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Comparing strategies for thromboprophylaxis in major orthopedic surgery using an estimation of net risk-benefit through probabilistic simulation. A clinical cost-effectiveness study.

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A clinical cost-effectiveness study.

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies
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Abstract

Clinical decisions should take into account the clinical risk and benefit of a new intervention compared to the reference treatment. A method was developed to compare multiple competing interventions using a clinical cost-effectiveness approach. A meta-analysis was conducted to estimate the clinical cost (major bleeding) and benefit (averted venous thromboembolism) of thromboprophylaxis with different anticoagulants in orthopedic surgery. The increment in cost and benefit of anticoagulants compared to placebo were calculated using replications of the values obtained through Monte Carlo simulations. Net clinical benefit was calculated for each replication across a range of risk acceptance values (risk-benefit acceptability threshold). Multiple anticoagulants were compared by calculating the probability that each agent had of achieving the highest net clinical benefit. The preferred anticoagulants varied depending on risk acceptance, type of surgery, bleeding and thrombosis definitions, and timing of anticoagulant initiation. This method allowed comparing multiple interventions in the absence of randomized trials.

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I dedicate this work to my most beloved ones: my wife Blanca and my son Alejandro III without whose love this task would have been impossible.

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1. Background

1.1. Overview of venous thromboembolic disease

Venous thromboembolic disease, or venous thromboembolism (VTE), is a leading cause of morbidity and mortality in developed countries. It is estimated that between 200,000 and 600,000 new cases require hospitalization each year in the United States with an annual incidence of 117 per 100,000 population or 1.92 per 1000 person-years[1-4] and, in spite of proper treatment, the in-hospital mortality of VTE may be as high as 12%[2,3,5]. Venous thromboembolism comprises two clinical entities, namely deep venous thrombosis (DVT) and pulmonary embolism (PE), and is usually treated with anticoagulant drugs due to its high mortality if untreated. The only randomized trial comparing anticoagulation with no treatment was published over 40 years ago and it showed that mortality in untreated PE patients exceeded 25%[6]. After this seminal work the need for anticoagulant therapy in patients with VTE has been consistently recognized and numerous studies have evaluated different anticoagulants, duration of treatment and schedules of administration[7]. There is a general consensus that treatment of VTE requires initial treatment with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for at least five days followed by at least 6 months of anticoagulation with a vitamin K antagonist for a first unexplained episode or 3 months if the episode is associated with a transient risk factor such as surgery[8].

1.1.1. Treatment versus no treatment of distal DVT

DVT can be clinically divided according to its anatomical localization in proximal, if localized in the veins extending cephalad from the region on the calf were the veins join the popliteal vein, or distal if it is confined to the calf[5]. A clot localized in the lower limb might detach in whole or in part and lodge into the pulmonary vasculature causing a PE. For this reason, DVT and PE are considered different presentations of the same pathological process. It has been estimated that up to 50% of the patients with a symptomatic proximal DVT will have signs suggestive of PE on lung scans without any suggestive clinical symptoms[9,10]. The relevance of a DVT or PE diagnosis can be estimated from the fact that about 50% of patients with an untreated symptomatic proximal DVT will experience a symptomatic PE within 3 months and around 10% of patients with a symptomatic PE will die shortly after onset[11,12]. It is therefore accepted that all patients with a PE or a proximal DVT require treatment with the aim of preventing a recurrence; however, there is controversy with respect to patients with an isolated distal DVT. Such controversy arises from several facts: firstly, thromboses occurring in association with surgery usually start in the veins of the calf; however, approximately one half will resolve spontaneously within 72 hours[11,13-15]. Second, only about 20% of symptomatic patients have thromboses confined to the calf[5]. Third, only about one fifth to one sixth of the patients with a symptomatic calf thrombosis will experience an extension of a calf clot into the proximal veins[5,8,16,17]. Fourth, although the risk of proximal extension in asymptomatic patients is likely lower, it remains unknown. Finally, the risk of PE is greatly increased when the thrombus extends into the proximal veins[13] but not if the clot remains confined to the calf[16-18]. For these reasons in many places the usual practice is to treat patients with proximal DVT or PE and to perform serial ultrasounds in patients with isolated calf thromboses and only those patients in whom the serial ultrasounds demonstrate an extension into the proximal veins are treated[5,16].

