequen Ira-op- Note G1 0.01 Y Peoptien Note Note 0.1 0.1 0.1 0.01 Y Peoptien Note 0.1 0.1 0.1 0.1 0.1 0.1 0.01 Y Peoptien Note 0.1	.nudson, 1994	23	٩	None	Thigh-length, sequen	Within 24 h or admiss, dur ns	None	None	Ŧ	DUS	z	ะย	d I–d 2I postop (at 5–7 d intervals)	Angio	รน	z	Rand ns
55 P Note Kree-length, Anastresia- Note Note Note Kree-length, Anastresia- Note Note<	osir, 1996	54	٩	None		Intra-op– 48 h postop		None	S	SUD	z	≻	Preop then d I, d 3, d 30 postop		None	≻	Rand ns
56 P None Kneelength, Nol: None None Kneelength, Nol: None None Feop-d5 notsys ns Y 57 P None Kneelength, d1-d5 None NR FUT N None None None None NR FUT None None <t< td=""><td>killman, 1978</td><td>55</td><td>۵.</td><td>None</td><td>Knee-length, single</td><td>Anaesthesia– ambulation (<17 d postop)</td><td>None</td><td>None</td><td>R</td><td>FUT</td><td>≻</td><td>≻</td><td>d I postop– discharge</td><td>None</td><td>None</td><td>z</td><td>Rand ns</td></t<>	killman, 1978	55	۵.	None	Knee-length, single	Anaesthesia– ambulation (<17 d postop)	None	None	R	FUT	≻	≻	d I postop– discharge	None	None	z	Rand ns
57 P Note Kree-length, d l-cl 14 Note Note FUT notsys ns Y sequen postop postop postop, d 1, d 14 Note Note Preop- pn only 58 P None Knee-length, Periop- None NR FUT ns Y Y 58 P None Knee-length, Retiop- None NR FUT Y N	ırpie I, 1977	56	۹.	None	Knee-length, single	Nol: admission, ol: d 1–d 5 post-op	None	None	R	FUT	z	รม	Preop–d 5 postop (14 d if non ambulant)		su	≻	Seq
58 P None Knee-length, Periop- None Nne NR FUT Y ns ns None None N ns d'6 postop	urpie II, 1979	57	٩	None	Knee-length, sequen	d 1– <d 14<br="">postop</d>	None	None	R	FUT/IPG	Y, not all	٤	FUT preop- <d 14<br="">postop, PPG: preop- d 3, d 5, d 7, d 10, d 14</d>	notsys pm only	SL	≻	Seq
	/eitz, 1986	58	٩		Knee-length, ns	Periop- d 6 postop	None	None	R	FUT	≻	SL	٤	None	None	z	Rand ns

Author, year Ref. No.													ä	Tahuha	
	Unit of randomi- sation	Background agent (all patients)	Treatment	Treatment regimen I	Treatment 2 Treatment regimen 2		Speciality 1	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	essment ded	data?	Method of randomisation
IPC combination Caprini, 1983 69	۵.	S	Thigh-length, sequen	Preop–3 d postop/ ambulant	2 eue N	None	Mixs	FUT/DUS N, some		٤	FUT: preop, postop then alt till amb, DUS: preop, postop then every 3 d till amb	Angio	٤	~	Елү
Lieberman, 1994 59	٩	Aspirin	Thigh-length, sequen	Postop- d 6-8 postop	None	None	ĒH	Veno I	z	~	d 6-d 8 postop	None	None	z	Rand nk
Pambianco, 1995 70	۵.	SCS	Thigh-length, single	night	None	None	MED	n sud	z	SU	Twice a week for 28 d/discharge	None	None	z	Rand nk
Rokito, 1996 71	ፈ	GCS	Thigh-length, sequen	Preop- d 5/7	None	None	SP	Śna	~	~	d 5-d 7 postop	None	None	z	Rand ns
Siragusa, 1994 60	д.	Heparin	ns, ns	su	None	None	EH	Veno 1	z	≻	d 10 postop	Scan, angio	۲	≻	Comp
Smith, 1978 61	٩	Dextran	ns, ns	Intraop	None	None	S	FUT	z		Preop- discharge/d 7 (alternate)	Scan	ะ	z	Rand nk
Turpie, 1989 31	۵.	GCS	Thigh-length, sequen	Periop-d 7	None	None	ĸ	FUT/IPG	~	~	FUT preop- d 14, IPG d 3, d 5, d 7, d 9, d 11, d 14	None	None	≻	Seq
Wautrecht, 1996 72	٩	900	Thigh-length, ns	Preop- d 10/ambulant	Vone	None	R	Veno 1	z	~	d 8–d 10 postop	Scan	SI	≻	Env
Footpump vs control Scurr, 1981 62	٩	None	Bilateral		None	None	ß	ET	~	SU	d I, 2, 3, 5, 7 None postop		None	z	Rand ns
Wilson, 1992 63	L	None	Foot of op leg Postop- d 9–10		None	None	X	Veno I	z	≻	d 9–10 postop (once)	Scan	SL	z	Rand ns
Footpump combination Fordyce, 1992 73	۵.	S	Foot of op leg Postop during sitting a bed res	t	Bilateral	Postop-ns h	H	Veno 1	z	≻	d 6–9 postop None		None	z	Seq
															continued

Author, year	Ref. No.	Unit of randomi- sation	Background agent (all patients)	Treatment I Treatment regimen I	Treatment regimen I	Treatment 2	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	۰	Hep/aspirin	Bilateral	Postop– discharge	H5000, A325	H d I, 3 A d 4, disch	Ш	DUS	~	~	Preop, d 7, d 14 postop	None	None	z	Rand ns
Above vs below knee-length Porteous, 1989 65	mee-lengt 65	th None	None	None	Preop- discharge	None	Preop-disch GS	ß	FUT	≻	ะน	Postop– discharge (alternate)	None	None	z	Rand ns
Williams, 1988	99	None	None	None	su	None	su	S	FUT	z	su	su	None	None	z	Env
Key to all tables Missing data na, not applicable, ns, not stated; nr, not recorded Unit of randomisation L, legs; P, patients	es le; ns, nc ation ts	x stated; nr, n	ot recorded													
Clinical setting CS, cardiac surge	ery, EH,	elective hip; E	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	G, gynaecology,	; GS, general su	ırgery; HF, hip 1	fracture; MED,	medical; Mix	xS, mixed;	NR, neurosurg	şery; PF, pelvi	c fracture; SP, s _i	pinal; TR, traur	ma; U, urology;	VS, vascula	r surgery
Venography method DUS, Doppler ultri	od Iltrasoun	d; FUT, fibrinc	Venography method DUS, Doppler ultrasound; FUT, fibrinogen uptake; IPG, impedance phlethysmograph; veno, venography. For PE: angio, angiography; fatal pm, PEs identified at post-mortem.	impedance phle	sthysmograph;	veno, venograp	hy. For PE: an§	gio, angiograf	phy; fatal p	am, PEs identifi	ed at post-me	ortem.				
Anticoagulant adjustment method INR, international normalised ra	justment al norme	· method ilised ratio; PT	Anticoogulant adjustment method INR, international normalised ratio; PT, prothrombin time; TT, thrombotest	ne; TT, thrombo	itest											
Randomisation method comp, on-site comput numbers not known if	nethod omputer own if cl	; env, sealed n osed or open;	Randomisation method comp, on-site computer; env, sealed not opaque 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, random tot specified; rand o, open list of random numbers; seq, sequentially numbered sealed opaque envelope	pe; env nk, env« isation method i	elope not know not specified; r	/n if sealed or c and o, open list	paque; pharm. of random nu	, pharmacy c mbers; seq, s	oded cont sequential	wn if sealed or opaque; pharm, pharmacy coded container administered sequentially; rand rand o, open list of random numbers; seq, sequentially numbered sealed opaque envelope	ared sequentic aled opaque (ally; rand c, clo: envelope	sed list of rand	om numbers; ri	and nk, list o	of random
Treatment detail aceno, acenocou nol, non-operate sequen, sequent	umarin; ¿ ed leg; oı ial; sc, su	adj, adjusted d bs, observed; ubcutaneously,	Treatment detail aceno, acenocoumarin; adj. adjusted dose; adm, admission; alt, alternate; bd, twice day; dex, dextran; dic, 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.	ion; alt, alternat ⁽ , operated leg; p daily; war, warfa	e; bd, twice dai vd, postdischar? ¤rin; w, week.	ly; d, day; dex, şe; periop, arou	dextran; dic, d ınd time of sur	licoumarol; d 'gery; phen, p	lisch, disch ohenproco	narge; fxd, fixed numon; plac, pla	l dose; h, hou 3cebo; po, by	r; intraop, durii mouth; postop	ng surgery; LM ., post surgery;	WH, low mole preop, before	cular weight surgery; nic	heparin; nicoumalone;
Other amb, ambulant;	pm, post	t-mortem; not	Other amb, ambulant; pm, post-mortem; notsys, no systematic assessment of pulmonary embolism; pmnch, found at post-mortem but not cause of death.	c assessment of	pulmonary em	bolism; pmnch,	found at post-	-mortem but	not cause	of death.						

≓. q												
Method of randomi- sation	Rand c	Pharm	Env	Rand c	bes	Rand ns	Rand nk	Seq	Rand o	Rand ns	Rand nk	Rand ns
Tabular data?	z	z	z	≻	z	z	z	z	≻	z	z	z
PE assessment blinded												
	s	su	па	su	su	па	па	su	па	SL	па	п
PE assessment	pm for fatal	na	na	na	X-ray	na	na	Scan	па	pm for fatal	ВП	pm for fatal
Timing of DVT assessment	3–4 w (once) pm for fatal	d I–d I4 postop/disch	d 5–d 12 postinjury	d 5 postop, DUS/IPG d 5	d 1–d 10 postop (daily)	d 1–d 10 postop (daily)	lmmed. postop disch	FUT d I–3 postop od, alt. IPG d 4–5 postop, alt. Veno 21 d	postop/discn d I-d 7 postop	l st-7th/ 10th days (daily)	I d pre-op, d I, d 2, d3 postop, then alt days	2–3 w post op, 25 had FUT alt days until d 7–10 postop
sment ed										_		
	≻	su	z	≻	ns	z	su	≻	≻	su	su	su
Venogram confirmed?	па	≻	na	≻	z	≻	≻	≻	z	z	≻	<i>≻</i>
B	Veno	ΕŢ	Veno	FUT	ΕŢ	FUT	FUT/DUS Y	FUT	FUT	ΕŢ	FUT	Veno/FUT Y
Speciality DVT meth	<u>ب</u> ۲	- -	۔ ۲	- 5	- 生	HF/EH I	- 5	ー 生	طر ا	MED	<u>-</u>	<u>َ</u>
2 Treatment regimen 2	None	None	None	None	None	None	None	None	None	None	None	None
Treatment Treatment 2 Treatment regimen I regimen 2	lone	None	None	None	lone	None	None	None	None	None	None	lone
tment Ti men l	Admission- None mobile	l w preop- N 3 w postop		eop-	Within 24 h None admission- mobile/3 m) d isch	Postop– N 21 d postop /dis	5 d preop- N d 14 postop	Admission– N ns		Admission- None ns
	Admissi mobile	3 – 8 8 6 7 6	Postop- d 14	l w pi disch	Within admissi mobile/	Premed- 2 w po	Mear	Postc 21 d /dis	5 d p d 14	Admi ns	Recovery room–ns	Adm ns
Treatment	Dic, PT 40 ms	Fixed low war	Phen, PT 2–2.5	Fixed low war	War, TT 10%	War, TT 5–15%	Fxd low + full	War, INR 2–2.7	Nic, PT 2-4	War, PT 10–35%	War, PT 1.5	War, TT 8–I 5%
Background agent (all patients)	None	None	None	None	None	None	None	None	None			
۰±	Å		Å			Ñ	Ñ		Ň	HEP	GCS	DEX
Unit of randomi- sation	Open	Placebo	Open	Placebo	Placebo	Open	Open	Placebo	Open	W vs H Open	Open	Open
Com- posi- tion	U	υ	υ	υ	υ	υ	υ	υ	U	W vs F	υ	U
Ref. No.	74	75	76	11	78	79	80	8	82	83	87	84
Author, year	OAC control/plac Borgstrom, 1965	Fordyce, 1991	Hamilton, 1970	MacCallum, 1990	Morris, 1976	Pinto, 1970	Poller, 1987	Powers, 1989	Taberner, 1978	OAC combination Habersberger, 1973	Hume, 1973	Korvald, I 973

 TABLE 2
 Trial characteristics – anticoagulants

Author, year	Ref. No.	Com- tion	Unit of Backg randomi- agent sation (all pa	Background agent (all patients)	Treatment Treatment Treatment 2 Treatment regimen regimen 2	Treatment regimen	Treatment 2		Speciality DVT meth	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomi- sation
Rokito, 1996	7	υ	Open	GCS	Low war PT 1.3–1.5	Preop- Noi d 4-5, postop	None	None	ß	DUS	~	≻	d 5–d 7 postop	na	na	-	Rand ns
van Geloven, 1977	85	υ	Placebo	HEP		d I postop- 30 d	p- None	None	MixS	FUT	z	su	opo	Scan if FUT	ns	z	Pharm
Woolson, 1991	86	υ	Open	IPC/GCS	Low war PT I.2–I.3	Preop-ns	None	None	Ш	Veno/DUS Most	S Most	z	7th postop day	Scan	รม	z	Rand c
OAC dose					Range		Dose										
Feller, 1992	88	Adj W vs fxd	na	Calf stim	War adj INR 2-4	Night Wa preop-d 3 postop (fixed) then adj	War I mg adj	Night preop– EH d 14 postop od	н	Veno	na	≻	d II–13 postop (once)	Scan	su	≻	Env
Poller, 1987	80	Adj nic vs fxd	па	None	Nic adj INR 2.4	5 d preop- War I mg disch (av 7.2 d stay)	War I mg	Mean 20 d preop- disch	Ъ	FUT/DUS Y	~	SL	lmmed. postop- disch	па	SL	z	Rand nk
OAC vs heparins Hume, 1973	87	ГОН	ца	ecs	War adj I.5 PTT	Recovery room–?	H5000IU sc	2 h preop, postop tds	Ш	FUT	≻	SL	l d preop, d l, d 2, d 3 postop then alt days	ца	ца	z	Rand ns
Poller, 1995	26	ГОН	na	None	War I mg	7 d preop- venogram (d 9–14) od	H5000IU sc	2 h preop- veno (d 9–14) tds	EH/EK	Veno	na	≻	d 9–14 n. postop (operated limb)	na b)	па	z	Rand nk
Taberner, 1978	82	ГОН	na	None	Nic adj 2-4 BCT	5 d preop- d 14 postop	H5000IU sc	2 h preop- d 7 postop bd	<u>ک</u>	FUT	z	≻	d I-d 7 postop	na	na	≻	Rand o
van Geloven, 1977	85	Ы	na	PLAC DEX	Aceno adj plac hep	d I postop–?	H4-5000IU sc plac OAC	2 h preop–? bd	MixS	FUT	z	su	d 1–d 10 postop od	Scan if FUT	su	z	Pharm
Friedman, 1994	98	ГММН	па	None	War adj PT I .2–I .5		H 50U/kg bd/90 od sc	Postop night- disch/mob (4-10 d)	EH/EK	IPG/DUS	≻	≻	d 4 postop disch (once)	Scan/angio	≻	~	Rand c
Gerhart, 1991	90	LMWH na	ца	None	War adj PT I–I.5	<u>-</u>	750U sc	Adm-d 9 postop bd + war d 7 postop-disch	또	FUT/IPG Y	≻	≻	d l postop- disch(daily)	Scan	ะ	z	Rand ns

2							
Method of randomi- sation	Rand nk	Rand ns	Comp	Rand nk	Pharm	Rand ns	Pharm
Tabular data?	z	z	z	z	≻	z	z
PE assessment blinded	~	su	SL	Па	≻	na	па
PE assessment	Scan/ angio/pm	Scan/ang/ I Xray	Scan/angio/ I pm				Scan/angio I
Timing of DVT assessment	d 10 postop (disch if earlier)	d 5–14 postop	Mean d 9 postop (scheduled d 14)	d 4–8 postop na or at disch	d 14 postop/ Scan disch	Mean d 7 ± 2 na	No timing details
DVT Venogram DVT method confirmed? assessment blinded	~	≻	≻	≻	≻	≻	su
Venogram confirmed?	ца	па	па	Па	DUS/IPG	z	Па
DVT method	Veno	Veno	Veno	Veno	Veno	Veno	Veno
Speciality	EH/EK	Ä	EH/EK	표	Ж	Ŧ	Ä
Treatment regimen 2	Preop-d 10 postop od	l d preop– d 14 postop/ disch bd	d l postop– d 14/disch od	2500 iu ± 2 h preop, 4 h postop, 5000 od		2 h preop od–disch	8 h postop– d 4–14 postop bd
Treatment 2	60IU/kg sc	LMWH 60 iu/kg sc	LMWH 75 iu/kg sc, plac war	2500–5000 iu 2500 iu ± sc, plac war 2 h preop, 4 h postop 5000 od	LMWH 30 mg d I postop- sc, plac war d 14 postop/ disch bd	LMWH preop, 5000 iu sc od	LMWH 30 mg sc
Treatment regimen I	Preop- d 10 postop	I d preop– LMWH d 14 postop 60 iu/kg sc /disch	lst postop night- d 14 post /disch	Night of surgery–?	Night of surgery- d 14 postop /disch	Preop night LMWH od postop preop, –disch 5000 iu	8 h postop- LMWH d 4-14 30 mg s postop
Treatment I	Aceno adj INR 2–3	War adj INR 2–3	War INR 2–3 plac H	War INR 2–3 plac H	War INR 2–3 Night (plac H surger d 14 p /disch	War PT I.4–I.5	War adj INR 2–3
Unit of Background Treatment I Treatment 2 Treatment Speciality DVT randomi- agent regimen 1 regimen 2 meth sation (all patients)	GCS	None	None	None	None	None	None
Com- Unit of posi- randomi- tion sation	па	Па	na	па	па	па	а
Com- tion	LMWH na	LMWH na	LMWH na	LMWH na	LMWH na	LMWH na	LMWH na
Ref. No.	6	92	93	94	95	96	89
Author, year	Hamulyak, 1 995	Heit, 1997	Hull III, 1993	Hull IV, 2000	Leclerc, 1996	Francis, 1997	Fitzgerald, 2001 89

 TABLE 2
 Trial characteristics – anticoagulants (cont'd)