1.1.2. Hemorrhagic complications of anticoagulant treatment

Although undoubtedly beneficial, anticoagulant therapy is not free from complications the most frequent of which is hemorrhage. Up to 17% of patients included in studies evaluating VTE treatment experience a major bleeding episode during the first 3 months of treatment[19] and it has been estimated that the case-fatality rate of major bleeding episodes is greater than 13%[20]. It is known that higher intensity of anticoagulation, longer duration of treatment and individual characteristics of the patient – such as comorbidity or concomitant medications – influence the risk of bleeding[19]. An issue that has complicated the evaluation of bleeding risks associated with the use of anticoagulants is that the definition of major bleeding has varied among studies and only recently a standard definition has been proposed[19,21]. The Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) proposed that a bleeding episode be considered as major if it was fatal, involved a critical organ or resulted in a significant decrease in hemoglobin[21]. A limitation of this definition is that it was proposed for non-surgical patients, and since recent surgery is a risk factor for bleeding, especially if associated with other risk factors[19], its use in surgical population might not be adequate. In spite of the high risk of bleeding associated with anticoagulant therapy it has been recommended that, for the purpose of clinical decision making, such risk cannot be considered alone and that it should be balanced with the potential decrease in thromboembolism[19]. Unfortunately, techniques to compare risks and benefits conjointly are scarce and this evaluation of risks and benefits is usually made on an individual and subjective manner.

1.1.3. Thromboembolism in surgical patients and surrogate endpoints

As previously mentioned, several conditions are associated with an increased risk of thrombosis. Among hospitalized medical or general surgery patients the prevalence of DVT ranges between 10% and 40%, but in some groups such as patients with stroke, major trauma, acute spinal cord injury or orthopedic surgery it might be as high as 80%[22,23]. As a consequence of this high prevalence, numerous efforts have been made in order to decrease the occurrence of DVT in patients at high risk through the use of either mechanical devices or anticoagulant drugs. However, relying on symptomatic events is impractical when planning a randomized trial evaluating VTE prophylaxis after a surgical procedure. The reasons are twofold: firstly, symptoms are difficult to standardize due to their subjective nature, and they might be difficult to assess if the surgical procedure involves the lower limbs, as is the case of orthopedic surgery. Second, because symptomatic events are relatively infrequent after surgery, in order to demonstrate relevant risk reductions large sample sizes would be required with the subsequent increase in research costs. For these reasons, surrogate endpoints have been sought and used as measures of efficacy in studies evaluating prophylaxis after surgical procedures. Compression ultrasound has been used as a screening technique after surgical procedures with poor results as can be judged from its poor inter-observer agreement, low sensitivity and failure to demonstrate a reduction in symptomatic complications after surgery[24,25]. Therefore, the usual endpoint in surgical trials is venography[26,27] because it is a standard radiological technique[28] with a good inter-observer agreement[29,30] that allows objective comparisons and central blinded adjudication of outcomes[26].

The use of venographic endpoints in VTE prophylaxis studies of surgical patients is still a matter of debate[26,31,32], but some authors argue that they are adequate[27,33,34] and they have been widely adopted in clinical trials evaluating VTE in surgical patients. However there are several potential concerns regarding the use of surrogate endpoints. According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, which provides standardized guidelines for the conduct of trials for regulatory approval in Europe, Japan and the United States, an appropriate surrogate endpoint needs biological plausibility, demonstration of its prognostic value for the clinical outcome and evidence that treatment effects on the surrogate correspond to effects on the clinical outcome[35]. In spite of the arguments in favor suggesting that a reduction in venographic thrombosis parallels a reduction in symptomatic events[27,33,34], the aforementioned conditions have not been convincingly demonstrated in studies evaluating VTE prophylaxis after orthopedic surgery, in great part because the natural history of asymptomatic venographically demonstrated DVT is not known since many clinicians find it difficult not to treat these patients. Furthermore, the same International Conference on Harmonisation has noted that surrogates are not necessarily interchangeable between products with different modes of action but used for treating the same disease.

An additional problem arises from the fact that most studies using venographic endpoints consider the endpoint achieved if there is any evidence of a thrombus detected by venography, independently of localization, size, symptom occurrence or clinical relevance. The uncertain clinical significance of isolated distal DVT complicates the interpretation of VTE prophylaxis studies relying on venographic endpoints due to the high proportion of thromboses confined to the calf that is detected by this technique. A particularly worrisome aspect of venographic endpoints in studies conducted in otherwise comparable populations is that it has been demonstrated that in spite of a good inter-observer reliability and standardized diagnostic criteria, there is substantial variation in the event rates between adjudicating centers[33]. This could be the result of systematic differences in the evaluation of the relevance of the findings derived from different clinical schools. All of the aforementioned concerns have prompted the search of alternate surrogate endpoints such as thrombus burden[36] to no abode, probably as a consequence of the lack of well conducted studies and easily reproducible outcomes.

1.2. Overview of venous thromboembolism in major orthopedic surgery

A situation with a particularly high risk for developing venous thromboembolism is major orthopedic surgery (MOS). Previous studies and systematic reviews have reported that without the use of prophylaxis following total hip replacement (THR), total knee replacement (TKR), or surgery for hip fracture (HFS) the prevalence of venographic VTE might be as high as 85% and that fatal pulmonary embolism may be present in up to 8% of patients (Table 1) [22,31,37-40].

Table 1. Prevalence of deep venous thrombosis and pulmonary embolism after major orthopedic surgery without the use of prophylactic measures

Procedure	*Deep Vein Thrombosis (%)*		*Pulmonary Embolism (%)*	
	Total	*Proximal*	*Total*	*Fatal*
Total Hip Replacement	42-57	17-36	0.9-29	0.1-2
Total Knee Replacement	41-85	5-22	1.5-10	0.1-1.7
Hip Fracture Surgery	46-60	23-30	3-11	2.5-8

Modified from references [22,40]

This information is derived from a variety of study designs including randomized trials, cohort studies and registry data and many studies date back to the mid 1960's. Since surgical practice and postoperative care have substantially changed in the last 40 years as a result of improved knowledge on pathophysiology, kinematics and materials science[41-44], it is likely that such changes have impacted on the prevalence of VTE. Some of the most relevant changes likely influencing the risk of VTE are: early postoperative ambulation and rehabilitation; preoperative autologous blood donation; hypotensive epidural anesthesia with epinephrine infusion; shorter surgical times, minimizing femoral vein occlusion and blood loss during surgery; pneumatic compression and patient mobilization with foot exercises immediately after surgery[45]. A review of the information derived from randomized controlled trials published after 1980 shows that in patients receiving placebo after MOS the frequency of proximal DVT and PE might be between 6% and 57% and that of total venographic DVT plus PE between 20% and 93% (Table 2).

Table 2. Prevalence of venous thromboembolism after major orthopedic surgery in patients receiving placebo included in trials published after 1980

Procedure	*Proximal DVT + PE (%)*	*Proximal and Distal DVT + PE (%)*	*Symptomatic VTE[a] (%)*
Total Hip Replacement	7.4 - 57.1	22.0 - 92.9	1.0 - 6.0
Total Knee Replacement	5.9 - 20.4	58.7 - 70.6	29.4

DVT Deep vein thrombosis; PE Pulmonary embolism; VTE Venous thromboembolism.
[a] Includes symptomatic DVT and PE, as well as deaths in which PE could not be excluded as the cause
Adapted from references [46-54]

The risk of developing postoperative VTE extends at least up to thirty-five days after the surgery and probably longer[55]. A large epidemiological study suggested that even after the adoption of widespread prophylaxis the incidence of VTE after MOS might be as high as 2.8% of patients at 91 days and that up to 76% of VTE events are diagnosed after hospital discharge[56]. However, in randomized studies evaluating thromboprophylaxis after MOS and reporting a follow-up between 42 and 180 days the occurrence of late events (i.e. those occurring after completing an initial course of prophylaxis of less than 15 days of duration) was not exceedingly common (Table 3), in spite of which several randomized trials have shown that extended-duration anticoagulation reduces the risk of venographic and symptomatic VTE after MOS[23,55,57-62] although one study did not find a significant reduction[63]. On the other hand, it has been argued that due to the low frequency of symptomatic events after MOS, extended prophylaxis is not required[32].

Table 3. Prevalence of venous thromboembolic events occurring after completing a course of short-term prophylaxis (< 15 days) in patients undergoing major orthopedic surgery

Drug	*Symptomatic DVT / PE % (95% CI)*	*Fatal Pulmonary Embolism % (95% CI)*
Ximelagatran	0.003 - 0.015	0 - 0.008
LMWH	0 - 0.031	0 - 0.007
UFH	0 - 0.027	0 - 0.007
Warfarin	0 - 0.015	0 - 0.001
Fondaparinux	0.006 - 0.017	0 - 0.007

DVT Deep venous thrombosis; PE Pulmonary embolism; CI Confidence interval; LMWH Low molecular weight heparin; UFH Unfractionated heparin.
Adapted from references[48,50,64-85]

All the previous data has led to recommend the use of measures to prevent VTE after MOS and probably the most widely disseminated guidelines are those proposed by the American College of Chest Physicians (ACCP)[22,23,86,87]. The current guidelines recommend administering prophylaxis for at least ten days and in the case of patients undergoing THR or HFS extending the duration up to 28 to 35 days. These recommendations have been made based on the best high quality available evidence and they are considered to be strong (i.e. ACCP Grade 1A, meaning that they are derived from well conducted randomized clinical trials with consistent results, and that there is a high level of certainty that benefits do, or do not, outweigh risks, burdens, and costs)[23,88]. The recommended agents for prophylaxis include different anticoagulant drugs such as low molecular weight heparin (LMWH) (e.g. Ardeparin, Dalteparin, Enoxaparin, Nadroparin, Reviparin and

Tinzaparin), vitamin K antagonists (VKA) and fondaparinux. However, other agents are or have been used or evaluated for this indication including aspirin, unfractionated heparin, ximelagatran, dextran, hirudins, danaparoid, dabigatran and argatroban, and some of them such as unfractionated heparin are still the standard of care in many countries[89,90].