Destront vs control Destront vs control Destront vs control None 70, 500 ml Periop, None 1979 Bergqvist I, 101 C Open None 70, 500 ml Periop, None 1980 Carter, 1973 102 C Placebo None 70, 500 ml Periop, None 1980 Evarts, 1971 103 C Placebo None 70, 500 ml Periop-ins None Fvarts, 1971 103 C Placebo None 70, 500 ml Periop-ins None Gruber, 1977 104 C Open None 40, 500 ml Periop-ins None Hubens, 1976 106 C Open None 40, 500 ml Periop-ins None Huttonen, 1977 104 C Open None 40, 500 ml Periop-ins None Huttonen, 1977 108 C Open None 70, 500 ml Periop-ins None Huttonen, 1977 108		regimen 2 method	Venogram d confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomi- sation
101 C Open None 70, 500 ml Periop, postop, d1, d3 102 C Placebo None 70, 500 ml Periop-not discharge 103 C Placebo None 70, 500 ml Periop-ns discharge 103 C Placebo None 70, 500 ml Periop-ns discharge 103 C Placebo None 40, 500 ml Periop-d1, d2 and d4 6 106 C Open None 40, 500 ml Periop then d2 and d4 77 108 C Open None 40, 500 ml Periop d1, d2 and d4 77 108 C Open None 70, 500 ml Periop d1, d2 and d4 77 108 C Placebo None 70, 500 ml Periop-d1, postop 8 109 C Open None 70, 500 ml Periop-d1, postop 8 109 C Open None 70, 500 ml Periop-d1, postop 9 100 C Open None 70, 500 ml Periop-d1, postop 10 C Open None 70, 500 ml Periop-d1, postop 9 109 C Open None 70, 5	None None	HF	z	~	Preop, d 1–10 postop (alt)	pm for fatal	ц	z	Env nk
C Placebo None 70, 500 ml Anaesthesia- discharge C Placebo None 1mw, 500 ml Periop-ns C Open None 40, 500 ml Periop-d l, d 2 postop C Open None 40, 500 ml Periop-d l, d 2 postop C Open None 40, 500 ml Periop then d 1 postop C Open None 40, 500 ml Periop then d 2 and d 4) C Open None 70, 500 ml Postop-d 1, postop C Open None 40,70, Anaesthesia- got d 4, C Open None 70,500 ml Periop-d 1, postop	None	GS/UR FUT	z	su	Preop, d 1–7 postop (daily/ alternate)/ disch	pm for fatal	ца	z	Rand nk
C Placebo None Imw, 500 ml Periop-ns (daily) C Open None 40, 500 ml Periop-d l, d 2 postop C Open None 40, 500 ml Periop then d 2 and d 4 C Open None 40, 500 ml Periop then d 1 postop C Open None 70, 500 ml Postop-d 1, d 1 postop C Open None 70, 500 ml Postop-d 1, d 2, d 6, d 9 C Open None 70, 500 ml Postop-d 1, postop C Open None 70, 500 ml Periop-d 1, postop	Vone None	GS FUT	≻	su	Preop- discharge (daily)	па	na	z	Rand nk
C Open None 40, 500 ml Periop-d l, C Placebo None 40, 500 ml Periop then C Open None 40, 500 ml Anaesthesia- C Open None 40, 500 ml Anaesthesia- C Open None 70, 500 ml Postop-(d 2 and d 4) C Open None 70, 500 ml Postop-(d 2 and d 4) C Open None 70, 500 ml Postop-(d 2 and d 4) C Open None 70, 500 ml Postop-(d 2 and d 4) C Open None 70, 500 ml Postop C Open None 70, 500 ml Postop C Open None 70, 500 ml Paresthesia- C Open None 70, 500 ml Postop C Open None 70, 500 ml Paresthesia, postop	None None	EH Veno	na	su	preop and d 10–d 12 postop (once)	na	na	Ē	Env nk
C Placebo None 40, 500 ml Periop then C Open None 40, 500 ml Anaesthesia- C Open None 70, 500 ml Postop-(d 2 and d 4) C Pacebo None 70, 500 ml Postop-(d 2 and d 4) C Pacebo None 70, 500 ml Postop-(d 2 and d 4) C Open None 70, 500 ml Postop-(d 2 and d 4) C Open None 70, 500 ml Postop-(d 2 and d 4) C Open None 70, 500 ml Periop-d 1, periop-d 1, periop-d 1, periop-d 1, periop-d 1, postop C Open None 70, 500 ml Paresthesia-postop C Open None 70, 500 ml Paresthesia, postop	None None	GS FUT	z	su	d 1–d 7 postop (daily)	pm for fatal	su	z	Seq
C Open None 40,500 ml Anaesthesia- d l postop C Open None 70,500 ml Postop-(d 2 and d 4) postop C Placebo None 40/70, Anaesthesia- 500 ml Periop-d 1, 200 ml Periop-d 1, 200 ml Periop-d 1, 200 ml Anaesthesia- 500 ml Periop-d 1, 200 ml Anaesthesia- 500 ml Periop-d 1, 200 ml Anaesthesia- d 1, d 2 postop	None None	HF Veno	na	su	d I-(d 5, d 6 or d7) postop	na	na	z	Seq
C Open None 70, 500 ml Postop–(d 2 and d 4) postop C Placebo None 40/70, Anaesthesia– 500 ml Periop–d I, Periop–d 1, 2, d, d 9 and d 12 postop C Open None 70, 500 ml Periop–d I, postop and d 12 postop	None None	GS FUT	z	su	Preop–d 7 postop (daily)	na	na	z	Rand nk
C Placebo None 40/70, Anaesthesia- 500 ml periop C Open None 70, 500 ml Periop–d I, d 2, d 6, d 9 and d 12 postop C Open None 70, 500 ml Anaesthesia, d 1, d 2 postop	None	EH Veno	na	≻	d 4–d 6 (once) and d 10–d 12 (once) postop	Scan	۔ ب	~	Env
C Open None 70, 500 ml Periop-d I, d 2, d 6, d 9 and d 12 postop C Open None 70, 500 ml Anaesthesia, d 1, d 2 postop	Vone None	MixS FUT	z	su	d 1–d 7 postop (alternate)	na	na	z	Pharm
110 C Open None 70, 500 ml Anaesthesia, d 1, d 2 postop	None None	HF Veno	па	SI SI	Daily clinical assess, veno <3 m	ца	ца	z	Rand o
-	None None	MixS FUT	z	su	su	pm for fatal	su	z	Env nk
van Hospenthal, I II C Placebo None 70, 500 ml Anaesthesia- None 1977 d I postop	Vone None	UR FUT	z	su	su	na	na	z	Seq
Welin-Berger, 112 C Open none 70, 500 ml Periop-(d l Noi and d 4) postop	None None	ВG	≻	SL	Preop and d 14 postop	Scan	su	z	Rand nk

Author, year	Ref. No.	Com- posi- tion	Unit of randomi- sation	Background - agent (all patients)	Treatment	Treatment regimen l	Treatment 2	Treatment regimen 2	Speciality	DVT method	Venogram confirmed? a	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomi- sation
Dextran combination Andersen, 1986 115	nation 6 115	υ	Open	ecs	70, 500 ml	Periop– mobile (alternate)	None	None	또	Veno	na	~	d 9–d 11 postop (daily)	ца	na	z	Rand nk
Schondorf, I 980	113	υ	Open	Heparin	40, 500 ml	Postop– d I, d 3	None	None	Ŧ	FUT	~	su	d 1–d 9/ d 10 postop (daily)	Scan	ะย	z	Rand nk
Smith, 1978	61	υ	open	IPC	70, 500 ml	Anaesthesia– None 8 h po for 4 h		None	S	E	z	~	Preop-d 7/ discharge postop (alternate)	Scan	su	z	Env nk
Swierstra, 1984 114	4 4	υ	Open	Aceno	40, 500 ml	Periop– d I postop	None	None	EH/EK	Veno	na	~	d 7 postop	na	na	z	Seq
van Geloven, 1977	85	υ	Placebo	Aceno	40, 500 ml	Periop– d I postop	None	None	MixS	FUT	z	su	d I–d 10 postop od	Scan if FUT+	su	z	Pharm
Dextran vs heparin Bergqvist 1, 1 1979	arin 100	ГОН	па	None	Dextran 70, 500 ml	Dextran Periop, postop, d l, d 3 postop	Heparin Heparin 5000 iu sc	<i>Heþarin</i> Diagnosis- d 5 postop bd	노	ΕŢ	z	≻	Preop, d 1–10 postop (alt)	pm for fatal	па	Ę	Env nk
Bergqvist II, I 980	101	ГОН	na	None	70, 500 ml	Periop, postop, d I, d 3 postop	Heparin 5000 iu sc	Preop-d 5 postop bd	GS/UR	FUT	z	SU	Preop, d 1–7 postop (daily/ alternate)/disch	E.	SU	z	Rand nk
Gruber, 1977	104	ГDН	na	None	40, 500 ml	Periop–d I, d 2 postop	Heparin 5000 iu sc	2 h preop– d 7 postop tds	ខ	FUT	z	su	d I–d 7 postop (daily)	pm for fatal	su	z	Seq
Hohl, 1980	116	LDH	па	None	70, 500 ml	Periop– d I postop	Heparin 5000 iu sc	2 h preop- d 7 postop tds	G	FUT	, ,	≻	Preop-d 7 postop (daily)	па	su	z	Env nk
Hubens, 1976	901	LDH	na	None	40, 500 ml	Anaesthesia, d I postop	Heparin 5000 iu sc	2 h preop- d 7 bd	MixS	FUT	z	su	Preop–d 7 postop (daily)	na	na	z	Rand nk
MacIntyre, 1974	011	ГDН	na	None	70, 500 ml	Anaesthesia, d I, d 2 postop	Heparin 5000 iu sc	2 h preop– 7 d postop bd	MixS	FUT	z	su	SU	pm for fatal	su	z	Env nk
Urbanyi, 1982	117	Б	na	None	60, 500 ml	Preop- d I, 2, 4, 6 postop	Heparin 5000 USP sc	Preop–d I, 2, 3, postop tds	SV	FUT	~	su	d 1–7 postop (daily)	Scan if FUT pm for fatal	su	z	Rand nk
Van Geloven, 1977	85	ГDН	na	Aceno + plac dex	40, 500 ml	Periop and d I postop	Heparin 4000 iu sc	2 h preop- d 4.5 postop, bd	MixS	FUT	z	SU	d 1–10 postop (daily)	Scan if FUT+	SU	z	Pharm
Welin-Berger, 1982	112	ГОН	па	None	70, 500 ml	Periop–(d I and d 4) postop	Heparin 5000 iu sc	Preop- d 7 postop bd	H	Ddl	- ~	su	Preop, day 14 postop	Scan	su	z	Rand nk
																	continued

TABLE 3 Trial characteristics – dextran (cont'd)

Author, year	Ref. o	Com- posi- tion	Unit of randomi- sation	Com- Unit of Background Treatment Treatr posi- randomi- agent I regim tion sation (all patients)	Treatment	Treatment regimen l	Treatment Treatment 2 Treatment Speciality DVT Venogram DVT Timing of regimen 1 regimen 2 method confirmed? assessment DVT blinded assessmen	Treatment regimen 2	Speciality	DVT method	Venogram confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE Tabular assessment data? blinded	Tabular data?	Tabular Method of data? randomi- sation
Wille- Jorgensen II, 1991	39	Ы	a	GCS	70, 500 ml	Periop–(d I and d 3) postop	Heparin 5000 iu sc	Preop- d 7 or mob bd	ខ	FUT	~	SU	d 1, d 3, d 5, d 7	Scan	SL	~	Seq
Dan Enox, 1991 99 LMWH na	66 166	LMWH	na	None	70, 500 ml	Periop- d 3/5 postop	_MWH 40.6 mg/ 0.4 ml sc	Preop-d 7 postop od	н	Veno	па	≻	d 7–11 postop	па	ца	z	Rand nk
Eriksson, 1988 118 LMWH na	8 118	LMWH	na	None	70, 500 ml	Periop, d I, 3 postop	LMWH 2500 iu sc	Preop- d 7 bd postop	H	FUT	~	~	d 1–14 postop (daily)	Scan	SU	≻	Seq
Matzsch, 1991 119 LMWH na	611 1	LMWH	na	None	70, 500 ml	Periop-d I, I 3, 5 postop	_MWH 50 u/kg sc	Preop- d 7 postop od	H	FUT	~	~	d l postop– d 7/10 postop (at)	Scan	≻	≻	Seq
Oertli, 1992		120 LMWH na	na	None	70, 500 ml	Anaes- 24 hrs postop tds	_MWH 3000 iu sc	Preop- d 10 postop od	ቿ	FUT	~	~	d 1–d 7 postop (daily)	Scan	z	≻	Env
Wiig, 1995	121	121 LMWH na	па	None	70, 500 ml + plac LMWH		LMWH 20 mg sc plac dex	2 h preop– d 10 postop/ mobile od	ß	Veno	na	~	d 4–6 postop	Scan	su	≻	Pharm

Author, year	Ref. No.	Unit of randomi- sation	Background agent (all patients)	Treatment I	Duration of treatment I	of Treatment 2 Duration of Speciality DVT t I treatment 2 meth	Duration of treatment 2	Speciality	DVT method	DVT Venogram method confirmed?	DVT assessment blinded	Timing of DVT assessment	PE assessment	PE assessment blinded	Tabular data?	Method of randomisation
Regional vs general					RA		ß									
Brichant, 1995	122	Open	LMWH+ GCS	Subarachnoid block	na	GA	na	Ш	Veno	z	~	01 P	na	z	z	Rand nk
Davis I, 1981	123	Open	None	Subarachnoid block	104 min	N ₂ O/O ₂ + pancuronium	104 min	生	FUT	z	~	Duration 7 d; no timing details	па	z	≻	Seq
Davis II, 1989	124	Open	GCS	Hypobaric spinal anaes	73 min	Narcotic– halothane– relaxant GA	79 min	Ш	FUT/IPG Y		~	postop d 4, 7, 11 postop (IPG) FUT od 7 d postop	Scan 4 FUT/IPG	z	≻	Seq
Fredin, 1986	125	Open	Dextran 70	Continuous epidural blockade	na	Neurolept anaesth	na	Ŧ	Veno	ца	~	d 10–14 postop (once)	Scan systematic	≻	~	Env
Hendolin I, 1981	126	Open	None	Continuous lumbar epidural	up to 24 h	g	па	Ъ	FI	z	su	l d preop, postop, d l, 2, 3, 5, 7 postop	па	па	z	Env nk
Hendolin II, 1982	127	Open	None	Continuous thoracic epidural	24 h	g	па	ß	ET	≻	su	l d preop, postop, d l, 2, 3, 5 postop	Па	Па	z	Rand nk
Jorgensen, 1991	128	Open	GCS	Continuous extradural anaesthesia	3 d	GA	Operation	Ä	Veno	ца	~	d 9–11 postop (once)	Scan	z	≻	Env
McKenzie, 1985	129	Open	None	Subarachnoid block	93.5 min	В	79 min	生	Veno	ца	z	d 7–10 postop (once) (1 pt on d 4 postop)	па	па	≻	Seq
Modig, 1986	17	Open	None	Continuous Iumbar epidural	l52 min	GA with parenteral analgesics	I 50 min	Ŧ	Veno	ца	~	d 12–14 postop (once)	Scan systematic	≻	z	Env nk
Rodrigo, 1994	130	Open	Dextran 40 + 7500 IU H	Lumbar epidural	na	Q	na	Ä	Veno	па	su	d 10 postop	รน	ะ	z	Rand nk
William-Russo, 1996	13	Open	ASA, GCS on non-op limb	па	па	na	na	ΕĶ	Veno	па	~	d 4–5 postop Scan (once) system	Scan systematic	~	≻	Seq

Author, year	Ref. No.	Numbers randomised	bers nised	DVT assessed	sessed	DVT	F	₽.	PVT	Non-fa	Non-fatal PE	Fatal PE	E	ali pe	H	Major	Major bleeds
		٩	υ	٩	υ	٩	υ	٩	υ	٩	υ	٩	υ	٩	υ	٩	υ
GCS vs control																	
Allan, 1983	23	211 total	otal	67	103	15	37	n	nr	na	na	na	na	na	na	r	nr
Barnes, 1978	24	8	0	8	0	0	S	0	4	0	m	0	0	0	m	'n	nr
Holford, 1976	25	50	48	48	47	=	23	_	m	0		0	0	0	_	'n	nr
Inada 1983	26	011	011	011	011	4	19	- L	, u		e u			, eu	Ē	Ľ	Ľ
Muir. 2000	27	65	32		32	. ~	-	ŝ	5	0	0	0	0	0	0	: L	Ľ
Rosengarten. 1970	28	25	25	25	25	- 00	- 00	0	0	na	na.	na	na	na	na	Ľ	u L
Shirai, 1985	29	126	126	126	126	ŋ	17	'n	n	na	na	na	па	na	na	Ľ	'n
Turner, 1984	30	104	92	104	92	0	4	n	nr	na	na	na	na	na	na	'n	'n
Turpie, 1989	31	80	8	80	81	7	16	_	2	na	na	0	0	na	na	n	nr
GCS combination																	
Bergqvist, 1984	32	88	88	80	80	0	8	0	_	na	na	na	na	na	na	'n	r
Fredin, 1989	33	l 50/3arms	arms	49	48	13	21	nr	nr	0	2	0	0	0	2	n	n
Kalodiki, 1996	34	39	38	32	32	œ	12	4	6	7	m	0	0	7	m	n	nr
Kierkegaard, 1993	35	80	80	80	80	0	8	0	0	na	na	na	na	na	na	'n	'n
Mellbring, 1986	67	4 tota	otal	54	54	7	9	nr total		na	na	na	na	na	na	'n	'n
Ohlund, 1983	36	63 total	otal	31	31	7	15	nr	nr	na	na	0	0	na	na	'n	'n
Rasmussen, 1988	37	89	85	89	85	23	25	nr	nr	na	na	na	na	na	na	'n	n
Scurr, 1987	68	78	78	78	78	_	7	0	0	na	na	na	na	na	na	'n	'n
Wille-Jorgensen I, 1985	39	94	102	86	60	_	7	nr	nr	7	2	0	_	7	9	n	'n
Wille-Jorgensen II, 1991	38	94	84	79	81	7	12	nr	л	0	0	_	0	_	0	n	nr
IPC vs control																	
Bachmann, 1976	40	26	28	26	28	4	<u>.</u>	nr	nr	_	2	na	na	_	S	'n	'n
Blackshear, 1987	4	20	20	20	20	0	0	nr	nr	na	na	na	na	na	na	'n	n
Butson, 1981	42	62	57	62	57	4	4	nr	nr	na	na	0	_	na	na	'n	n
Bynke, 1987	43	31	31	31	31	0	9	nr	nr	na	na	na	na	na	na	'n	nr
Clark, 1974	44	36	36	36	36	0	7	nr	nr	na	na	na	na	na	na	'n	'n
Clarke-Pearson I, 1984	45	59	57	55	52	ъ	17	_	4	7	_	0	0	7	_	r	'n
Clarke-Pearson II, 1984	46	104	105	67	76	4	=	ъ	_	m	0	_	_	4	_	'n	'n
Coe, 1978	47	31	24	29	24	_	ъ	n	nr	0	_	0	0	0	_	'n	'n
Fisher, 1995	48	345 total	otal	145	159	4	6	4	6	9	8	0	_	9	6	'n	'n
Gallus, 1983	49	95 total	btal	43	47	15	25	0	12	na	na	na	na	na	na	n	'n
Hills, 1972	50	I55 total	otal	20	70	7	23	nr	nr	na	na	na	na	na	na	n	'n

A C A	A C A	Author, year	Ref. No.	Numbers randomised	bers nised	DVT as	assessed	ΤΛΟ	۲	ፈ	PVT	Non-f	Non-fatal PE	Fata	Fatal PE	All PE	FE	Major	Major bleeds
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{bmatrix} 122 & 138 & 124 & 135 & 36 & 77 & 22 & 42 & 0 & 1 & 1 & 0 & 1 & 1 & 1 & 1 \\ 26 & 39 & 26 & 39 & 0 & 5 & 0 & 5 & 0 & 0 & 0 & 0 & 0 & 0$			٩	υ	٩	υ	۲	υ	٩	υ	٩	υ	٩	υ	٩	υ	۲	υ
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Hull II, 1990	52	152	158	124	135	36	11	22	42	0	-	-	0	-	-	Ŀ	F
	$ \begin{bmatrix} 137 \text{ in 3 arrvs} & 25 & 45 & 0 & 0 & \text{rr} & \text{rr} & \text{ra} & $	Knudson, 1994	53	26	39	26	39	0	S	0	5	0	0	0	0	0	0	'n	'n
	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Kosir, 1996	54	I37 in	3 arms	25	45	0	0	nr	n	na	na	na	na	na	na	'n	ŗ
	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Skillman, 1978	55	47	48	47	48	4	12	nr	nr	0	0	0	0	0	0	'n	'n
	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Turpie I, 1977	56	82	79	65	63	8	13	0	2	na	na	0	0	na	na	'n	nr
	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Turpie II, 1979	57	112	901	102	67	8	20	m	8	na	na	na	na	na	na	n	'n
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		Veitz, 1986	58	ß	6	ъ	6	0	2	n	n	na	na	na	na	na	na	nr	n
	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	PC combination																	
94 59 130 13 118 7 9 0 1 na n	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Caprini, 1983	69	102	total	38	39	_	S	0	_	_	_	0	_	_	2	'n	ŗ
95 70 117 115 116 115 8 6 m m m m m m m m m m m m m m m m m m	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	-ieberman, 1994	59	130	130	113	118	7	6	0	_	na	na	0	0	na	na	'n	'n
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	^a ambianco, 1995	20	117	115	116	115	8	9	nr	ŗ	na	na	na	na	na	na	ŗ	nr
60 35 35 35 5 6 10 5 4 0 <td>35 35 35 35 5 6 10 5 4 0<td>lokito, 1996</td><td>71</td><td>33</td><td>42</td><td>33</td><td>42</td><td>0</td><td>0</td><td>nr</td><td>'n</td><td>na</td><td>na</td><td>na</td><td>na</td><td>na</td><td>na</td><td>'n</td><td>nr</td></td>	35 35 35 35 5 6 10 5 4 0 <td>lokito, 1996</td> <td>71</td> <td>33</td> <td>42</td> <td>33</td> <td>42</td> <td>0</td> <td>0</td> <td>nr</td> <td>'n</td> <td>na</td> <td>na</td> <td>na</td> <td>na</td> <td>na</td> <td>na</td> <td>'n</td> <td>nr</td>	lokito, 1996	71	33	42	33	42	0	0	nr	'n	na	na	na	na	na	na	'n	nr
	305 in 3ams 97 97 18 21 nr nr 3 5 0 0 0 0 3 5 1	iragusa, 1994	60	35	35	35	35	9	0	S	4	0	0	0	0	0	0	'n	'n
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	78 80 78 80 7 1 <td>imith, 1978</td> <td>61</td> <td>305 in</td> <td>3 arms</td> <td>67</td> <td>76</td> <td>8</td> <td>21</td> <td>nr</td> <td>n</td> <td>m</td> <td>9</td> <td>0</td> <td>0</td> <td>m</td> <td>S</td> <td>'n</td> <td>n</td>	imith, 1978	61	305 in	3 arms	67	76	8	21	nr	n	m	9	0	0	m	S	'n	n
1996 72 25 10 18 5 0 2 0 1 0<	25 10 18 5 0 1	Turpie, 1989	31	78	80	78	80	7	7	_	_	na	na	0	0	na	na	'n	'n
sontrol 62 33 33 33 5 15 nr nr na 0 0 na na 92 63 28 32 28 32 5 19 0 6 0 0 0 0 0 0 92 63 28 32 28 32 5 19 0 6 0 0 0 0 0 932 73 42 42 39 40 2 16 2 13 na na na na na 996 64 25 25 0 5 0 5 na na na na 989 66 44 44 6 8 nr nr na na na na	33 35 5 10 1 1	Vautrecht, 1996	72	25	0	8	Ω	0	2	0	_	0	0	0	0	0	0	n	nr
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64 25 25 25 0 5 na na 0 0 na na 65 60 64 56 58 3 1 nr na na </td <td>1 25 25 25 0 5 na na 0 0 na na nr 1 <td< td=""><td>ordyce, 1992</td><td>73</td><td>42</td><td>42</td><td>39</td><td>4</td><td>7</td><td>16</td><td>7</td><td>2</td><td>na</td><td>na</td><td>na</td><td>na</td><td>na</td><td>na</td><td>'n</td><td>'n</td></td<></td>	1 25 25 25 0 5 na na 0 0 na na nr 1 <td< td=""><td>ordyce, 1992</td><td>73</td><td>42</td><td>42</td><td>39</td><td>4</td><td>7</td><td>16</td><td>7</td><td>2</td><td>na</td><td>na</td><td>na</td><td>na</td><td>na</td><td>na</td><td>'n</td><td>'n</td></td<>	ordyce, 1992	73	42	42	39	4	7	16	7	2	na	na	na	na	na	na	'n	'n
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66 44 44 44 44 6 8 nr nr na na na na na na	6 44 44 44 44 6 8 nr nr na na na na na na na nr	² orteous, 1989	65	60	64	56	58	m	_	n	n	na	na	na	na	na	na	'n	'n
	A, active treatment; C, control.	Williams, 1988	99	44	4	44	44	9	8	nr	n	na	na	na	na	na	na	'n	'n

0AC control/placebo Borgstrom, 1965 Fordyce, 1991 Hamilton, 1970 MacCallum, 1990		randomised	andomised		sessed		_	۲ ا	2	Non-fa	Non-fatal PE	Fatal PE	BE	AII PE	E E	Major bleeds	bleeds
AC control/placebo orgstrom, 1965 ordyce, 1991 familton, 1970 1acCallum, 1990		۷	υ	A	υ	۲	υ	۲	υ	۷	υ	۷	υ	۷	υ	۷	υ
orgstrom, 1965 ordyce, 1991 łamilton, 1970 1acCallum, 1990																	
ordyce, 1991 łamilton, 1970 1acCallum, 1990	74	29	29	23	25	7	n E	n	nr	na	na	0	7	na	na	0	0
łamilton, 1970 1acCallum, 1990	75	74	74	74	74	25	61	9	ъ	na	na	na	na	na	na	'n	n
1acCallum, 1990	76	38	38	38	37	0	8	nr	'n	na	na	na	na	na	na	=	6
	11	76	67	40	46	7	ъ	0	0	na	na	na	na	na	na	4	7
Morris, 1976	78	80	80	75	74	23	50	0	ц.	C	2	C	Ŷ	C	œ	6	~
Pinto 1970	62	35	35	5.5	25	ا م	, œ				1 2	• c) C			. –	ı c
Poller 1987	U U U U U	27	2 2	27	2 6	• 4) =	5	5			, c	, c			- 2	о и
01151, 1 /0/ 011/0255 1000	8 9	70	5	70	5 5	+ 2	- 0	≡ ◄	≡ 2		<u>ه</u> د				<u>ة</u> ر	<u>-</u>	י ר
rowers, 1707 Taharnar 1978	<u> </u>	48 84	60 48	60 84	48 48	<u>-</u> ~	47 	0 2	<u> </u>	2	7 6			2	7 6	n n	n c
	5	2	2	2	2	7	=	3	=	5	5	>	>	1	5	7	>
OAC combination																	
Habersberger, 1973	83	133 total	otal	53	63	ъ	8	0	0	na	na	0	0	na	na	nr	nr
Hume 1973	87	17	61	17	61	m	4	'n	'n	ВЦ	ВЦ	ВЦ	ВЦ	ВЦ	ВЦ	_	
Korvald 1973	8	99 total	, letc	68	43	• 4	. <u>ר</u>	-	: ~			c	!			- L	- L
		21	2		5 5	· c	<u>.</u>		1							:	- C
KOKITO, 1776	- L - C	0 1 1	4 -	35	4 0	<u> </u>	<u>د</u> د	L	L	na L	La	ua	ua v	na L	r na	7 -	. .
van Geloven, 1977	ŝ	331 total	otal	/4	08	<u>2</u>	<u>ر</u>	nr	nr	7	ი	С	Э	7	ი	_	Э
Woolson 1991	86	69	76	69	76	0	0	9	6	0	0	0	0	0	0	0	0
OAC dose comparison																	
Feller, 1992	88	00	00	98	67	16	30	4	=	0	0	_	0	_	0	0	7
Poller, 1987	80	35	32	35	32	_	m	nr	nr	na	na	0	0	na	na	8	4
UAL vs neparins		!					,										I
Hume, 1973	87	17	8	17	8	m	m	'n	nr	na	na	na	na	na	na	_	~
Poller, 1995	67	47	43	З	37	15	œ	m	0	na	na	0	0	na	na	m	m
Taberner, 1978	82	48	49	48	49	m	m	nr	n	na	na	0	0	na	na	m	ъ
van Geloven, 1977	85	331 to	total	80	80	20	15	nr	nr	6	S	0	0	6	S	_	0
Friedman, 1994	98	407	800	321	648	87	120	33	4	_	_	0	0	_	_	21	45
Gerhart, 1991	90	145	144	131	132	28	6	7	m	_	0	0	0	_	0	2	œ
Hamulyak, 1995	16	342	330	257	260	50	43	15	17	0	0	0	0	0	0	œ	ъ
Heit, 1997	92	279	277	222	232	85	62	15	15	0	_	0	0	0	_	12	22
Hull III, 1993	93	721	715	603	579	231	185	47	36	0	0	0	0	0	0	6	20
Hull IV, 2000	94	501	0001	363	712	8	80	=	9	na	na	na	na	na	na	22	76
Leclerc, 1996	95	334	336	211	206	601	76	22	24	m	_	0	0	m	_	9	7
Francis, 1997	96	292	288	190	192	49	28	91	0	na	na	na	na	na	na	4	9
Fitzgerald, 2001	89	176	173	176	173	80	44	20	23	0	0	0	0	0	0	4	6

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TABLE 6 Trial events – oral anticoagulants

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ABLI

Author, year	Ref. No.	Numbers randomised	oers nised	DVT ass	ssessed	ΤΛΟ		PVT	۲	Non-fatal PE	al PE	Fatal PE	H	AII PE	ш	Major bleeds	oleeds
		٩	υ	٩	υ	٩	υ	٩	υ	٩	υ	٩	υ	٩	υ	٩	υ
Dextran vs control																	
Bergqvist I, 1979	8	80 total/3 arms	3 arms	27	22	<u>13</u>	20	nr	nr	na	na	0	0	na	na	0	0
Bergqvist II, 1980	101	57	58	52	51	15	4	0	8	na	na	0	0	na	na	0	0
Carter, 1973	102	901	101	901	101	_	0	'n	nr	na	na	na	na	na	na	nr	nr
Evarts, 1971	103	8	21	8	21	4	0	'n	nr	na	na	na	na	na	na	nr	nr
Gruber, 1977	104	113	113	92	8	20	36	0	4	na	na	_	4	na	na	nr	nr
Hefley, 1990	105	45	42	45	42	15	4	'n	nr	na	na	na	na	na	na	nr	nr
Hubens, 1976	901	39	4	39	4	ъ	6	_	2	na	na	na	na	na	na	0	0
Hurson, 1979	107	55	51	55	51	15	6	ъ	7	8	8	0	_	8	6	nr	nr
Huttunen, 1977	108	150	75	150	75	52	25	nr	nr	na	na	_	0	na	na	nr	nr
Johnsson, 1968	601	27	25	27	25	_	13	nr	nr	na	na	na	na	na	na	0	0
4	0	130	128	128	128	32	47	n	nr	na	na	0	2	na	na	nr	nr
van Hospenthal, 1977	Ξ	6	49	39	47	m	7	n	nr	na	na	na	na	na	na	0	0
Welin-Berger, 1982	112	20	20	16	8	4	ъ	m	2	0	_	0	0	0	_	nr	nr
Dextran combination																	
Andersen, 1986	115	29	<u>-</u>	29	31	ъ	4	nr	nr	na	na	na	na	na	na	nr	nr
Schondorf, 1980	113	54	55	54	55	6	œ	'n	nr	0	—	_	_	_	2	0	0
Smith, 1978	61	12 excl/3 arms	3 arms	67	95	8	36	nr	n	m	S	0	0	m	ъ	4	7
Swierstra, 1984	114	71	8	71	8	21	34	4	23	na	na	na	na	na	na	17	8
van Geloven, 1977	85	331 total	otal	79	80	6	20	nr	nr	4	6	0	0	4	6	7	_
		18 exc/4 arms	4 arms														
Dextran vs heparin																	
Bergqvist I, 1979	8	80 total/3 arms	3 arms	27	28	13	8	nr	nr	na	na	0	_	na	na	0	0
Bergqvist II, 1980	101	57	53	52	46	15	6	0	m	na	na	0	0	na	na	0	7
Gruber, 1977	104	113	611	92	94	20	12	0	_	na	na	_	6	na	na	_	œ
Hohl, 1980	116	237 total	otal	117	115	17	7	m	_	na	na	na	na	na	na	nr	nr
Hubens, 1976	901	39	39	39	39	ъ	4	_	0	na	na	na	na	na	na	0	0
MacIntyre, 1974	0	130	128	128	125	32	15	r	'n	na	na	0	0	na	na	0	_
Urbanyi, 1982	117	46	43	46	43	7	_	'n	nr	0	0	0	0	0	0	0	0
Van Geloven, 1977		331 total, 18 exc/4 arm	8 exc/4 ar		74	6	13	n	nr	4	7	0	0	4	2	2	_
Welin-Berger, 1982	112	20	20	16	17	4	œ	m	m	0	0	0	0	0	0	nr	nr
Wille-Jorgensen II, 1991	39	98	94	85	79	<u>m</u>	7	'n	nr	_	0	0	_	_	_	_	0
Dan Enox, 1991	66	126	120	Ξ	108	24	7	6	7	na	na	0	0	na	na	nr	nr
Eriksson, 1988	118	51	50	49	49	22	0	m	0	7	7	0	0	7	2	0	0
Matzsch, 1991	611	123	120	108	Ξ	36	22	2	2	4	2	0	0	4	2	0	0
Oertli, 1992	120	103	113	95	103	м З	16	_	7	0		_	_	_	7	0	0
Wiig, 1995	121	164	165	134	128	38	35	0	٣	0	0	0	0	0	0	0	0
A active treatment. C control	ontrol																

Author, year	Ref. No.	Num rando	Numbers randomised	DVT a:	DVT assessed	TVD	F	₽.	ΓΛ	Non-fatal PE	tal PE	Fatal	PE	All PE	PE	Major	Major bleeds
		٩	υ	٩	υ	٩	υ	٩	υ	٩	υ	۲	υ	٩	υ	٩	υ
Regional vs general anaesthesia trials	sthesia trial	s															
Brichant, 1995	122	54	52	46	42	4	13	n	nr	na	na	na	na	na	na	0	0
Davis I, 1981	123	64	68	37	39	17	28	'n	nr	na	na	0	Υ	na	na	0	ъ
Davis II, 1989	124	69	68	69	68	6	61	m	8	0	Υ	0	0	0	m	nr	nr
Fredin, 1986	125	30	30	26	25	=	12	_	7	9	7	0	0	9	7	0	0
Hendolin I, 1981	126	17	21	17	20	7	=	'n	nr	na	na	na	na	na	na	nr	ŗ
Hendolin II, 1982	127	28	40	28	40	_	2	'n	nr	na	na	na	na	na	na	0	0
Jorgensen, 1991	128	24	24	17	22	m	13	_	m	0	_	0	0	0	_	0	0
McKenzie, 1985	129	20	20	20	20	œ	16	r	nr	na	па	na	na	na	na	0	0
Modig, 1986	17	50	50	48	46	21	38	8	30	ъ	15	0	0	ъ	15	nr	n
Rodrigo, 1994	130	=	=	=	=	ъ	7	_	4	0	0	0	0	0	0	nr	ŗ
Williams-Russo, 1996	131	188	88 total	76	8	39	39	0	0	0	9	0	0	0	9	0	0
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 trials²³⁻⁶⁴ 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 stockings²⁸ [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 belowknee 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 trials⁴⁰⁻⁵⁸ 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 $\beta(b)$, 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 trial⁶⁴ 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 nicoumalone⁸² and acenocoumarin⁸⁵ 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 (\sim 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 nine⁷⁴⁻⁸² assessing

oral anticoagulant as monotherapy and six^{71,83–87} as adjunctive therapy. Overall, the reduction in DVT appeared similar for moderate and lowintensity 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 lowdose 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 trials¹⁰⁰⁻¹¹² (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 ${\rm five}^{61,85,107,112,113}$ 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 lowdose 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*).