In addition to those proposed by the ACCP[22,23,86,87], numerous professional organizations have published their own guidelines. Examples are the Finnish Medical Society[91], the University of Iowa Gerontological Nursing Research Center[92], the NIH Consensus Development Conference on Total Knee Replacement[93], the Scottish Intercollegiate Guidelines Network[94], the Institute for Clinical Systems Improvement[95], the Southern African Society for Thrombosis and Hemostasis[96], and the Thrombosis Interest Group of Canada[97]. Although different in several aspects, a common characteristic to all these guidelines is that they provide recommendations based on the level and quality of the available evidence[88], and they avoid favoring a specific agent, in order to let the clinicians decide the best choice. Therefore, the choice of the agent, timing of initiation and dosage used for prophylaxis depends in great part on the availability and personal preferences of the clinicians involved in the care of MOS patients. This is likely due to the fact that the available information is derived mainly from randomized trials involving parallel groups and there is not a single trial comparing all the agents of interest.

Another point remaining unanswered is the optimal time to initiate prophylaxis. There is evidence that administering the first dose of anticoagulant prophylaxis in close proximity to surgery results in a lower proportion of VTE[98]; however it has also been suggested that this timing schedule is associated with a higher bleeding risk[99]. Given the high case-fatality rate of major bleeding (*vide supra*)[20], and the fact that bleeding is the most frequent complication of anticoagulant prophylaxis, avoiding an excess bleeding risk is as important as achieving a good preventive effect. To this object, a multiple agent and schedules comparison is highly desirable because it would allow clinicians to evaluate all the agents in terms of their efficacy and it would permit to establish differences in their risk profiles. This is important because the use of prophylactic anticoagulants is associated with an increased risk of bleeding that is assumed to be essentially equivalent among the different agents, notwithstanding the fact that there is some information indicating that some of them seem to convey a higher risk of developing hemorrhagic complications[100]. Information derived from such a trial would be very useful because from a clinical point of view, the preferred treatment should be the one providing the highest benefit with the least risk. Only if all treatments are equivalent could the clinician be indifferent between choices and take into account other considerations such as the administration route, the need to monitoring the therapy and other seldom observed untoward effects. Since the most frequent side effect observed with the use of these agents is bleeding, in general the other rare side effects are unlikely to largely influence the selection of the agent, except under special circumstances such as heparin-induced thrombocytopenia[101].

As desirable as a study evaluating all agents would be, it is almost certain that a trial comparing all the available agents and schedules will never be conducted because multiple methodological issues, inability to obtain pharmaceutical industry support, and financial constraints would hamper its feasibility. Particularly important is the fact that due to the relative low absolute frequency of bleeding events, an exceedingly large number of patients should be randomized in order to evaluate differences in the risk. Furthermore, such trial would need to be repeated with the development of each new agent. Thus, an alternate analytical strategy for the comparison of all agents is needed and an appealing strategy is the use of techniques applied in health economics. In this work I propose that a modification of a technique used by health economists – the cost-effectiveness analysis – can be used to this purpose by considering the costs and the benefits of anticoagulant VTE prophylaxis in orthopedic surgery from a clinical perspective. In this clinical situation I considered that, due to their clinical relevance in terms of morbidity and mortality, the main clinical cost of prophylaxis is the occurrence of major bleeding events and the main clinical benefit is the prevention of proximal DVT and PE.

1.3. The clinical cost-effectiveness study: an economics approach to clinical decision making

1.3.1. The clinical decision framework

The decision making process in clinical practice and health policy involves two similar main steps: first, an evaluation – monetary or clinical – of the costs and the outcomes of the decision, either beneficial or harmful; and second, a comparison of such benefits, harms, and costs. A fundamental piece in this process is the evaluation of the desirability of the outcomes[102]. In daily clinical practice clinicians face a similar situation: they are frequently presented with disjunctives involving competing treatment alternatives for the same clinical condition. The decision to use a particular alternative depends on a number of issues including the expected clinical benefits and risks derived from each alternative, the uncertainty of these parameters, the personal preference regarding the trade-off between benefits and risks, and other variables such as local availability[103]. Some basic notions should be noted regarding clinical decisions. First, if two or more alternatives are available for a disease and all of them are equally effective, the preferred one should be the one conveying the lesser risk. Conversely, if all alternatives are equally risky, the clinician should opt for the one conferring the higher benefit. Thus, it follows that if all options are equally effective and risky from a clinical standpoint, the clinician's choice will be based on other considerations. Second, if the risk associated with a particular alternative outweighs the expected benefit such alternative is usually not chosen. An obvious derivation from these two premises is that the choice of an alternative should rely on a conjunct assessment of risk and benefit; however, usual practice is to evaluate them separately. Since incorporating available evidence in clinical practice might become a cumbersome problem, a technique capable of providing the clinician with joint information on risks and benefits for different competing interventions is highly desirable. Furthermore, since there are variations in personal preference for the optimal cutoff value for the trade-off between risks and benefits, this information should be presented with a range of trade-off values.