	No. of trials	Deep v throm			ratified atistics		atio and e interval	% odds reduction
Category	with data	Compression	Control	O-E	Variance	(compressio	on : control)	(SE)
(a) Compression (mo	onotherapy)							
Graduated	9	57/665	133/627	-39.7	37.2			66% (10
compression st	ockings	(8.6%)	(21.2%)					,
Intermittent	19	112/1108	268/1147	-76.3	71.0			66% (7
pneumatic com	pression	(10.1%)	(23.4%)					
Footpump	2	11/61	34/65	-10.7	7.3 -			77% (19
. corpanip	-	(18.0%)	(52.3%)	10.7	7.5			////0(1/
		(10.070)	(32.370)					
(a) subtotal	30	180/1834	435/1839	-126.7	115.5			67% (6
(u) subtotui	50	(9.8%)	(23.7%)	120.7	115.5			2p < 0.0000
		(7.070)	(23.770)					2p < 0.0000
(b) Compression (ad	unctive therapy)						
Graduated	8	54/564	108/556	-28.I	30.7	— — —		60% (12
compression st	ockings	(9.6%)	(19.4%)					,
Intermittent	3	31/262	40/262	-4.5	14.7			26% (22
pneumatic com	pression	(11.8%)	(15.3%)					(
Footpump	.p. 000.011	0/25	5/25	-2.5	. 			100% (42
		(0.0%)	(20.0%)	2.0				
(b) subtotal	12	85/851	153/843	-35.1	46.5			53% (10
(-)		(10.0%)	(18.1%)					2p < 0.0000
(c) All patients (mon	o or adjunctivo	thorrow						
Graduated		111/1229	241/1183	-67.8	67.9	_		63% (8
compression st		(9.0%)	(20.4%)	-07.0	07.7			05 /0 (0
Intermittent	OCKINGS 22	143/1370	(20.4%)	-80.8	85.7	i		(10/ /7
			-	-00.0	05.7			61% (7
pneumatic com		(10.4%)	(21.9%)	12.2	0.4	_		700/ /17
Footpump	3	11/86	39/90	-13.2	8.4 -	-		79% (17
		(12.8%)	(43.3%)					
All trials	42	265/2685	588/2682	-161.8	162.0			63% (5
7 th that5	12	(9.9%)	(21.9%)	101.0	102.0	\diamond		2p < 0.0000
	050/ 51							
-∎- 99% or <⊃	95% confidence	ce intervals			0.0	0.5	I.0 I.5	2.0
Heterogeneity of odd	ls reductions bet	tween:			0.0		1	
– compression m	onotherapy vs a	djunctive therap	y: $\chi^2 = 3.9$:	þ = 0.05		Compression	Compres	
· · · ·		ries of tests in (a			s	better	worse	9
		ries of tests in (t			-	Trootmont offo	ct 2p < 0.00001	

Figures showing the main results for each comparison



	No. of trials	Deep ve throm			ratified atistics	confider	ratio and Ice interval	% odds reduction
Category	with data	Compression	Control	0-Е	Variance	(compress	ion : control)	(SE)
(a) Compression (m	nonotherapy)							
(a) Orthopaedic		66/460	172/502	-49.3	38.9			72% (9)
() 1		(14.3%)	(34.3%)			1		
(b) General surg	ery II	60/654	150/673	-44.7	40.7	- B		67% (10)
		(9.2%)	(22.3%)			i i		
(c) Neurosurgei	y/spinal 6	27/357	69/354	-21.1	20.8	_		64% (14)
0	<i>,</i> ,	(7.6%)	(19.5%)					
(d) Gynaecologi	cal 3	Ì9/267	32/254	-6.8	11.0			46% (22)
() , 0		(7.1%)	(12.6%)					
(e) Mixed surge	ry I	Ì/31	5/24	-2.4	1.3 —	• · ·		84% (40)
() 0	/	(3.2%)	(20.8%)					
(f) Medical/unki	nown I	7/65	7/32	-2.4	2.7 –	i		
.,		(10.8%)	(21.9%)			1		
		. ,	. ,					
(a) subtotal	30	180/1834	435/1839	-126.7	115.4	Φ_{-}		67% (6)
		(9.8%)	(23.7%)					2p < 0.00001
(b) Compression (a								
(a) Orthopaedic	6	41/309	72/307	-15.8	21.0			53% (15)
	-	(13.3%)	(23.5%)					(00/ // 5)
(b) General surg	jery 5	44/462	73/456	-15.3	23.6			48% (15)
		(9.5%)	(16.0%)	4.0				
(c) Medical/unki	nown I	0/80	8/80	-4.0	1.9■	1		100% (34)
		(0.0%)	(10.0%)					
(b) subtotal	12	85/85 I	153/843	-35.I	46.5			53% (10)
(D) Subtotal	12	(10.0%)	(18.1%)	-55.1	10.5	\sim		2p < 0.00001
		(10.070)	(10.170)			i I		20 < 0.00001
(c) All patients (mo	no- or adiunctive	therapy)						
(a) Orthopaedic		107/769	244/809	-65.I	59.9			66% (8)
		(13.9%)	(30.2%)			Ť		
(b) General surg	ery 16	Ì04/1116	223/1129	-60.0	64.3	-		61% (8)
		(9.3%)	(19.8%)					
(c) Neurosurgei	y/spinal 6	27/357	69/354	-21.1	20.8	_		64% (14)
0	<i>,</i> ,	(7.6%)	(19.5%)					
(d) Gynaecologi	cal 3	19/267	32/254	-6.8	11.0			46% (22)
		(7.1%)	(12.6%)					
(e) Mixed surge	ry I	1/31	5/24	-2.4	1.3 —	= :	1	84% (40)
		(3.2%)	(20.8%)					
(f) Medical/unki	nown 2	7/145	15/112	-6.4	4.6 —			75% (25)
		(4.8%)	(13.4%)					
		A / F /A / A F	F00/2 / 02	141.6				100/ (T)
All trials	42	265/2685	588/2682	-161.8	161.9	\diamond		63% (5)
		(9.9%)	(21.9%)					2p < 0.00001
000 /	050/ 01	:						
- 99% or <	 95% confiden 	ce intervals			0.0	0.5	I.0 I.	5 2.0
Heterogeneity of oc	lds reductions be	tween:			0.0			
	nonotherapy vs a		y: $\chi^2_1 = 3.9;$	p = 0.05		Compression		ression
•		ries of tests in (a			S	better	wo	orse
	- the 3 catego	ries of tests in (b	$v^2 = 3.7$	$b = 0 \cdot N$	s	Treatment ef	fect 2p < 0.0000	I



	Ref	Deep ve throm			ratified atistics	Odds ra confidenc		
Study	no.	Compression	Control	O-E	Variance	(compressio	on : control) (SE))
(a) GCS (monotherapy)								_
Allan	23	15/97	37/103	-10.2	9.7		65% (2	20)
Barnes	24	0/8	5/10	-2.2	0.9		100% (4	44)
Holford	25	11/50	23/48	-6.3	5.6 -		68% (2	25)
Inada	26	4/110	16/110	-6.0	4.6 —	-	73% (2	26)
Muir	27	7/65	7/32	-2.4	2.7 —			
Rosengarten	28	8/25	8/25	0.0	2.8		• >	
Shirai	29	5/126	17/126	-6.0	5.0 -		70% (2	26)
Turner	30	0/104	4/92	-2.I	I.0			
Turple	31	7/80	16/81	-4.4	5.0		59% (2	30)
(a) subtotal		57/665	133/627	-39.7	37.2		66% (10)
		(8.6%)	(21.2%)				2p < 0.000)0ĺ
(b) GCS (adjunctive therapy)								
Bergqvist (D)	32	0/88	8/88	-4.0	1.9=		100% (3	35)
Fredin (D)	33	13/49	21/48	-4.2	5.6		53% (30)
Kalodiki (LMWH)	34	8/39	12/38	-2.1	3.7			*
Kierkegaard (A)	35	0/80	8/80	-4.0	I.9		100% (3	35)
Ohlund (D)	36	7/31	15/31	-4.0	3.6 —		67% (32)
Rasmussen (H)	37	23/89	25/85	-1.6	8.7		·	
Wille-Jorgensen 1, 1985 (H)	39	I/94	7/102	-2.8	I.9 —		77% (3	38)
Wille-Jorgensen II, 1991 (H)	38	2/94	12/84	-5.4	3.2 —		81% (2	27)
(b) subtotal		54/564	108/556	-28. I	30.7		60% (12)
		(9.6%)	(19.4%)				2p < 0.000	01
All trials		111/1229	241/1183	-67.8	67.9	\Leftrightarrow	63%	
		(9.0%)	(20.4%)				2p < 0.000	101
- 99% or <>> 95% con	fiden	ce intervals			L			
Heterogeneity of odds reduction	ns:				0.0		.0 I.5 2.0	
– between 9 trials of		monotherapy	$\chi^2 = 6.6: b >$	0.1: NS		Compression	Compression	
- between 8 trials of GCS as	s adju	nctive therapy: ;	$\chi_7^2 = 13.3; p$	= 0.07		better	worse	
	,	., ,	-, -,			Treatment effe	ct $2p < 0.00001$	

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.

	Ref	Deep v throm			ratified atistics	Odds rat confidence		odds luction
Study	no.	Compression	Control	0-Е	Variance	(compression	: control)	(SE)
(a) GCS – above knee								
Barnes	24	0/8	5/10	-2.2	0.9 =			% (44)
Holford	25	11/50	23/48	-6.3	5.6 -		68	% (25)
Inada	26	4/110	16/110	-6.0	4.6 —			% (26)
Muir	27	7/65	7/32	-2.4	2.7 -			- ` `
Shirai	29	5/126	17/126	-6.0	5.0 -		70	% (26)
Turple	31	7/80	16/81	-4.4	5.0		59	% (30)
(a) subtotal		34/439 (7.7%)	84/407 (20.6%)	-27.4	23.8		68 2p < 0	% (12) .00001
(b) GCS – below knee Rosengarten	28	8/25	8/25	0.0	2.8			\rightarrow
(b) subtotal		8/25 (32.0%)	8/25 (32.0%)	0.0	2.8			—— % (60) D. I ; NS
(c) GCS – siting unspecified								
Allan	23	15/97	37/103	-10.2	9.7			
Turner	30	0/104	4/92	-2.I	1.0 ■		65	% (20)
(c) subtotal		15/201 (7.5%)	41/195 (21.0%)	-12.3	10.6			% (18) 0.0002
All trials		57/665 (8.6%)	133/627 (21.2%)	-39.7	37.2		66 2p < 0	% (10) .00001
→ 99% or <>> 95% o	onfide	nce intervals			0.0	0.5 1.0) 1.5	2.0
Heterogeneity between 3	3 subto	tals: $\chi^2_2 = 3.4$: b =	= 0.1: NS		0.0	0.5 1.0	J. 1.J	2.0
Heterogeneity withir	n subto	tals: $\chi_6^{\bar{2}} = 3.1; p$	> 0.1; NS			Compression better	Compression worse	
Heterogeneity betwe	en 9 tr	iais: $\chi_8^2 = 6.5; p$	> U.1; NS			Treatment effect	2b < 0.00001	

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

	Ref	Deep v throm			ratified atistics			atio and ce interval	% odds reduction
Study	no.	Compression	Control	0-Е	Variance	(compressi	on : control)	(SE)
(a) IPC (monotherapy)									
Bachmann	40	4/26	13/28	-4.2	3.0 —				76% (31)
Blackshear	41	0/20	0/20						
Butson	42	4/62	4/57	-0.2	1.9	i			\longrightarrow
Bynke	43	0/31	6/31	-3.0	1.4				100% (39)
Clarke	44	0/36	7/36	-3.5	1.6				100% (36)
Clarke-Peason I	45	5/59	17/57	-6.2	4.5 —	-			75% (26)
Clarke-Pearson II	46	14/104	11/105	1.6	5.5				>
Coe	47	1/31	5/24	-2.4	1.3 —				
Fisher	48	4/145	9/159	-2.2	3.1 -				\longrightarrow
Gallus	49	15/43	25/47	_4.I	5.6				52% (30)
Hills	50	7/70	23/70	-8.0	5.9 -	-			74% (23)
Hull I	51	2/32	19/29	-9.0	3.5 -	{			92% (19)
Hull II	52	36/152	77/158	-19.4	18.0				66% (14)
Knudson	53	0/26	5/39	-2.0	.l •			_	
Kosir	54	0/25	0/45			1			
Skillman	55	4/47	12/48	-3.9	3.4 —				69% (32)
Turpie I	56	8/82	13/79	-2.7	4.6			_	
Turpie II	57	8/112	20/106	-6.4	6.1 -	!		_	65% (25)
Weitz	58	0/5	2/9	-0.7	0.4				> ´
(a) subtotal		112/1108	268/1147	-76.3	71.0				66% (7)
		(10.1%)	(23.4%)						2p < 0.00001
(b) IPC (adjunctive therapy)									
Lieberman (A)	59	7/130	9/130	-1.0	3.8				\longrightarrow
Siragusa (H)	60	6/35	10/35	-2.0	3.1 -				\longrightarrow
Smith (D)	61	18/97	21/97	-1.5	7.8				
(b) subtotal		31/262	40/262	-4.5	14.7	_			26% (22)
		(11.8%)	(15.3%)						2p > 0.1; NS
All trials		143/1370	308/1409	-80.8	85.7				61%(7)
		(10.4%)	(21.9%)						2p < 0.00001
	onfider	ice intervals			L				
Listenseensity of add du-	+i				0.0	0.5		1.0 1.5	2.0
Heterogeneity of odds reduc			2 00 1	0.02		Compre	ssion	Compre	ession
 between 19 trials 						bette		wor	
 between 3 trials of IPC 	as adju	nctive therapy: χ	$r_2^2 = 0.5; p >$	0.1; NS				ect 2p < 0.00001	

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

6 1	Ref	thron	venous nbosis	sta	atified	Odds ratio confidence in	nterval reduction
Study	no. Compression Control O-E Variance (compression : contro		: control) (SE)				
(a) IPC – sequential compre	ssion						
Blackshear	41	0/20	0/20				
Fisher	48	4/145	9/159	-2.2	3.1		
Hull II	52	36/152	77/158	-19.4	18.0	i	66% (14)
Knudson	53	0/26	5/39	-2.0	1.1	8	
Kosir	54	0/25	0/45				
Turple II	57	8/112	20/106	-6.4	6.I		65% (25)
(a) subtotal		48/480 (10.0%)	/527 (2 . %)	-30.0	28.4		65% (12) 2p < 0.00001
		(10.070)	(21.170)				2p < 0.00001
(b) IPC – single compression							
Bachmann	40	4/26	13/28	-4.2	3.0		76% (31)
Butson	42	4/62	4/57	-0.2	1.9		
Bynke	43	0/3 I	6/31	-3.0	1.4		100% (39)
Clark	44	0/36	7/36	-3.5	1.6		100% (36)
Clarke-Pearson I	45	5/59	17/57	-6.2	4.5		75% (26)
Clarke-Pearson II	46	14/104	11/105	1.6	5.5		
Coe	47	1/31	5/24	-2.4	1.3		
Gallus	49	15/43	25/47	-4.I	5.6		52% (30)
Hills	50	7/70	23/70	-8.0	5.9		74% (23)
Hull I	51	2/32	19/29	-9.0	3.5		92% (19)
Skillman	55	4/47	12/48	-3.9	3.4		69% (32)
Turpie I	56	8/82	13/79	-2.7	4.6		
(b) subtotal		64/623 (10.3%)	155/611 (25.4%)	-45.6	42.2		66% (9) 2p < 0.00001
(c) IPC – unknown type							
Weitz	58	0/5	2/9	-0.7	0.4		
(c) subtotal		0/5	2/9	-0.7	0.4		
		(0.0%)	(22.2%)				2p > 0.1; NS
All trials		2/ 08 (10.1%)	268/1147 (23.4%)	-76.3	71.0	·	66% (7) 2p < 0.00001
- 000/ - 050/	<u>.</u>		()				, , , , , , , , , , , , , , , , , , , ,
- ■ - 99% or < > 95%					0.0	0.5 1.0	1.5 2.0
Heterogeneity betw Heterogeneity v						Compression	Compression

FIGURE 6	Effects of type of intermittent	pneumatic compression	(IPC) on deep venous thrombosis
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Study	Ref no.	Deep vo throm Compression	bosis		ratified <u>atistics</u> Variance	Odds ratio ar confidence inte (compression : co	rval reduction
(a) Footpump (monot	herapy)						
Scurr	62	6/33	15/33	-4.5	3.6 —	֥	71% (30)
Wilson	63	5/28	19/32	-6.2	3.6 —		82% (25)
(a) subtotal		11/61	34/65	-10.7	7.3		77% (19)
		(18.0%)	(52.3%)				2p = 0.00007
(b) Footpump (adjunct	tive therapy)						
Stannard (A, H)		0/25	5/25	-2.5	I.I •		- 100% (43)
(b) subtotal	64	0/25	5/25	-2.5	I.I		100% (43)
		(0.0%)	(20.0%)				2p = 0.02
All trials		11/86	39/90	-13.2	8.4		79% (17)
All tridis		(12.8%)	(43.3%)	-13.2	**.0		2p < 0.00001
- 99% or <>	95% confiden	ce intervals			L		
					0.0	0.5 1.0	1.5 2.0
Heterogeneity of odds – between 2 trials of fo		otherapy: $\chi_1^2 = 0$.4; p > 0.1; N	NS		Compression better	Compression worse
						Treatment effect 2p	< 0.00001

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

No. o trials				ratified atistics			% odds reduction
Category with da	ta Compression	Control	0-Е	Variance	(compres	sion : control)	(SE)
(a) Compression (monotherapy)							
Graduated 5	5/228	11/196	-3.7	3.6 —	=		64% (33)
compression stockings	(2.2%)	(5.6%)			I I		
Intermittent 9	45/755	90/779	-21.0	28.5			52% (13)
pneumatic compression	(6.0%)	(11.6%)					()
Footpump	0/28	6/32	-2.8	.4 ■			100% (42)
	(0.0%)	(18.8%)					
(a) subtotal 15	50/1011	107/1007	-27.5	33.5			56% (12)
()	(4.9%)	(10.6%)					2p < 0.00001
(b) Compression (adjunctive thera	ру)						
Graduated 3	4/207	10/206	-3.I	3.0 —			_
compression stockings	(1.9%)	(4.9%)					
Intermittent 2	5/165	5/165	0.0	2.2			>
pneumatic compression	(3.0%)	(3.0%)					
Footpump	0/25	5/25	-2.5	I.I 			100% (42)
	(0.0%)	(20.0%)	2.0				
(b) subtotal 6	9/397	20/396	-5.6	6.5			59% (26)
	(2.3%)	(5.1%)					2p = 0.03
(c) All patients							
Graduated 8	9/435	21/402	-6.7	6.6			64% (24)
compression stockings	(2.1%)	(5.2%)			-		
Intermittent II	50/920	95/944	-21.0	30.8			49% (13)
pneumatic compression	(5.4%)	(10.1%)					()
Footpump 2	0/53	ÌI/57	-5.3	2.5			100% (30)
	(0.0%)	(19.3%)					
All trials 21	59/1408	127/1403	-33.0	39.8			56% (11)
	(4.2%)	(9.1%)					2p < 0.00001
99% or <>> 95% confid	ance intervals			L			
—				0.0	0.5	1.0 1.	5 2.0
Heterogeneity of odds reductions: – between the 3 categorie		nonotherapy:	$\chi^2_2 = 2.3$:	p > 0.1; NS	Compression	Compr	
- between the 3 categories of con					better	wo آfect 2p < 0.0000	

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

	No. of trials	Pulmon emboli	,		ratified atistics		s ratio and ence interval	% odds reduction
Category	with data	Compression	Control	0-E	Variance	(compres	ssion : control)	(SE)
(a) Compression (mon	otherapy)							
Graduated	3	0/123	4/90	-1.8	0.9	I I		
compression sto	ckings	(0.0%)	(4.4%)					
Intermittent	8	14/590	18/618	-1.6	7.6			
pneumatic comp	ression	(2.4%)	(2.9%)					
Footpump	I	0/28	0/32					
		(0.0%)	(0.0%)					
(a) subtotal	12	4/74	22/740	-3.4	8.5			33% (28)
		(1.9%)	(3.0%)					2p > 0.1; NS
(b) Compression (adju	nctive therapy)						
Graduated	4	5/276	11/272	-2.9	3.9 -	= ;		
compression sto	ckings	(1.8%)	(4.0%)					
Intermittent	2	3/132	5/132	-1.0	I.9 —			>
pneumatic comp	ression	(2.3%)	(3.8%)					
Footpump	0			(n	o data)			
(b) subtotal	6	8/408	16/404	-3.9	5.8			49% (30)
(b) subtotal	Ŭ	(2.0%)	(4.0%)	5.7	5.0			2p > 0.1; NS
(c) All patients								
Graduated	7	5/399	15/362	-4.8	4.8 –			63% (29)
compression sto		(1.3%)	(4.1%)	1.0	1.0			0370(27)
Intermittent	10	17/722	23/750	-2.6	9.6			
pneumatic comp		(2.4%)	(3.1%)	-2.0	7.0	1		
Footpump		0/28	0/32			1		
rootpump	I	(0.0%)	(0.0%)					
All trials	18	22/1149	38/1144	-7.4	14.3			40% (21)
		(1.9%)	(3.3%)				-	2p = 0.05
- 99% or <>	95% confiden	e intervals			L			· · · · · · · · · · · · · · · · · · ·
					0.0	0.5	I.0 I	.5 2.0
	3 categories o	f compression m				Compression better		pression prse
- between the 3 categ	ories of compr	ession as adjunc	tive therapy:	$\chi_1^2 = 0.1;$	p > 0.1; NS		effect $2p = 0.006$	

FIGURE 9 Effects of compression methods of thromboprophylaxis on pulmonary embolism

.	No. of trials	thror	venous nbosis	st	ratified atistics	Odds rat confidence	e interval reduct	ion
Category	with data	Compressio	n Control	0-Е	Variance	(compression	n : control) (SE))
(a) Type of data								
(I) Tabular	9	38/563	104/562	-33.2	27.8		700/	5(11)
GCS	7	(6.7%)	(18.5%)	-33.2	27.0		70%	S(11)
IPC	9	60/522	Ì16/538	-27.5	34.0		55%	6 (12)
FP	0	(11.5%)	(21.6%)	(no	data)			
(I) subtotal	18	98/1085	220/1100	-60.7	61.8	- ♦		% (8)
(II) Published		(9.0%)	(20.0%)				2p < 0.0	0001
GCS	8	73/666	137/621	-34.6	40.0		58%	(II)
IPC	13	(11.0%) 83/848	(22.1%) 192/871	-53.3	51.6	- -	649	% (9)
FP	3	(9.8%) 11/86	(22.0%) 39/90	-13.2	8.4		79%	6 (17)
FF	3	(12.8%)	(43.3%)	-13.2	0.7		///	,(17)
(II) subtotal	24	167/1600 (10.4%)	368/1582 (23.3%)	-101.1	100.0	¢	649 2¢ < 0.0	% (6)
		(10.+70)	(23.370)				2p < 0.0	0001
(b) Randomisation methe (I) Robust allocation								
GCS	9	49/559	111/523	-33.9	30.6		67%	5 (11)
IPC	11	(8.8%) 73/780	(21.2%) 158/780	-42.7	45.5	_	61%	6 (10)
		(9.4%)	(20.3%)				01/0	. (10)
FP (I) subtotal	0 20	122/1339	269/1303	(na) –76.6	o data) 76.1	((639	% (7)
		(9.1%)	(20.6%)	, 0.0			2p < 0.0	
(II) Less robust meth GCS	od 8	62/670	130/660	-33.9	37.3	- <u>-</u>	60%	5 (11)
		(9.3%)	(19.7%)					
IPC	11	70/590 (11.9%)	150/629 (23.8%)	-38.I	40.2		61%	6 (10)
FP	3	11/86	`39/90´	-13.2	8.4		79%	6 (17)
(II) subtotal	22	(12.8%) 143/1346	(43.3%) 319/1379	-85.2	85.9	\	63%	6(17)
		(10.6%)	(23.1%)				2p < 0.0	0001
(c) Assessment of DVT (I) Blinded assessor								
GCS	9	53/710	124/668	-37.7	34.7		66%	6 (10)
IPC	14	(7.5%) 116/962	(18.6%) 235/998	-57.8	64.2	-	599	% (8)
FP	2	(12.1%) 5/53	(23.5%) 24/57	-8.7	4.8		84%	o (21)
		(9.4%)	(42.1%)					
(I) subtotal	25	174/1725 (10.1%)	383/1723 (22.2%)	-104.2	103.7	¢	639 2p < 0.0	% (6) 000 I
(II) Other/unknown						1		
GCS	8	58/519 (11.2%)	117/515 (22.7%)	-30.I	33.2		60%	6 (I I)
IPC	8	27/408	73/411	-23.0	21.5		66%	6 (13)
FP	1	(6.6%) 6/33	(17.8%) 15/33	-4.5	3.6		71%	s (30)
		(18.2%)	(45.5%)					
(II) subtotal	17	91/960 (9.5%)	205/959 (21.4%)	-57.6	58.3	Ø	2p < 0.0	% (8) 0001
(d) DVT confirmation		()	,					
(I) Venogram GCS	8	34/546	100/546	-33.I	26.7		71%	5 (11)
IPC	13	(6.2%) 97/849	(18.3%) 220/858	-60.I	57.7			% (8)
		(11.4%)	(25.6%)			E		
FP	2	6/58 (10.3%)	20/58 (34.5%)	-7.0	4.8		77%	6 (24)
(I) subtotal	23	137/1453	340/1462	-100.2	89.2	- \$		% (6)
(II) Other method		(9.4%)	(23.3%)				2p < 0.0	0001
GCS	9	77/683	141/637	-34.8	41.1	- -	57%	5 (11)
IPC	9	(11.3%) 46/521	(22.1%) 88/551	-20.7	28.0		52%	6(13)
		(8.8%)	(16.0%)					
FP	I	5/28 (17.9%)	19/32 (59.4%)	-6.2	3.6		82%	o (25)
(II) subtotal	19	128/1232	248/1220	-61.7	72.7	- \lapha		% (8)
		(10.4%)	(20.3%)				2p < 0.0	0001
- 99% or <>> 95	5% confidenc	e intervals						
Heterogeneity between	22 categories	$\chi^2_{21} = 21.6$:	o > 0.1; NS		0.0		.0 I.5 2.0)
Heterogeneity between	8 subtotals: χ	² ₇ = 3.1; p > 0).1; NS			Compression	Compression	
Heterogeneity within sul	ptotals: $v^2 =$	$ 85 \cdot p > 0 $	· NS			better	worse	

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

- .	Ref	thron	venous nbosis	st	ratified atistics	Odds ratio a confidence int	erval reduction
Study	no.	Oral a/c	Control	0-Е	Variance	(oral a/c : con	trol) (SE)
(a) Oral anticoagulant (mon	otherapy)						
Borgstrom	74	2/29	13/29	-5.5	2.8 —	<u> </u>	86% (26)
Fordyce	75	25/74	19/74	3.0	7.8		_
Hamilton	76	10/38	18/38	-4.0	4.5 –		59% (31)
MacCallum	77	2/97	5/97	-1.5	1.7 —		>
Morris	78	23/80	50/80	-13.5	10.0 _		74% (17)
Pinto	79	9/25	8/25	0.5	2.9		• · · · · · · · · · · · · · · · · · · ·
Poller	80	4/67	11/37	-5.7	3.0 —		85% (26)
Powers	81	13/65	29/63	-8.3	7.1 –		69% (22)
Taberner	82	3/48	11/48	-4.0	3.0 —	-	- 73% (32)
(a) subtotal		91/523 (17.4%)	164/491 (33.4%)	-39.0	42.7		60% (10) 2p < 0.00001
 (b) Oral anticoagulant (adjur (i) With pharmacologica 		ру)					
Habersberger (H)	83	5/53	8/63	-0.9	2.9		>
Korvald (D)	83 84	3/33 4/39	15/43	_0.9 _5.0	3.7 —		75% (28)
van Geloven (H)	85	13/74	15/80		5.8		>
(i) subtotal		22/166 (13.3%)	38/186 (20.4%)	-6.4	12.3		41% (22) 2p = 0.07
(ii) With compression m	ethod						
Hume (GCS)	87	3/17	4/19	-0.3	1.4 —		>
Rokito (GCS)	71	0/35	0/42				
Woolson (IPC/GCS)	86	0/69	0/76				
(ii) subtotal		3/121	4/137	-0.3	1.4		
		(2.5%)	(2.9%)				19% (75) 2p > 0.1; NS
							20
(b) subtotal (all adjunction	ve therapy)	25/287 (8.7%)	42/323 (13.0%)	-6.7	13.8		38% (21) 2p = 0.07
All trials		116/810 (14.3%)	206/814 (25.3%)	-45.7	56.5		55% (9) 2p < 0.00001
- 99% or <>> 95%	confidence	()	. ,		L		·
Heterogeneity between 3 su					0.0	0.5 1.0	1.5 2.0
neren offenerik hermeeri 2 20	τοτοταίδ. χ ₂	_ 2.0, <i>p</i> ≥ 0	, , , , , , , ,			Oral a/c better	Oral a/c worse
						Treatment effect 2p	< 0.00001

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.

	No. of trials		venous nbosis	Stratified statistics		Odds ratio a confidence int	
Category	with data	Oral a/c	Control	<u>о-е</u>	Variance	(compression : c	
(a) Oral anticoagulant (monotherapy)						
Fixed low dose +	3	31/238	35/208	-4.2	12.4		29% (24)
very low/normal		(13.0%)	(16.8%)				
Low	5	57/237	118/235	-30.8	27.3		68% (11)
		(24.1%)	(50.2%)				
Moderate	I	3/48	11/48	-4.0	3.0 —		74% (32)
		(6.3%)	(22.9%)			1	()
	0	01/522	144401	20.0	42.7		60% (10)
(a) subtotal	9	91/523	164/491	-39.0	42.7	\Leftrightarrow	2p < 0.00001
		(17.4%)	(33.4%)				
(b) Oral anticoagulant (adjunctive ther	apy)					
Fixed low dose +	3	3/121	4/137	-0.3	1.4 -		>
very low/normal		(2.5%)	(2.9%)				
Low	2	Ì7/113	30/123	-5.5	9.4		44% (25)
		(15.0%)	(24.4%)				
Moderate	I	5/53	8/63	-0.9	2.9		>
		(9.4%)	(12.7%)				
(b) subtotal	6	25/287	42/323	-6.7	13.8		38% (21)
(b) subtotal	0	(8.7%)	(13.0%)	-0.7	15.0		2p = 0.07
(c) All patients							
Fixed low dose +	6	34/359	39/345	-4.5	13.9		28% (23)
very low/normal	Ū	(9.5%)	(11.3%)	1.5	13.7		2070 (23)
Low	7	74/350	148/358	-36.3	36.7		63% (10)
LOW	,	(21.1%)	(41.3%)	-50.5	50.7		0378 (10)
Moderate	2	8/101	19/111	-4.9	5.9		E404 (20)
ribuerate	2	(7.9%)	(17.1%)	-1.7	5.7		56% (28)
		(7.770)	(17.170)				
All trials	15	116/810	206/814	-45.7	56.5		
		(14.3%)	(25.3%)				55% (9) 2p < 0.00001
	5% confidenc	e intervals					
Heterogeneity of odds	reductions:				0.0	0.5 1.0	1.5 2.0
- between the 3	categories of	oral anticoagu	lant monother	apy: $\chi_2^2 =$	5.9; $p = 0.03$	5 Oral a/c	Oral a/c
 between the 3 categories 	ries of oral ant	icoagulant as a	adiunctive the	rapy: $\chi_2^2 =$	0.3: p > 0.1:	better	worse
– between the 3	categories of	oral anticoard	lant in all natio	ents: $v^2 =$	45.0 = 01	NS Treatment effect 2p	< 0.00001
Diffe	rence between	trootmont off	laste in (a) and	(b): χ^2_2 –	10.5 > 0.1		

FIGURE 12 Effects of oral anticoagulant intensity on deep venous thrombosis

	Ref	Deep v throm			ratified atistics	Odds rat confidence		% odds reductior
Study	no.	Moderate	Fixed	0-Е	Variance	(moderate	: fixed)	(SE)
Feller	88	16/100	30/100	-7.0	8.9		_	54% (23)
Poller	80	1/35	3/32	-1.1	1.0 —			>
All trials		17/135 (12.6%)	33/132 (25.0%)	-8.I	9.9			56% (22) 2p = 0.01
		idence intervals			0.0	0.5 1.0		2.0
Difference betwe	en treatment e	ffects in 2 trials: χ_1^2 =	= 0.1; 2p > 0	.1; NS		Moderate dose better	Fixed dose worse	
						Treatment effe	t 2b = 0.010	

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





	No. of trials	Proxima thron	l venous 1bosis		ratified atistics			ratio and nce inter	-	% odds reduction
Category	with data	Oral a/c	Control	O-E	Variance		(oral a/c : control)			(SE)
(a) Oral anticoagulant (mo	onotherapy)					1				
Fixed low dose	2	6/171	5/171	0.5	2.6					>
+ very low/normal		(3.5%)	(2.9%)							
Low	2	6/145	24/143	-9.2	6.3 —	-				77% (21)
		(4.1%)	(16.8%)							
Moderate	0	()	(*****)	(no	data)					
(a) subtotal	4	12/316	29/314	-8.7	8.8					63% (21)
		(3.8%)	(9.2%)							2p = 0.003
(b) Oral anticoagulant (ad	junctive thera	apy)								
Fixed low dose	, I	6/69	9/76	-1.1	3.4					>
+ very low/normal		(8.7%)	(11.8%)							
Low	1	Ì/39	2/43	-0.4	0.7 —					>
		(2.6%)	(4.7%)							
Moderate	1	0/53	0/63							
		(0.0%)	(0.0%)							
(b) subtotal	3	7/161	11/182	-1.6	4.1					
(-)		(4.3%)	(6.0%)							31% (41)
		((2p > 0.1; NS
(c) All patients										
Fixed low dose	3	12/240	14/247	-0.6	5.9			•		>
+ very low/normal		(5.0%)	(5.7%)							
Low	3	7/184	26/186	-9.6	7.0 -	-				75% (21)
		(3.8%)	(14.0%)			1				
Moderate	I	0/53	0/63							
		(0.0%)	(0.0%)							
All trials	7	19/477	40/496	-10.2	12.9	-				55% (19)
		(4.0%)	(8.1%)							2p = 0.004
- 99% or <>> 95%)/ eenfidenee	internele								
_		intervais			0.0	0.5	5	1.0	1.5	2.0
Heterogeneity of odds re		$d(b) = x^2 - 1$	0. 5 5 0 1. 10			Oral	a/c		Oral a/c	
 between treatment eff between the 3 categor 	ies of anticoa	gulant intensi	ty: $\chi_1^2 = 5.2; p$	= 0.02		bett	er		worse	
0		-				Tr	eatment ef	fect 2p =	0.00006	

FIGURE 15 Effects of oral anticoagulant intensity on proximal venous thrombosis

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- .	Ref	Pulmo embo	lism	sta	ratified atistics		Odds ratio and onfidence interva		% odds reduction
Study	no.	Oral /ac	Control	0-Е	Variance	(0	oral a/c : control)		(SE)
(a) Oral anticoagulant (mon	otherapy)								
Borgstrom	74			(no	data)				
Fordyce	75			· ·	data)	:			
Hamilton	76				data)				
MacCallum	77				data)	1			
Morris	78	0/80	8/80	-4.0	1.9		_		100% (35)
Pinto	79	-,	-,		data)				
Poller	80			· ·	data)				
Powers	81	0/65	2/63	-1.0	0.5	1			>
Taberner	82	0,00	2,00		data)				
(a) subtotal		0/145	10/143	-5.0	2.4				100% (31)
(a) subtotal		(0.0%)	(7.0%)	5.0	2.1				2p = 0.001
		(01070)	(11070)						_p 0.000.
	ativa thana								
 (b) Oral anticoagulant (adjur (i) With pharmacologica)у)							
Habersberger (H)	83			(no	data)	1			
Korvald (D)	84			· ·	data)				
van Geloven (H)	85	2/74	5/80	-1.4	1.7 —	-			>
(i) subtotal		2/74	5/80	-1.4	1.7				56% (53)
		(2.7%)	(6.3%)			1			2p > 0.1; NS
						1 1 1			2p > 0.1; 1NS
(ii) With compression m	ethod					1 1 1			
Hume (GCS)	87			(no	data)				
Rokito (GCS)	71			(no	data)				
Woolson (IPC/GCS)	86	0/69	0/76			1			
(ii) subtotal		0/69	0/76						
() Subtotal		(0.0%)	(0.0%)						
(b) subtotal (all adjunctiv	o thorson)	2/143	5/156	-1.4	1.7	1 1 1			
(b) subtotal (all aujunctiv	e therapy)	(1.4%)	(3.2%)	1.1					56% (52)
		()	(1 1 1			2p > 0.1; NS
All trials						1			
		2/288	15/299	-6.4	4.1				79% (25)
		(0.7%)	(5.0%)		<				2p = 0.002
- 99% or <>> 95%	confidence	intervals			0.0	0.5	I.0	1.5	2.0
Difference between treatme	nt effects in	2 subtotals:	$\chi_{1}^{2} =$	= 1.6; p > 0).1; NS	Oral a/c		Oral a/c	
						better		worse	
						Treat	tment effect 2p =	0.002	

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.