According to Willan and coworkers the preference for a specific agent should be established by its net risk-benefit ratio[104]. A proposed approach to this problem is the use of the number needed to treat (the reciprocal of the absolute risk reduction) and the number needed to harm that is the risk analogue[105,106]. However these estimations are usually used in an independent manner and the combination of both parameters in a risk-benefit or benefit-risk ratio is seldom done and difficult to interpret and extrapolate to settings outside the clinical trial that generated the information. A major problem with this approach is that it is not easy to assess uncertainty with respect to a ratio because the estimation of confidence intervals is problematic[107]; this situation is analogous to that posed by the necessity to incorporate uncertainty around an estimate of the incremental cost-effectiveness ratio (ICER) used in health economics. Although some work in developing methods to approximate confidence intervals around a ratio has been published[108], a possible way to solve this issue could be the use of modeling techniques that have been applied to clinical decision analysis[109,110]. These techniques allow the investigator to introduce a term of uncertainty around the estimate of a parameter of interest using strategies such as Monte Carlo simulation or non-parametric bootstrapping. The purpose of these techniques is to examine the robustness of an estimated result using different alternative values for uncertain parameters[111].

Recently, Lynd and O'Brien have proposed an interesting approach to this problem[103]. Their method involves the estimation of the joint density of incremental risk and incremental benefit using probabilistic simulation, which is then plotted in a risk-benefit plane analogous to the cost-benefit plane used in economics[112]; then, a risk-benefit acceptability curve (RBAC), which is analogous to the cost-effectiveness acceptability curve[113], is created. A RBAC plots the proportion of risk-benefit joint density under a given risk-benefit threshold. In other words, it shows the proportion of net risk-beneficial interventions at a given threshold for risk acceptance. This method can be extended to compare multiple competing interventions in clinical practice. A thorough explanation is presented in the following sections.

1.3.2. Introduction to the clinical cost-effectiveness study

It is usually accepted that when comparing several alternatives the best evidence is derived from randomized trials. If there are several trials evaluating the same interventions their results can be summarized using meta-analytical techniques. However, randomized trials are usually conducted comparing only two (and seldom three) therapeutic options because the inclusion of more treatments would require larger sample sizes with an associated increase in research costs. The consequence is that if several therapeutic alternatives are available, studies comparing all of them at the same time are usually lacking. Some methods have been developed to indirectly compare interventions that have not been tested on a head-to-head basis, using meta-analysis of the information available from other randomized trials[114]. These methods involve a comparison of effects sizes and have two disadvantages: a) they result in pooled effect size estimates with wide confidence intervals which are difficult to interpret, and b) the effect size can be estimated only for individual outcomes but not for joint outcomes.

The cost-effectiveness analysis is a type of full economic evaluation in which costs are measured in monetary units and benefits from the intervention being evaluated are expressed in natural units, such as life-years gained, cases prevented or deaths averted. It is typically used when a decision maker has to optimize the utilization of a limited budget in order to maximize the outcome of interest[115].

In the case of a clinical cost-effectiveness analysis we will assume that the use of certain therapeutic option has a cost from a clinical standpoint. This is particularly certain when potentially harmful therapies are used, such as chemotherapy, surgery or anticoagulant drugs. A pivotal concept is that the benefits and the risks of such therapeutic interventions are inter-related: you cannot have one without the other. Clearly, clinicians opt for such therapeutic options because they expect to obtain a benefit that outweighs the potential risk. For example, if we accept that open abdominal surgery has an associated risk of mortality, in the case of patients with bowel perforations the mortality that can be expected from the surgery itself is less than the mortality if no surgery is performed. However, when the rates of major complications (costs) or clinical effectiveness (benefits) from different options vary, the choice of the best option might become less clear. Furthermore, the willingness of the clinicians to accept the risks inherent to an intervention might differ depending on a number of issues such as their knowledge and experience, the setting of their practice, the characteristics of the patient, or their attitude towards the risk. Similar to its economic counterpart, the clinical cost-effectiveness analysis provides a framework incorporating clinical risks and benefits in a conjoint fashion for each of the competing interventions. In an analogous manner to the cost-effectiveness analysis used in economics[112], the clinical cost-effectiveness analysis uses a graphical representation of risks and benefits –the risk-benefit plane– in which the risk and the benefit of the intervention are plotted together in a graph that also incorporates a risk-benefit acceptability threshold (RBAT) representing the tradeoff between risks and benefits that the decision maker is willing to accept and that is inherently variable (Fig. 1). Thus any intervention providing more benefit with less risk (quadrant IV) will be deemed to be dominant and any intervention providing less benefit with more risk will be dominated (quadrant II).