	Ref	Major ext ble			ratified atistics		ratio and nce interval	% odds reduction
Study	no.	Oral a/c	Control	0-Е	Variance	(oral a/	c : control)	(SE)
(a) Oral anticoagulant (mono	otherapy)							
Borgstrom	177	0/29	0/29					
Fordyce	74	0,27	0/2/	(n	o data)			
,	75	11/20	0/20					
Hamilton	76	11/38	9/38	1.0	3.7			
MacCallum	77	4/97	2/97	1.0	1.5			>
Morris	78	9/80	2/80	3.5	2.6		1	•>
Pinto	79	1/25	0/25	0.5	0.3 <		1	\longrightarrow
Poller		12/67	5/37	1.0	3.3			
Powers	80	5/65	5/63	-0.I	2.3		-	
Taberner	81	3/48	0/48	1.5	0.7			>
	82	0, .0	0, 10		•			
(a) subtotal		45/449	23/417	8.5	14.4			-80% (36)
(a) subtotal				0.5	17.7			
		(10.0%)	(5.5%)					2p = 0.03
								adverse
 (b) Oral anticoagulant (adjun (i) With pharmacologica Habersberger (H) 	l agent 83	ру)			o data)			
Korvald (D)	84				o data)			
van Geloven (H)	85	I/74	0/80	0.5	0.2 <			>
(i) subtotal		I/74	0/80	0.5	0.2			
		(1.4%)	(0.0%)					-701% (675)
		()	()					2p > 0.1; NS
(ii) With compression me	ethod							adverse
Hume (GCS)	87	1/17	1/19	0.1	0.5 ←			>
Rokito (GCS)		2/35	0/42	1.1	0.5			>
	71			1.1	0.5			
Woolson (IPC/GCS)	86	0/69	0/76					
(ii) subtotal		3/121	1/137	1.1	1.0			
		(2.5%)	(0.7%)					–255% (193)
								2p > 0.1; NS
								adverse
(b) subtotal (all adjunctive	e therapy)	4/195	1/217	1.6	1.2			
	177	(2.1%)	(0.5%)					-279% (191)
		(,0)	(0.070)					2p > 0.1; NS
								adverse
								auverse
All suists		10// 14	24/224		15.4			000/ (04)
All trials		49/644	24/634	10.1	15.6			-92% (36)
		(7.6%)	(3.8%)				-	2p = 0.01
								adverse
- 99% or <>> 95% o	confidence	intervals			L	. I .		
—			2-04-5-	0.1. NC	0.1	0.25 0.5	1.0 2.5	5 5 10
Difference between treatme	ni enects in	i ∠ sudtotals:	$\chi_1 = 0.6; p >$	U.1; NS		Oral a/c	Oral	alc
						better	WO	56

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

	No. of trials		venous nbosis		ratified atistics	Odds ratio		% odds reduction
Category	with data	Oral a/c	Control	0-Е	Variance	(Oral a/c : c	ontrol)	(SE)
(a) Type of data								
Tabular	2	5/145 (3.4%)	16/145 (11.0%)	-5.5	4.7 -	-		69% (27
Published	13	111/665 (16.7%)	190/669 (28.4%)	-40.2	51.8			54% (10
(b) Randomisation meth	od							
Robust	5	84/331 (25.4%)	3 /335 (39.1%)	-23.3	35.1			49% (12
Less robust	10	32/479 (6.7%)	75/479 (15.7%)	-22.4	21.4			65% (13
(c) Assessment of DVT								
Blinded assessor	5	20/274 (7.3%)	58/279 (20.8%)	-19.3	14.7			73% (15
Other/unknown	10	96/536 (17.9%)	148/535 (27.7%)	-26.4	41.9			47% (11
(d) DVT confirmation								
Venogram	9	60/488 (12.3%)	91/476 (19.1%)	-17.3	27.6			47% (14
Other method	6	56/322 (17.4%)	115/338 (34.0%)	-28.4	29.0			62% (12
All trials	15	116/810 (14.3%)	206/814 (25.3%)	-45.7	56.6			55% (9 2p < 0.0000
- 99% or <>> 9	5% confidence	intervals			0.0	0.5 1.0	.5	2.0
Heterogeneity between	8 categories: χ	$c_4^2 = 9.5; p =$	0.1; NS		0.0	Oral a/c	Oral a/c worse	2.0
						Treatment effect	2p < 0.00001	

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

	Ref		venous nbosis		ratified atistics		lds ratio and idence interva		% odds reduction
Study	no.	Oral a/c	Heparin	0-E	Variance		l a/c : heparin)		(SE)
(a) Oral a/c vs (low o	dose) unfractio	nated heparin							
Hume	87	3/17	3/18	0.1	1.3 —			<u>+</u>	>
Poller	80	15/47	8/43	3.0	4.3				→
Taberner	82	3/48	3/49	0.0	1.4 —		-		>
van Geloven	85	20/80	15/80	2.5	6.9			-	>
(a) subtotal		41/192	29/190	5.6	13.9				
		(21.4%)	(15.3%)						-50% (33)
		. ,	. ,						2p > 0.1; NS
(b) Oral a/c vs low m	nolecular weig	ht heparin						i i	adverse
Fitzgerald	89	80/176	44/173	17.5	20.0				>
Francis	96	49/292	28/288	10.2	16.7				\rightarrow
Friedman	98	87/407	120/800	17.2	38.4			_ _	>
Gerhart	90	28/145	9/144	9.4	8.1			<u> </u>	>
Hamulyak	91	50/342	43/330	2.7	20.1				
Heit	92	85/279	62/277	11.2	27.1				\rightarrow
Hull III	93	231/721	185/715	22.1	73.9				
Hull IV	94	81/501	80/1000	27.3	32.0				\longrightarrow
Leclerc	95	109/334	76/336	16.8	33.5				>
(b) subtotal		800/3197	647/4063	134.4	269.8			\triangleleft	>
		(25.0%)	(15.9%)						-65% (8)
									2p < 0.00001 adverse
All trials		841/3389	676/4253	140.0	283.7			$ \leq $	>
		(24.8%)	(15.9%)					Ĩ	-64% (8)
									2p < 0.00001 adverse
- 99% or <>>	050/64								adverse
₩ 99% or <↓>	- 73% contide	ence intervais			0.0	0.5	1.0	1.5	2.0
Difference between	treatment effe	cts in 2 subtotals:	$\chi_1^2 = 0.0; p >$	0.1; NS		Oral a/c		Heparin	
						better	ect 2p < 0.000	better	

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

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	Ref	Pulmember	onary olism		ratified atistics	-	odds ratio and Ifidence interv		% odds reduction
Study	no.	Oral a/c	Heparin	0-Е	Variance		al a/c : heparii		(SE)
(a) Oral a/c vs (low d	ose) unfraction	ated heparin							
Hume	87			(no	data)				
Poller	97			· ·	data)				
Taberner	82			(no	data)				
van Geloven	85	9/80	5/80	2.0	3.2				→
(a) subtotal		9/80	5/80	2.0	3.2	_			
		(11.3%)	(6.3%)						-86% (7)
									2p > 0.1; N
(b) Oral a/c vs low me	olecular weigh	t heparin							advers
Fitzgerald	89				data)				
Francis	96			(no	data)				
Friedman	98	1/407	1/800	0.3	0.4 —				>
Gerhart	90	1/145	0/144	0.5	0.2 —				>
Hamulyak	91	0/342	0/330						
Heit	92	0/279	1/277	-0.5	0.2				>
Hull III	93	0/721	0/715						
Hull IV	94				data)				
Leclerc	95	3/334	1/336	1.0	1.0				\longrightarrow
(b) subtotal		5/2228	3/2602	1.3	1.9				
		(0.2%)	(0.1%)						-98% (103
		~ /	~ /						2p > 0.1; N
All trials		14/2308	8/2682	3.3	5.2				advers
		(0.6%)	(0.3%)						-91% (62
									2p > 0.1; N
									advers
- 99% or <>	95% confider	nce intervals			0.0	0.5	l	1.5	2.0
			2		0.0		1.0	1.5	2.0
Difference between ti	reatment effec	ts in 2 subtotals	$\chi_1^2 = 0.0; p >$	0.1; NS		Oral a/c better		Heparin better	
						Treatment e	effect $2p > 0.1$;	NS adverse	

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

	Ref		tracranial eds		ratified atistics		lds ratio and idence interval		% odds reduction
Study	no.	Oral a/c	Heparin	0-Е	Variance	(ora	l a/c : heparin)		(SE)
(a) Oral a/c vs (low c	lose) unfractio	nated heparin							
Hume	87	1/17	7/18	-2.9	1.6 —				84% (37)
Poller	97	3/47	3/43	-0.I	1.4 —				>` ´
Taberner	82	3/48	5/49	-1.0	1.9 —				\longrightarrow
van Geloven	85	1/80	0/80	0.5	0.3 —				>
(a) subtotal		8/192	15/190	-3.5	5.1				49% (32)
		(4.2%)	(7.9%)						2p > 0.1; NS
(b) Oral a/c vs low m	olecular weigl	nt heparin				1			
Fitzgerald	89	4/176	9/173	-2.6	3.1 —				
Francis	96	4/292	6/288	-1.0	2.5 —				\longrightarrow
Friedman	98	21/407	45/800	-1.3	14.0		-		
Gerhart	90	5/145	8/144	-1.5	3.1 -	•			\longrightarrow
Hamulyak	91	8/342	5/330	1.4	3.2 —	1			\longrightarrow
Heit	92	12/279	22/277	-5.I	8.0				47% (26)
Hull III	93	9/721	20/715	-5.6	7.1 -				54% (26)
Hull IV	94	22/501	76/1000	-10.7	20.4				41% (17)
Leclerc	95	6/334	7/336	-0.5	3.2	1 			\longrightarrow
(b) subtotal		91/3197 (2.8%)	198/4063 (4.9%)	-26.8	64.5		-		34% (10) 2p = 0.0009
		(2.070)	(1.770)						2p = 0.0007
All trials		99/3389	213/4253	-30.3	69.6		_		35% (10)
		(2.9%)	(5.0%)						2p = 0.0003
- 99% or <	95% confide	ence intervals			L				
			2 0 0		0.0	0.5	1.0	1.5	2.0
Difference between t	reatment effe	cts in 2 subtotals	: χ ₁ = 0.3; ρ >	0.1; NS		Oral a/c better		Heparin better	
						Treatme	nt effect $2p = 0$.	0003	

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

(a) Dextran (monotherapy) Bergqvist I 100 13/27 Bergqvist II 101 15/57 Carter 102 1/106 Evarts 103 4/18 Gruber 104 20/113 Hefley 105 15/45 Hubens 106 5/39 Hurson 107 15/55 Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 2 (b) Dextran (adjunctive therapy) () () (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 39/204 39/204	control 20/22 14/58 10/101 10/21 36/113 14/42 9/41 9/51 25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216 (28.7%)	-5.2 0.6 -4.6 -2.5 -8.0 0.0 -1.8 2.5 0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	Variance 2.7 5.5 2.6 2.3 10.6 4.9 2.9 4.7 11.3 2.6 13.8 1.2 1.8 66.8 3.6 8.8 6.0			(SE) 85% (27) 83% (29) 53% (22) 33% (22) 33% (21) 33% (21) 33% (21) 33% (21) 33% (21) 33% (21) 33% (21) 33% (21) 33% (22) 38% (10) 2p = 0.00009 38% (10) 2p = 0.00009 38% (20) 38% (20) 38
Bergqvist II 101 15/57 Carter 102 1/106 Evarts 103 4/18 Gruber 104 20/113 Hefley 105 15/45 Hubens 106 5/39 Hurson 107 15/55 Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 22 (a) subtotal 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (i) subtotal 39/204 (19.1%)	14/58 10/101 10/21 36/113 14/42 9/41 9/51 25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	0.6 -4.6 -2.5 -8.0 0.0 -1.8 2.5 0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	5.5 2.6 2.3 10.6 4.9 2.9 4.7 11.3 2.6 13.8 1.2 1.8 66.8 3.6 8.8			$\begin{array}{c c} & & & & \\ & & & & \\ & & & & \\ & & & & $
Bergqvist II 101 15/57 Carter 102 1/106 Evarts 103 4/18 Gruber 104 20/113 Hefley 105 15/45 Hubens 106 5/39 Hurson 107 15/55 Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 22 (a) subtotal 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (i) subtotal 39/204 (19.1%)	14/58 10/101 10/21 36/113 14/42 9/41 9/51 25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	0.6 -4.6 -2.5 -8.0 0.0 -1.8 2.5 0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	5.5 2.6 2.3 10.6 4.9 2.9 4.7 11.3 2.6 13.8 1.2 1.8 66.8 3.6 8.8			$\begin{array}{c c} & & & & \\ & & & & \\ & & & & \\ & & & & $
Carter 102 1/106 Evarts 103 4/18 Gruber 104 20/113 Hefley 105 15/45 Hubens 106 5/39 Hurson 107 15/55 Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 2 (a) subtotal 180/827 2 (b) Dextran (adjunctive therapy) () () (i) With pharmacological agent Schondorf (H) 113 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) ()	10/101 10/21 36/113 14/42 9/41 9/51 25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	-4.6 -2.5 -8.0 0.0 -1.8 2.5 0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	2.6 — 2.3 — 10.6 4.9 2.9 4.7 11.3 2.6 — 13.8 1.2 1.8 – 66.8 3.6 8.8			$ \begin{array}{c} $
Evarts 103 $4/18$ Gruber 104 20/113 Hefley 105 15/45 Hubens 106 5/39 Hurson 107 15/55 Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 2 (b) Dextran (adjunctive therapy) (i) (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (19.1%)	10/21 36/113 14/42 9/41 9/51 25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	-2.5 -8.0 0.0 -1.8 2.5 0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	2.3 — 10.6 4.9 2.9 4.7 11.3 2.6 — 13.8 1.2 1.8 66.8			53% (22) $53% (23)$ $91% (23)$ $43% (21)$ $38% (10)$ $2p = 0.00009$ $- 41% (26)$
Gruber 104 20/113 Hefley 105 15/45 Hubens 106 5/39 Hurson 107 15/55 Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 2 (b) Dextran (adjunctive therapy) (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (19.1%)	36/113 14/42 9/41 9/51 25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	-8.0 0.0 -1.8 2.5 0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	10.6 4.9 2.9 4.7 11.3 2.6 13.8 1.2 1.8 66.8			$\begin{array}{c} & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & &$
Hefley 105 15/45 Hubens 106 5/39 Hurson 107 15/55 Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 2 (b) Dextran (adjunctive therapy) () (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) ()	14/42 9/41 9/51 25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	0.0 -1.8 2.5 0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	4.9 2.9 4.7 11.3 2.6 13.8 1.2 1.8 66.8 3.6 8.8			$\begin{array}{c} & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & &$
Hefley 105 15/45 Hubens 106 5/39 Hurson 107 15/55 Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 2 (b) Dextran (adjunctive therapy) () (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) ()	14/42 9/41 9/51 25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	0.0 -1.8 2.5 0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	4.9 2.9 4.7 11.3 2.6 13.8 1.2 1.8 66.8 3.6 8.8			$\begin{array}{c} & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & &$
Hurson 107 15/55 Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 2 (b) Dextran (adjunctive therapy) (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (i) subtotal 39/204 (19.1%)	9/51 25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	2.5 0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	4.7 11.3 2.6 13.8 1.2 1.8 66.8 3.6 8.8			$\begin{array}{c c} & & & & \\ & & & & \\ & & & & \\ & & & & $
Hurson 107 15/55 Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 2 (b) Dextran (adjunctive therapy) (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (i) subtotal 39/204 (19.1%)	9/51 25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	2.5 0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	4.7 11.3 2.6 13.8 1.2 1.8 66.8 3.6 8.8			$\begin{array}{c} & & & \\ & & & & \\ & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ &$
Huttunen 108 52/150 Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 2 (a) subtotal 180/827 2 (b) Dextran (adjunctive therapy) (1) (1) (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (1)	25/75 13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	0.7 -6.3 -7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	2.6 13.8 1.2 1.8 66.8 3.6 8.8			91% (23) 43% (21)
Johnsson 109 1/27 MacIntyre 110 32/130 von Hospenthal 111 3/40 Welin-Berger 112 4/20 (a) subtotal 180/827 2 (b) Dextran (adjunctive therapy) (1) (1) (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (1)	13/25 47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	-7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	13.8 1.2 1.8 66.8 3.6 8.8			$ \begin{array}{c} 43\% (21) \\ \hline \hline $
MacIntyre11032/130von Hospenthal1113/40Welin-Berger1124/20(a) subtotal180/8272(b) Dextran (adjunctive therapy)(1)(i) With pharmacological agentSchondorf (H)Schondorf (H)1139/54Swierstra (OAC)11421/71van Geloven (OAC)859/79(i) subtotal39/204(19.1%)(1	47/128 2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	-7.8 0.8 -0.5 -32.1 0.6 -4.7 -5.4	13.8 1.2 1.8 66.8 3.6 8.8		· · · · · · · · · · · · · · · · · · ·	$ \begin{array}{c} 43\% (21) \\ \hline \hline $
von Hospenthal III 3/40 Welin-Berger II2 4/20 (a) subtotal 180/827 2 (21.8%) ((b) Dextran (adjunctive therapy) (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (2/49 5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	0.8 -0.5 -32.1 0.6 -4.7 -5.4	1.2 1.8 66.8 3.6 8.8			38% (10) 2p = 0.00009 - 41% (26)
Welin-Berger1124/20(a) subtotal180/8272(21.8%)(21.8%)(21.8%)(b) Dextran (adjunctive therapy)(1)113(i) With pharmacological agent Schondorf (H)1139/54Swierstra (OAC)11421/71 van Geloven (OAC)859/79(1)subtotal39/204 (19.1%)	5/20 214/746 (28.7%) 8/55 34/81 20/80 62/216	-0.5 -32.1 0.6 -4.7 -5.4	1.8 - 66.8 3.6 8.8			> $38% (10)$ $2p = 0.0000$ $>$ $ 41% (26)$
 (a) subtotal (b) Dextran (adjunctive therapy) (i) With pharmacological agent Schondorf (H) H13 9/54 Swierstra (OAC) H4 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) 	214/746 (28.7%) 8/55 34/81 20/80 62/216	-32.1 0.6 -4.7 -5.4	66.8 3.6 8.8			38% (10 2p = 0.0000 - 41% (26
 (a) External (adjunctive therapy) (b) Dextran (adjunctive therapy) (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (19.1%) 	(28.7%) 8/55 34/81 20/80 62/216	0.6 _4.7 _5.4	3.6 8.8			2p = 0.0000
 (21.8%) ((b) Dextran (adjunctive therapy) (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (8/55 34/81 20/80 62/216	-4.7 -5.4	8.8		-	- 41% (26
 (b) Dextran (adjunctive therapy) (i) With pharmacological agent Schondorf (H) 113 9/54 Swierstra (OAC) 114 21/71 van Geloven (OAC) 85 9/79 (i) subtotal 39/204 (19.1%) (19.1%) 	8/55 34/81 20/80 62/216	-4.7 -5.4	8.8		•	- 41% (26
	(28.7%)	-9.5	18.4		>	40% (18
(ii) With compression method	()					2p = 0.03
Andersen (GCS) 15 5/29	14/31	-4.2	3.3 —	-		72% (31
Smith (IPC) 61 18/97	36/95	-9.3	9.8		_	61% (21
	50/126 (39.7%)	-13.5	13.1			64% (17 2p = 0.0002
	112/342 (32.7%)	-23.0	31.5			52% (13 2p = 0.0000
	326/1088 (30.0%)	-55.I	98.2	\Rightarrow		43% (8 2p < 0.0000
- 99% or <>> 95% confidence intervals			0.0	0.5	1.0	I.5 2.0
Heterogeneity between 3 subtotals: $\chi_2^2 = 3.4$; $p > 0.1$;	; NS			Dextran better	1	Dextran worse
					' t effect 2p < 0.0	

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

	Ref	Deep v thron			ratified atistics	Odds ratio a confidence int	
Study	no.	Dextran	control	O-E	Variance	(dextran : control)	ntrol) (SE)
(a) Dextran 40 (monotherapy)							
Gruber	104	20/113	36/113	-8.0	10.6		53% (22)
Hefley	105	15/45	14/42	0.0	4.9		
Hubens	106	5/39	9/41	-1.8	2.9 —		>
Huttunen	108	32/75	25/75	3.5	8.9		
(a) subtotal		72/272	84/271	-6.3	27.3		21% (17)
		(26.5%)	(31.0%)				2p > 0.1; NS
(b) Dextran 70 (monotherapy)							
Bergqvist I	100	13/27	20/22	-5.2	2.7 —		85% (27)
Bergqvist II	101	15/57	14/58	0.6	5.5		— ———————————————————————————————————
Carter	102	1/106	10/101	-4.6	2.6 —		83% (29)
Hurson	107	15/55	9/51	2.5	4.7		 >
Huttunen	108	20/75	25/75	-2.5	7.9		
Johnsson	109	1/27	13/25	-6.3	2.6 —		91% (23)
MacIntyre	110	32/130	47/128	-7.8	13.8	_	43% (21)
van Hospital	111	3/40	2/49	0.8	1.2 -	i	
Welin-Berger	112	4/20	5/20	-0.5	1.8 —		>
(b) subtotal		104/537	145/529	-23.0	42.7		42% (12)
		(19.4%)	(27.4%)				2p = 0.0004
(c) Dextran, molecular weight (· ·					
Evarts	103	4/18	10/21	-2.5	2.3 —		
(c) subtotal		4/18	10/21	-2.5	2.3		66% (40)
		(22.2%)	(47.6%)				2p > 0.1; NS
All trials		180/827 (21.8%)	239/821 (29.1%)	-31.8	72.3		36% (10) 2p = 0.0002
		(21.070)	(27.170)				_p 0.0001
- ■ - 99% or <⇒ 95% con	fidence	e intervals			0.0	0.5 1.0	1.5 2.0
Heterogeneity between 3 subto	tals: χ	$\frac{1}{2} = 2.6; p > 0$	0.1; NS			Dextran	Dextran
						better	worse
						Treatment effect 2p	-0.0002

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

	No. of trials		venous nbosis		ratified atistics		atio and e interval	% odds reduction
Category	with data	Dextran	Control	0-Е	Variance	(dextran : control)		(SE)
Elective hip or knee	5	53/218 (24.3%)	66/228 (28.9%)	-4.5	21.2			19% (20)
Hip fracture	4	34/128 (26.6%)	61/120 (50.8%)	-15.6	3.5 –			69% (16)
Other surgical procedure	9	Ì55/81Í (19.1%)	199/740 (26.9%)	-39.4	62.6	-		47% (9)
All trials	18	242/1157 (20.9%)	326/1088 (30.0%)	-59.5	97.3	\Leftrightarrow		46% (8) 2p < 0.00001
- 99% or <>> 959	% confidence	e intervals			L			
Heterogeneity between 3	categories:)	$\chi_2^2 = 7.4; p =$	0.02		0.0	0.5 Dextran better	I.0 I.5	
						Treatment offe	ct 2p < 0.00001	

(a) Dextran (monotherapy) Bergqvist I 100 (no data) Bergqvist I 101 10/57 8/58 1.1 3.8 Carter 102 (no data) (no data) (no data) Gruber 104 0/113 4/113 -2.0 1.0 Helley 105 (no data) (no data) (no data) Hubens 106 1/39 2/41 -0.5 0.7 Hutson 108 (no data) (no data) (no data) (no data) (no data) (no data) (no data) (no data) (no data) (no data) (no data) (a) subtotal 19/284 23/283 -2.1 9.3 (a) subtotal 19/284 23/283 -2.1 9.3 (b) Dextran (adjunctive therapy) (6.7%) (2.8/%) -3.3 7.0 (i) with compression method Andersen (GCS) 115 (no data) (no data) (ii) withotal (14/71 23/81 -3.3 7.0 37% (ii) subtotal (a) dajunctive therapy) 14/71 23/81 -3.3		Ref	Proxima thron			ratified atistics	confide	s ratio and ence interval	% odds reduction
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Study	no.	Dextran	control	O-E	Variance	(dextr	an : control)	(SE)
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	(a) Dextran (monotherapy	()					1		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $					(no	data)			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		101	10/57	8/58					>
Gruber 104 0/113 4/113 -2.0 1.0 (no data) (no data) (no data) (no data) (no data) Hubens 106 1/39 2/41 -0.5 0.7 $(no data)$ Hurson 107 5/55 7/51 -1.2 2.7 $(no data)$ Johnson 109 (no data) (no data) (no data) Johnson 109 (no data) (no data) MacIntyre 110 (no data) (no data) Velin-Berger 112 3/20 2/20 0.5 1.1 Wein-Berger 112 3/20 2/20 0.5 1.1 (a) subtotal 19/284 23/283 -2.1 9.3 20% (b) Dextran (adjunctive therapy) (i (a.14/71 23/81 -3.3 7.0 0.7 0.7 0.7 0.7 0.7 0.7 (i) subtotal 14/71 23/81 -3.3 7.0 0.7 0.7 0.7 0.7 0.7 0.7 0.7 0.7 0.7		102			(no	data)			
Hefley 105 (no data) Hubens 106 1/39 2/41 -0.5 0.7 Hurson 107 5/55 7/51 -1.2 2.7 Hurson 107 5/55 7/51 -1.2 2.7 Hurson 108 (no data) (no data) Johnsson 109 (no data) (no data) won Hospenthal 111 (no data) (no data) von Hospenthal 111 (no data) (no data) (a) subtotal 19/284 23/283 -2.1 9.3 20% (b) Dextran (adjunctive therapy) (no data) (no data) 2p > 0.1 (b) Dextran (adjunctive therapy) (14/71 23/81 -3.3 7.0 37% (i) subtotal 14/71 23/81 -3.3 7.0 2p > 0.1 (ii) with compression method (no data) (no data) 2p > 0.1 (ii) subtotal (no data) (no data) 2p > 0.1 (ii) subtotal (no data) (no data) 2p > 0.1 (iii) subtotal (al adjunctive	Evarts	103			(no	data)			
Hubens 106 1/39 2/41 -0.5 0.7 Hurson 107 5/55 7/51 -1.2 2.7 Hurtunen 108 (no data) (no data) Johnson 109 (no data) (no data) Mathyre 110 (no data) (no data) von Hospenthal 111 (no data) (no data) (a) subtotal 19/284 23/283 -2.1 9.3 20% (b) Dextran (adjunctive therapy) (6.7%) (8.1%) -2.1 9.3 20% (i) With pharmacological agent (no data) (no data) 20% 20% 20% (i) subtotal 14/71 23/81 -3.3 7.0 37% 2p > 0.1 (ii) subtotal 14/71 23/81 -3.3 7.0 37% 2p > 0.1 (ii) subtotal 14/71 23/81 -3.3 7.0 37% 2p > 0.1 (ii) subtotal 14/71 23/81 -3.3 7.0 37% 2p > 0.1 (iii) subtotal (lPC) 61 (no data) 2p > 0.1	Gruber	104	0/113	4/113	-2.0	Í.0			
Hurson 107 5/55 7/51 -1.2 2.7 Hurtunen 108 (no data) (no data) Johnson 109 (no data) (no data) MacIntyre 110 (no data) (no data) von Hospenthal 111 (no data) (no data) (a) subtotal 19/284 23/283 -2.1 9.3 (b) Dextran (adjunctive therapy) (6.7%) (8.1%) -2.1 9.3 (i) With pharmacological agent (no data) (no data) 20% Schondorf (H) 113 (no data) (no data) (i) subtotal 14/71 23/81 -3.3 7.0 (ii) subtotal 14/71 23/81 -3.3 7.0 (iii) with compression method (no data) (no data) 2p > 0.1 (ii) subtotal (and data) (no data) 37% 2p > 0.1 (ii) subtotal 14/71 23/81 -3.3 7.0 37% (iii) subtotal (no data) (no data) 2p > 0.1 37% (iii) subtotal (no data) (no data	Hefley	105			(no	data)			
Huttunen 108 (no data) Johnson 109 (no data) Machtyre 110 (no data) Von Hospenthal 111 (no data) (a) subtotal 19/284 23/283 -2.1 9.3 (b) Dextran (adjunctive therapy) (6.7%) (8.1%) -2.1 9.3 (i) With pharmacological agent (no data) 20% Swierstra (OAC) 114 14/71 23/81 -3.3 7.0 (i) subtotal 14/71 23/81 -3.3 7.0 37% (ii) subtotal 14/71 23/81 -3.3 7.0 37% (iii) subtotal 14/71 23/81 -3.3 7.0 37% (ii) subtotal (no data) (no data) 2p > 0.1 37% (iii) subtotal (no data) (no data) 37% 2p > 0.1 (ii) subtotal (all adjunctive therapy) 14/71 23/81 -3.3 7.0 37% (b) subtotal (all adjunctive therapy) (14/71 23/81 -3.3 7.0 37% (a) (b) subtotal (a		106	1/39	2/41	-0.5	0.7 —			\longrightarrow
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Hurson	107	5/55	7/51	-1.2	2.7 —			\longrightarrow
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Huttunen	108			(no	data)			
von Hospenthal 111 (no data) (a) subtotal 19/284 23/283 -2.1 9.3 (a) subtotal 19/284 23/283 -2.1 9.3 (b) Dextran (adjunctive therapy) (6.7%) (8.1%) -2.1 9.3 (i) With pharmacological agent Schondorf (H) 113 (no data) Swierstra (OAC) 85 (no data) (no data) (i) subtotal 14/71 23/81 -3.3 7.0 (ii) With compression method (19.7%) (28.4%) -3.3 7.0 (iii) With compression method (no data) (no data) 2p > 0.1 (ii) subtotal 14/71 23/81 -3.3 7.0 (iii) subtotal (19.7%) (28.4%) -3.3 7.0 (ii) subtotal (no data) (no data) 2p > 0.1 (iii) subtotal (al adjunctive therapy) 14/71 23/81 -3.3 7.0 (ii) subtotal (al 33/355 46/364 -5.4 16.4 28% (b) subtotal (all adjunctive therapy) (14.71 23/81 -5.4 16.4	Johnsson	109			(no	data)	1		
Welin-Berger 112 $3/20$ $2/20$ 0.5 1.1 (a) subtotal 19/284 $23/283$ -2.1 9.3 20% (b) Dextran (adjunctive therapy) (6.7%) (8.1%) -2.1 9.3 20% (b) Dextran (adjunctive therapy) (6.7%) (8.1%) -2.1 9.3 20% (10 With pharmacological agent Schondorf (H) 113 $(no \ data)$ $(no \ data)$ 37% (10 Subtotal 14/71 $23/81$ -3.3 7.0 37% $2p > 0.1$ (10 with compression method Andersen (GCS) 115 $(no \ data)$ $14/71$ $23/81$ -3.3 7.0 $2p > 0.1$ (10 With compression method $(no \ data)$ $(no \ data)$ $2p > 0.1$ 37% $2p > 0.1$ (10 Subtotal $(1P,7\%)$ (28.4%) -3.3 7.0 37% $2p > 0.1$ (11 subtotal $(no \ data)$ $(no \ data)$ (19.7%) (28.4%) $2p > 0.1$ (11 subtotal $(all \ adjunctive \ therapy)$ $14/71$ $23/81$ -3.3	MacIntyre	110			(no	data)			
Welin-Berger 112 $3/20$ $2/20$ 0.5 1.1 (a) subtotal 19/284 $23/283$ -2.1 9.3 20% (b) Dextran (adjunctive therapy) (6.7%) (8.1%) -2.1 9.3 20% (b) Dextran (adjunctive therapy) (6.7%) (8.1%) -2.1 9.3 20% (10 With pharmacological agent Schondorf (H) 113 $(no \ data)$ $(no \ data)$ 37% (10 Subtotal 14/71 $23/81$ -3.3 7.0 37% $2p > 0.1$ (10 with compression method Andersen (GCS) 115 $(no \ data)$ $14/71$ $23/81$ -3.3 7.0 $2p > 0.1$ (10 With compression method $(no \ data)$ $(no \ data)$ $2p > 0.1$ 37% $2p > 0.1$ (10 Subtotal $(1P,7\%)$ (28.4%) -3.3 7.0 37% $2p > 0.1$ (11 subtotal $(no \ data)$ $(no \ data)$ (19.7%) (28.4%) $2p > 0.1$ (11 subtotal $(all \ adjunctive \ therapy)$ $14/71$ $23/81$ -3.3	von Hospenthal	111			(no	data)			
(b) Dextran (adjunctive therapy) (i) With pharmacological agent (no data) Schondorf (H) 113 (no data) Swierstra (OAC) 114 14/71 23/81 -3.3 7.0 (i) subtotal 14/71 23/81 -3.3 7.0 37% (ii) subtotal 14/71 23/81 -3.3 7.0 2p > 0.1 (iii) With compression method (19.7%) (28.4%) 2p > 0.1 37% (ii) subtotal (no data) (no data) 2p > 0.1 (ii) subtotal (no data) (no data) 2p > 0.1 (ii) subtotal (no data) (no data) 2p > 0.1 (ii) subtotal (no data) (no data) 2p > 0.1 (ii) subtotal (all adjunctive therapy) 14/71 23/81 -3.3 7.0 All trials 33/355 46/364 -5.4 16.4 28% (p > 0.1 (12.6%) (12.6%) -5.4 16.4 28%		112	3/20	2/20	0.5	í.i –			>
(b) Dextran (adjunctive therapy) (i) With pharmacological agent (no data) Schondorf (H) 113 (no data) Swierstra (OAC) 114 14/71 23/81 -3.3 7.0 (i) subtotal 14/71 23/81 -3.3 7.0 37% (ii) subtotal 14/71 23/81 -3.3 7.0 2p > 0.1 (iii) With compression method (19.7%) (28.4%) 2p > 0.1 37% (ii) subtotal (no data) (no data) 2p > 0.1 (ii) subtotal (no data) (no data) 2p > 0.1 (ii) subtotal (no data) (no data) 37% (b) subtotal (all adjunctive therapy) 14/71 23/81 -3.3 7.0 (ii) subtotal (no data) 2p > 0.1 37% 2p > 0.1 All trials 33/355 46/364 -5.4 16.4 28%									
(b) Dextran (adjunctive therapy) (i) With pharmacological agent Schondorf (H) 113 (no data) Swierstra (OAC) 114 14/71 23/81 -3.3 7.0 (no data) (i) subtotal 14/71 23/81 -3.3 7.0 2 2 $p > 0.1$ (ii) With compression method Andersen (GCS) 115 (no data) (ii) subtotal (all adjunctive therapy) 14/71 23/81 -3.3 7.0 2 2 $p > 0.1$ (ii) subtotal (all adjunctive therapy) 14/71 23/81 -3.3 7.0 2 2 $p > 0.1$ All trials 33/355 46/364 -5.4 16.4 28% (9.3%) (12.6%) -5.4 16.4 28%	(a) subtotal				-2. I	9.3			20% (29
(i) With pharmacological agent Schondorf (H) 113 Swierstra (OAC) (no data) (i) subtotal 14/71 23/81 -3.3 7.0 (no data) (i) subtotal 14/71 23/81 -3.3 7.0 (no data) (ii) with compression method Andersen (GCS) 115 Smith (IPC) (no data) (ii) subtotal (no data) (no data) (ii) subtotal (14/71 23/81 (no data) -3.3 7.0 (ii) subtotal (19.7%) (28.4%) -3.3 7.0 (ii) subtotal (19.7%) (28.4%) -3.3 7.0 (ii) subtotal (ada) (no data) (no data) (b) subtotal (all adjunctive therapy) 14/71 23/81 (28.4%) -3.3 7.0 All trials 33/355 46/364 (9.3%) -5.4 16.4 28% 2p > 0.1			(6.7%)	(8.1%)					2p > 0.1; N
(ii) With compression method $2p > 0.1$ (iii) With compression method $(no \ data)$ Smith (IPC) 61 (ii) subtotal $(no \ data)$ (b) subtotal (all adjunctive therapy) $14/71$ $23/81$ (19.7%) (28.4%) (28.4%) -3.3 7.0 (19.7%) (28.4%) $2p > 0.1$ All trials $33/355$ $46/364$ -5.4 16.4 $2p > 0.1$ $2p > 0.1$ $2p > 0.1$	Schondorf (H) Swierstra (OAC)	3 4	4/7	23/81	_3.3	7.0			
Andersen (GCS) 115 (no data) Smith (IPC) 61 (no data) (ii) subtotal (no data) (b) subtotal (all adjunctive therapy) 14/71 23/81 -3.3 7.0 All trials 33/355 46/364 -5.4 16.4 28% $(p, 3\%)$ (12.6%) 0.1 2p > 0.1	(i) subtotal			-	-3.3	7.0			37% (30 2p > 0.1; N
Andersen (GCS) 115 (no data) Smith (IPC) 61 (no data) (ii) subtotal (no data) (b) subtotal (all adjunctive therapy) 14/71 23/81 -3.3 7.0 All trials 33/355 46/364 -5.4 16.4 28% $(p, 3\%)$ (12.6%) 0.1 2p > 0.1	(ii) With compression	method							
Smith (IPC) 61 (no data) (ii) subtotal (no data) (b) subtotal (all adjunctive therapy) $14/71$ $23/81$ -3.3 7.0 (b) subtotal (all adjunctive therapy) $14/71$ $23/81$ -3.3 7.0 $2p > 0.1$ All trials $33/355$ $46/364$ -5.4 16.4 28% $(p, 3\%)$ (12.6%) 0.1 $2p > 0.1$					(no	data)			
(b) subtotal (all adjunctive therapy) $14/71$ $23/81$ -3.3 7.0 37% (19.7%) (28.4%) $2p > 0.1$ All trials $33/355$ $46/364$ -5.4 16.4 28% (9.3%) (12.6%) $2p > 0.1$									
All trials $33/355$ $46/364$ -5.4 16.4 28% (9.3%) (12.6%) $2p > 0.1$	(ii) subtotal				(no	data)			
(9.3%) $(12.6%)$ $2p > 0.1$	(b) subtotal (all adjunc	tive therapy)		-	-3.3	7.0			37% (30 2p > 0.1; N
- 99% or <>> 95% confidence intervals	All trials				-5.4	16.4			28% (21 2p > 0.1; N
0.0 0.5 1.0 1.5 2.0	- 99% or <>> 959	6 confidence	intervals			0.0	0.5		1.5 2.0
Heterogeneity between 2 subtotals: $\chi_1^2 = 0.2$; $p > 0.1$; NS Dextran better Dextran	Heterogeneity between 2	= 0.2; p > 0	.1; NS			Dextran	D	extran	
Treatment effect $2p > 0.1$; NS									

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

	Ref	Pulme			ratified atistics		Odds ratio and nfidence interva	% od reduc	
Study	-	Dextran	control	0-Е	Variance	(de	extran : control)	(SE)
(a) Dextran (monotherapy)						1			
Bergqvist I	100			(no	data)	-			
Bergqvist II	101			· ·	data)				
Carter	102			· ·	data)	i i			
Evarts	102				data)				
Gruber	103				data)				
Hefley	105				data)				
Hubens	105			· ·	data)				
Hurson	100	8/55	9/51	-0.8	3.6		_	_	
Huttunen	107	0/33	7/51		data)		-		-
ohnsson	108			```	data)				
				· ·	,				
MacIntyre	110			(data)				
von Hospenthal	111	0/20	1/20	(data)	1			_
Welin-Berger	112	0/20	1/20	-0.5	0.3				-
(-)		8/75	10/71	1.2	2.0	i			
(a) subtotal			10/71	-1.3	3.8			200/	((13)
		(10.7%)	(14.1%)					29% 2p > 0.	6 (43)
(h) Devetuen (ediumetive them								2p > 0.	1; 145
(b) Dextran (adjunctive thera									
(i) With pharmacologica		1/54	2/55	-0.5	0.7 —	i			
Schondorf (H) Swierstra (OAC)	113	1/34	2/55					>	•
()	114	4/70	0/00	(data)	_			
van Geloven (OAC)	85	4/79	9/80	-2.5	3.0 —				
(i) subtotal		5/133	11/135	-2.9	3.7			550/	6 (36)
		(3.8%)	(8.1%)	-2.7	5.7			2p > 0.	
		(3.070)	(0.170)					2p > 0.	1,145
(ii) With compression me	ethod								
Andersen (GCS)	115			(no	data)				
Smith (IPC)	61	3/97	5/95	-1.0	í.9 —			>	≻
(ii) subtotal		3/97	5/95	-1.0	1.9 -				
		(3.1%)	(5.3%)					42%	6 (56)
								2p > 0.	I; NS
(b) subtotal (all adjunctive	e therapy)	8/230	16/230	-3.9	5.6			50%	6 (30)
		(3.5%)	(7.0%)					2p =	= 0.10
All trials		16/305	26/301	-5.3	9.5			43%	6 (25)
		(5.2%)	(8.6%)					2p =	= 0.09
- 99% or <> 95% o	onfidence	intervals				i			`
					0.0	0.5	1.0	1.5 2.0	,
Heterogeneity between 3 sub	totals: χ^2_2	= 0.4; p > 0	.1; NS			Dextran		Dextran	
						better		worse	
						Treat	ment effect $2p =$	0.09	

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.