An interesting question arises when a strategy results in an increased benefit with an associated increase in the risk or else, when it provides less benefit with

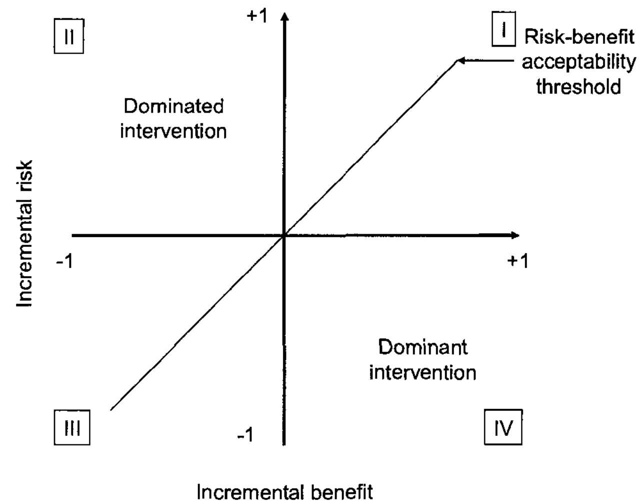


Figure 1. The risk-benefit plane. Incremental risk and benefit are plotted as probabilities. (Adapted from[103,112]).

less risk. If a strategy lies in quadrants I or III, whether it is chosen will depend on the maximum cost-effectiveness ratio –or the analogous risk-benefit acceptability threshold– one is willing to accept. Thus, it is of the utmost importance to determine the extra risk that the decision maker is willing to accept for the sake of an increase in the benefit. An obvious problem of this approach is that the point estimates of risk and benefit derived from the clinical trials are assumed to be certain but in reality they are not. Thus the incorporation of uncertainty around these estimates becomes fundamental in the estimation of net risk-benefit.

The approach proposed by Lynd and O'Brien uses a Bayesian framework in which the incremental benefit and the incremental risk (i.e. the cost) are considered random variables described in terms of a beta distribution. Their approach incorporates several steps. First, taking advantage of the properties of the beta distribution, a probabilistic analysis using Monte Carlo simulation is done to generate several thousands of replications of the risk-benefit data of a new and a reference intervention. In a second step the results of the replications are used to calculate incremental risk and benefit and incremental risk-benefit ratios – representing the joint risk-benefit – which are then plotted in a risk-benefit plane in order to obtain the proportion of the replications that lie below the RBAT (Fig.2). This proportion represents the probability that the intervention has of being net-beneficial at a specific value of the RBAT.

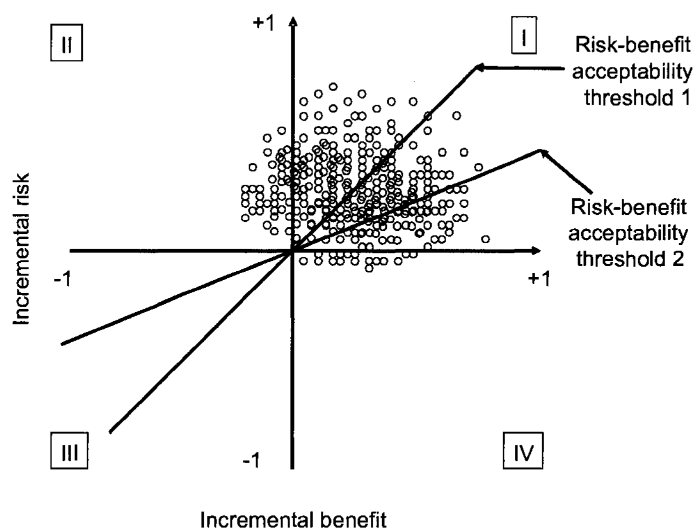


Figure 2. Risk-benefit plane showing a hypothetical conjoint risk-benefit analysis. In this hypothetical example, each point represents a joint risk-benefit observation calculated from a replication obtained from the Monte Carlo simulation. The percentage of the observations lying below the risk-benefit acceptability threshold represents the probability of the intervention being net-beneficial for that specific threshold. It can be seen that a higher value of the threshold (threshold 1) will result in a higher probability of the intervention being net-beneficial than a lower value of the threshold (threshold 2).

The value of the RBAT is then varied across a range of values and the probabilities thus obtained are the plotted in a risk-benefit acceptability curve in which the probability of the intervention being net-beneficial is presented across a range of risk-benefit acceptability thresholds (Fig. 3).