	Ref	Major ext ble			ratified atistics			Odds confide	ratio a nce inte			% odds reduction
Study	no.	Dextran	control	0-Е	Variand	e		(dextra	in : con	trol)		(SE)
(a) Dextran (monotherapy)											-	
Bergqvist I	100	0/27	0/22								1	
Bergqvist II	101	0/57	0/58									
Carter	102			(no	data)						1	
Evarts	103			· · ·	, data)						1	
Gruber	104				data)						1	
Hefley	105				data)						1	
Hubens	106	0/39	0/41	(,						1	
Hurson	107			(no	data)						1	
Huttunen	108				data)						1	
ohnsson	109	0/27	0/25	(,						1	
MacIntyre	110			(no	data)						1	
von Hospenthal	111	0/40	0/49		,						1	
Welin-Berger	112			(no	data)						1	
0					,						-	
(a) subtotal		0/190	0/195								i.	
		(0.0%)	(0.0%)								-	
											1	
(b) Dextran (adjunctive thera											-	
(i) With pharmacologica											1	
Schondorf (H)	113	0/54	0/55								1	
Swierstra (OAC)	114	17/71	8/81	5.3	5.2						<u>;</u>	
van Geloven (OAC)	85	2/79	1/80	0.5	0.7	←				-	!	\longrightarrow
		10/00/	0/01/									
(i) subtotal		19/204	9/216	5.8	6.0						-	
		(9.3%)	(4.2%)								1	-165% (69
(::) \A /:+	- داء - ما										1	2p = 0.02
(ii) With compression m Andersen (GCS)	115			(no	data)						i i	adverse
Smith (IPC)	61	14/79	2/95	5.9	3.7						<u> </u>	
Smith (IPC)	01	14/77	2/75	5.7	3.7						1 -	
(ii) subtotal		14/97	2/95	5.9	3.7							
(II) Subtotal		(14.4%)	(2.1%)	5.7	5.7							-398% (129
		(0/ ד.דו)	(2.170)								i i	2p = 0.002
											1	adverse
(b) subtotal (all adjunctiv	o thorany)	33/301	/3	11.7	9.7							adverse
	e the apy)	(11.0%)	(3.5%)	11.7	7.1							-234% (62
		(11.070)	(0.070)								1	2p = 0.0002
											:	adverse
All trials		33/491	11/506	11.7	9.7					<	\rightarrow	
		(6.7%)	(2.2%)							-	{	-237% (63
		(,•)	(/								-	2p = 0.0002
											:	adverse
											-	
- 99% or <> 95% o	confidence	intervals				0.0	0.25	0.5	1.0	2.5	5.0	 10
						0.0			1.0			ĨŬ
Heterogeneity between 2 sul	Dtotals: χ_1^2	= 0.9; þ > 0	. I; NS				Dextra				extran	
							bette	r		v	/orse	
							Treatm	ent effec	t 2b = 0	.0002. a	lverse	

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

		No. of trials		venous nbosis		ratified atistics		Odds rati confidence	interval	% odds reduction
Cat	egory	with data	Dextran	Control	0-Е	Variance		(dextran : c	control)	(SE)
(a)	Type of data									
()	Tabular	I	15/55	9/51	2.5	4.7	_			>
			(27.3%)	(17.6%)						
	Published	17	227/1102	317/1037	-57.6	93.5		⊢ ∣		46% (8)
			(20.6%)	(30.6%)						()
(b)	Randomisation metho	d								
. ,	Robust	11	202/825	253/757	-38.9	75.9				40% (9)
			(24.5%)	(33.4%)						
	Less robust	7	40/332	73/331 [´]	-16.2	22.3				52% (15)
			(12.0%)	(22.1%)						()
(c)	Assessment of DVT									
	Blinded assessor	5	72/279	113/280	-20.8	29.2				51% (13)
			(25.8%)	(40.4%)						
	Other/unknown	13	170/878	213/808	-34.3	69.0	_			39% (9)
			(19.4%)	(26.4%)						
(d)	DVT confirmation									
	Venogram	3	14/180	23/176	-4.6	8.0				44% (27)
			(7.8%)	(13.1%)						
	Other method	15	228/977	303/912	-50.5	90.2	_			43% (8)
			(23.3%)	(33.2%)						
	All trials	18	242/1157	326/1088	-55.I	98.2	\bigtriangledown	>		43% (8)
			(20.9%)	(30.0%)						2p < 0.00001
-	- 99% or <⊃ 959	% confidence	intervals			0.0) 1.5	2.0
He	erogeneity between 8	categories: χ	$^{2}_{4} = 7.6; p >$	0.1; NS		0.0		l l		
	- •	2 /	т ,				Dextra bette		Dextra wors	
							Tre	atment effect	2p < 0.00001	

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

	Ref	Deep v throm			ratified atistics		dds ratio and fidence interva	I	% odds reduction
Study	no.	Dextran	Heparin	0-Е	Variance	(de	xtran : heparin)	(SE)
(a) (Low dose) unfractio	nated hepari	n							
Bergqvist I	100	13/27	18/28	-2.2	3.4 —				>
Bergqvist II	101	15/57	6/53	4.1	4.3				\rightarrow
Gruber	104	20/113	12/119	4.4	6.9	-			>
Hohl	116	17/117	2/115	7.4	4.4				>
Hubens	106	5/39	4/39	0.5	2.0				>
MacIntyre	110	32/130	15/128	8.3	9.6				>
Urbanyi	117	2/46	1/43	0.4	0.7 —				>
van Geloven	85	9/79	13/74	-2.4	4.7 -				
Welin-Berger	112	4/20	8/20	-2.0	2.2 —				>
Wille-Jorgensen	39	3/98	2/94	5.3	3.5		— —		>
(a) subtotal		130/726	81/713	24.0	41.8				
		(17.9%)	(11.4%)						-78% (21)
(b) Low molecular weig	ht heparin								2p = 0.0002 adverse
Dan Enox	99	24/126	7/120	8.1	6.8				>
Eriksson	118	22/5 I	10/50	5.8	5.5				>
Matzsch	119	36/123	22/120	6.6	11.1				- B ¹ >
Oertli	120	31/103	16/113	8.6	9.2		<u> </u>		>
Wiig	121	38/164	35/165	1.6	14.2				>
(b) subtotal		151/567	90/568	30.8	46.9				
		(26.6%)	(15.8%)						-93% (21) 2p < 0.00001
مال د		201/1202	171/1281	F 4 0	00 (adverse
All trials		281/1293 (21.7%)	(13.3%)	54.8	88.6				-86% (15)
	115	. ,	-						2p < 0.0000 l
	61								adverse
- 99% or <>> 95	5% confiden	ce intervals			L				
			2		0.0	0.5	1.0 I	1.5	2.0
Difference between trea Het		s in 2 subtotals: /ithin subtotals:				Dextran better		Heparin better	
		tween 15 trials:				Trootmont	ffect 2p < 0.000) advarsa	

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

	Ref		tracranial eds	Stratified statistics			Odds ratio and confidence interval		
Study	no.	Dextran	Heparin	0-Е	Variance	(dex		(SE)	
(a) Dextran vs (low do	se) unfractio	nated heparin							
Bergqvist I	100	0/27	0/28						
Bergqvist II	101	0/57	2/53	-1.0	0.5	1			\longrightarrow
Gruber	104	1/113	8/119	-3.4	2.2 —				79% (34)
Hohl	116			(ne	o data)	1			
Hubens	106	0/39	0/39			1			
MacIntyre	110	0/130	1/128	-0.5	0.2				>
Urbanyi	117	0/46	0/43			1			
van Geloven	85	2/79	I/74	0.5	0.7 —				\rightarrow
Welin-Berger	112			(no	o data)	i i			
Wille-Jorgensen	39	1/98	0/94	0.5	0.2 —	1			\rightarrow
<i>.</i>									
(a) subtotal		4/589	12/578	-4.0	3.9 -	\leq			64% (32)
		(0.7%)	(2.1%)						2p = 0.04
(b) Dextran vs low mo	lecular weigl	nt heparin							
Dan Enox	99	•		(ne	o data)	1			
Eriksson	118	0/51	0/50		,				
Matzsch	119	0/123	0/120			1			
Oertli	120	0/103	0/113						
Wiig	121	0/164	0/165						
(b) subtotal		0/441	0/448						
		(0.0%)	(0.0%)						
All trials		4/1030	12/1026	-4.0	3.9 -				64% (32)
, ui ti iais		(0.4%)	(1.2%)	-1.0	3.7				2p = 0.04
- 99% or <>>	95% confide	nce intervals			L				
					0.0	0.5	1.0	1.5	2.0
						Dextran better		Heparin better	
						Treatm	ent effect $2p = 0$	0.04	

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

	Ref	Pulmember	onary olism		atified tistics		Odds ratio and confidence interval		% odds reduction
Study	no.	Dextran	Heparin		Variance	(dex	tran : heparin))	(SE)
(a) Dextran vs (low dose	e) unfractiona	ated heparin							
Bergqvist I	100			(no	data)				
Bergqvist II	101			(no	data)				
Gruber	104			(no	data)				
Hohl	116			(no	data)				
Hubens	106			(no	data)				
MacIntyre	110			(no	data)				
Urbanyi	117	0/46	0/43						
van Geloven	85	4/79	2/74	0.9	1.4				\rightarrow
Welin-Berger	112	0/20	0/20						
Wille-Jorgensen	39	1/98	1/94	0.0	0.5 ——		-		\longrightarrow
(a) subtotal		5/243	3/231	0.9	1.9				
		(2.1%)	(1.3%)						–57% (91
(b) Dextran vs low mole	cular weight	heparin							2p > 0.1; N advers
Dan Enox	99	-		(no	data)				
Eriksson	118	2/51	2/50	0.0	I.0 —				>
Matzsch	119	4/123	2/120	1.0	1.5		+		→
Oertli	120	1/103	2/113	-0.4	0.7 —				>
Wiig	121	0/164	0/165						
(b) subtotal		7/441	6/448	0.5	3.2				
		(1.6%)	(1.3%)						-17% (61 2p > 0.1; N
									adverse
All trials		12/684	9/679	1.4	5.1				210/ /51
		(1.8%)	(1.3%)						-31% (51 2p > 0.1; N
									adverse
- 99% or <> 95	% confiden	ce intervals				0.5		1.5	
			2		0.0		1.0 		2.0
Difference between treat	ment effects	in 2 subtotals:	$\chi_1^* = 0.1; p >$	0.1; NS		Dextran better		Heparin better	
						Treatment off	ect 2p > 0.1; N	IS adverse	

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

		Deep			atified		ds ratio and		% odds
Study	Ref no.	thron Regional	General	statistics O–E Variance		confidence interval (regional : general)			reduction (SE)
···· /		itegional	Chicrai	• -	variance	(-8			
Brichant	122	14/54	13/52	0.2	5.1				\longrightarrow
Davis I	123	17/64	28/68	-4.8	7.5				48% (27)
Davis II	124	9/69	19/68	-5.I	5.6 -				60% (28)
Fredin	125	11/30	12/30	-0.5	3.6	i	•		\longrightarrow
Hendolin I	126	2/17	11/21	-3.8	2.2 —				83% (32)
Hendolin II	127	1/28	2/40	-0.2	0.7 —				\longrightarrow
Jorgensen	128	3/24	13/24	-5.0	2.7 —				84% (28)
McKenzie	129	8/20	16/20	-4.0	2.5 —				80% (31)
Modig	17	21/50	38/50	-8.5	6.1 —	-			75% (22)
Rodrigo	130	5/11	7/11	-1.0	I.4 —				>
Williams-Russo	131	39/97	39/81	-3.5	10.9				
All trials		130/464 (28.0%)	198/465 (42.6%)	-36.2	48.3				53% (10) 2p < 0.00001
- 99% or <>>	> 95% confid	ence intervals			L				
					0.0	0.5	1.0	1.5	2.0
Heterogeneity betwe	een 11 trials: χ	$p_{10}^2 = 16.8; p = 0.0$	08			Regional better		General better	
						T	effect 2p > 0.0	0001	

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

	No. of trials		venous nbosis		ratified atistics	Odds rat confidence		% odds reduction
Category	with data	Regional	General	0-Е	Variance	(regional :	general)	(SE)
Effective knee	3	47/132 (35.6%)	59/116 (50.9%)	-9.5	15.1		_	47% (19)
Elective hip	4	55/203 (27.1%)	82/200 (41.0%)	-13.9	20.4			49% (16)
Hip fracture	2	25/84 (29.8%)	44/88 (50.0%)	-8.8	9.9			59% (21)
Urological surgery	I	2/17 (11.8%)	11/21 (52.4%)	-3.8	2.2 —			82% (32)
General surgery	Ι	1/28 (3.6%)	2/40 (5.0%)	-0.2	0.7			>
All trials	11	l 30/464 (28.0%)	198/465 (42.6%)	-36.2	48.3			53% (10) 2p < 0.00001
- 99% or <>	95% confidence	intervals			0.0	0.5 I.		2.0
Heterogeneity betwee	n 5 categories: χ	$p_{4}^{2} = 2.8; p >$	0.1; NS		0.0	Regional better	Gener bette	ral
						Treatment effec	t 2h < 0 00001	

FIGURE 33 Comparison of the effects of regional anaesthesia and general anaesthesia on deep venous thrombosis among different types of patients
Study	Ref no.	Proximal venous thrombosis		Stratified statistics			Odds ratio and confidence interval			% odds reduction
		Regional	General	<u>о-Е</u>	Variance			al : genera		(SE)
Brichant	122			(no	data)					
Davis I	123			, (no	data)					
Davis II	124	3/69	8/68	-2.5	2.5 -					
Fredin	125	1/30	2/30	-0.5	0.7 —					>
Hendolin I	126			(no	data)					
Hendolin II	127			(no	data)					
Jorgensen	128	1/24	3/24	-1.0	0.9 —					>
McKenzie	129			(no	data)					
Modig	17	8/50	30/50	-11.0	5.9 —	-				84% (19
Rodrigo	130	1/11	4/11	-1.5	I.0 —	+				>
Williams-Russo	131	0/97	0/81							
All trials		14/281 (5.0%)	47/264 (17.8%)	-16.5	11.2					77% (16 2p < 0.0000
	> 95% confid	ence intervals			L				I	
					0.0	0.	5	1.0	1.5	2.0
Heterogeneity betwo	een 5 trials: χ_4^2	= 2.0; p = 0.1; N	15			Regio bett			General better	
						Treatment effect $2p < 0.0001$				

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





	Ref	Major extracranial bleeds		Stratified statistics		Odds ratio and confidence interval			% odds reduction		
Study	no.	Regional	General	0-Е	Variance		(regior	al : gene	eral)		(SE)
Brichant	122	0/54	0/52								
Davis I	123	0/64	5/68	-2.4	1.2 ←						100% (45)
Davis II	124			(no	data)						
Fredin	125	0/30	0/30								
Hendolin I	126			(no	data)						
Hendolin II	127	0/28	0/40								
Jorgensen	128	0/24	0/24								
McKenzie	129	0/20	0/20								
Modig	17			(no	data)						
Rodrigo	130			(no	data)						
Williams-Russo	131	0/97	0/81								
All trials		0/317	5/315	-2.4	.2 ←			-			100% (45)
		(0.0%)	(1.6%)								2p = 0.03
- 99% or <=>	> 95% confid	ence intervals			L						
	, , , , , , , , , , , , , , , , , , ,				0.1	0.25	0.5	1.0	2.5	5.0	10
						Regior bette			Gene bett		
						Treatment effect $2p = 0.03$					

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

	No. of trials	Deep venous thrombosis		Stratified statistics		Odds ratio and confidence interval		% odds reduction
Category	with data	Regional	General	0-Е	Variance	(regiona	l : general)	(SE)
a) Type of data								
Tabular	6	87/304 (28.6%)	27/29 (43.6%)	-22.9	32.8			50% (13
Published	5	43/160 (26.9%)	(13.070) 71/174 (40.8%)	-13.3	15.5			58% (17
b) Randomisation met	hod							
Robust	8	110/371 (29.6%)	176/362 (48.6%)	-35.2	41.1			58% (10
Less robust	3	20/93 (21.5%)	22/103 (21.4%)	-1.0	7.2			\longrightarrow
c) Assessment of DV	г							
Blinded assessor	7	114/388 (29.4%)	162/373 (43.4%)	-27.2	41.5			48% (11
Other/unknown	4	(21.1%)	36/92 (39.1%)	-9.I	6.8 —	-		74% (21
d) DVT confirmation								
Venogram	3	24/151 (15.9%)	34/160 (21.3%)	-5.I	11.4			36% (24
Other method	8	106/313 (33.9%)	164/305 (53.8%)	-31.1	36.9			57% (11
All trials	Ш	130/464 (28.0%)	198/465 (42.6%)	-36.2	48.3	\rightarrow		53% (10 2p < 0.0000
- 99% or <>	95% confidenc	e intervals			L			I
Heterogeneity betwee	n 8 categories:	$\chi_4^2 = 7.5; p >$	0.1; NS		0.0	0.5 Anaesthesia better	I.0 I.5 Anaesth wors	
						Treatment eff	ect 2p < 0.00001	

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 metaanalyses 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 aboveknee 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 'minidose' 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 minidose 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 I

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

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- 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
- (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*
- (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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We look forward to hearing from you.

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