From a simple analysis of the risk-benefit acceptability curve depicted in figure 3 it can be appreciated that as the willingness-to-accept the risk increases, as reflected by a higher RBAT, the higher the probability that the intervention has of being net beneficial. However, a major limitation of the method of Lynd and O'Brien is that each curve only compares two interventions and, while curves can be superimposed for multiple agents in a single chart, such chart will only inform the probability for each agent of being net beneficial but it would not allow determining which agent has the highest probability of having the best risk-benefit profile.

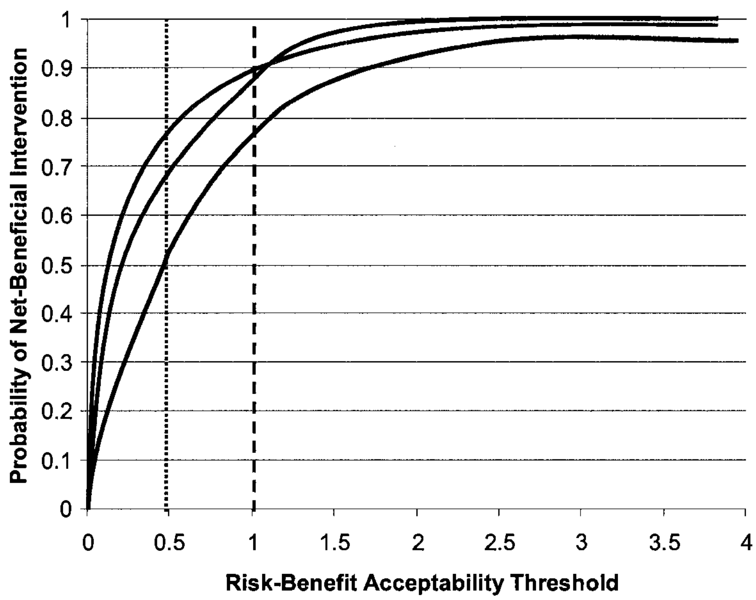


Figure 3. Risk-benefit acceptability curve. (Adapted from[103]). In this example if the risk-benefit acceptability threshold is 1 (dashed line), that is, if we are willing to accept 1 adverse event for each beneficial event, the probability of the intervention being net-beneficial for intervention 1 (red) is 0.89, for intervention 2 (blue) is 0.87, and for intervention 3 (green) is 0.75. On the contrary if the risk-benefit acceptability threshold is 0.5 (dotted line), then the probability of the intervention being net-beneficial would be 0.77 for intervention 1, 0.69 for intervention 2 and 0.50 for intervention 3. However, although this plot shows that the probability of being net beneficial for interventions 1 and 2 is similar and always higher than intervention 3, it does not inform which intervention has the best risk-benefit profile.

In order to overcome its limitations, in the present work I have developed a further extension of the method proposed by Lynd and O'Brien in which multiple agents are compared. The advantage of this extension is that it provides an evaluation of the probability for each agent of having the best risk-benefit profile compared with the others. In other words, this extension shows which therapeutic option(s) result(s) in a greater clinical benefit when the risk derived from the intervention has been accounted for.

A comparison of multiple agents can be done by calculating for each agent the probability of having the highest net clinical benefit –and thus be preferred– across a range of values of the RBAT (Fig. 4). Thus the best option can be chosen according to the level of risk that the decision maker is willing to accept.

The net clinical benefit (NCB) is further explained in the following sections but briefly, the net clinical benefit, which is analogous to the net monetary benefit, is a way to assign a clinical value to the increment in clinical benefit that is obtained from the new treatment, subtracting from this the increment in the clinical cost derived from such treatment. If the NCB is positive it means that the cost of achieving an additional benefit is less than the value of the benefit achieved. If the NCB is negative then the treatment should not be accepted since the cost exceeds the value of the benefit achieved[116].

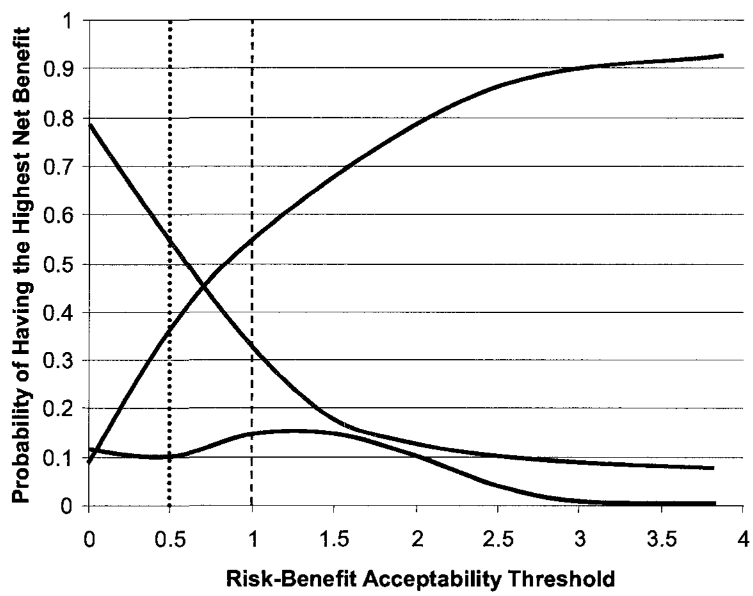
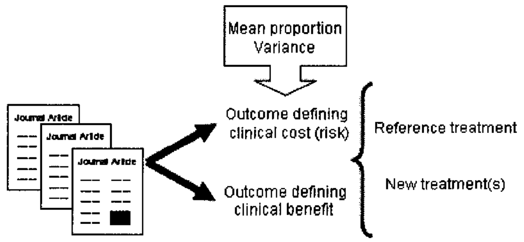


Figure 4. Net clinical benefit probability curve. In this hypothetical example comparing 3 interventions, if the risk-benefit acceptability threshold is 0.5 (dotted line), the intervention with the highest probability of having the highest net clinical benefit – and thus be preferred – would be intervention 1 (red). On the contrary if the threshold is 1 (dashed line), then the intervention with the highest probability of having the highest net clinical benefit would be intervention 2 (blue). Note that intervention 3 (green) is never preferred at any threshold and that, for each value of the threshold all probabilities add up to 1. It can be easily appreciated that the choice of the preferred intervention depends on the level of risk acceptance.

A schematic representation of the clinical cost effectiveness analysis is shown in Box 1 and an illustrative example is shown at the end of each of section in Boxes 2 – 4.

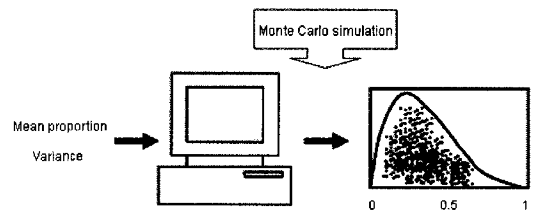
Box 1. Schematic representation of the clinical cost-effectiveness study

Step 1. Estimation of costs and benefits



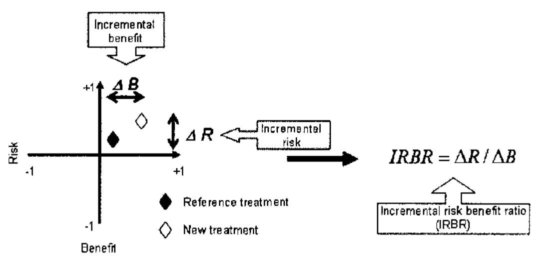
A systematic review and meta-analysis is used to obtain pooled estimates of the mean proportion (and variance) of patients experiencing the outcomes defining clinical cost (risk) and clinical benefit of the reference and new treatment options for the clinical situation being studied. Note that herein the terms cost and risk are used interchangeably.

Step 2. Probabilistic simulation



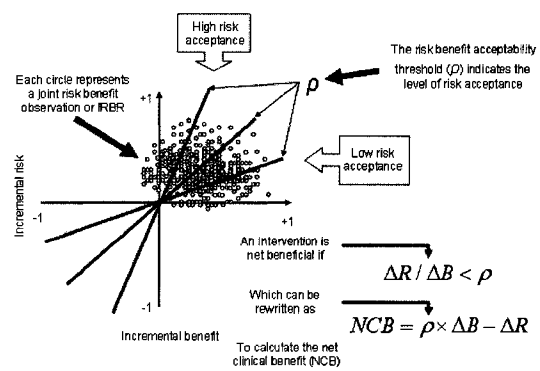
A Monte Carlo simulation is then conducted. In this, the computer picks randomly a predetermined number of values from a probability distribution curve whose shape was defined using the mean proportion and variance of the outcomes obtained in Step 1. Each value is called a replication. A separate simulation is done for each outcome of interest and for each treatment option in order to obtain replications of the cost and benefit of each option

Step 3. Calculation of incremental risk, incremental benefit and incremental risk-benefit ratio



The next step is to determine the amount of extra benefit and risk that that would be obtained using the new treatment(s) compared to the reference. The differences in the benefit and in the risk derived from the new treatment compared to the reference treatment are calculated using the values of each replication. Such differences are called incremental benefit and incremental risk, respectively. The ratio of the incremental risk to the incremental benefit, called the Incremental risk benefit ratio or IRBR, is then calculated for each replication. The IRBR represents a joint risk-benefit measure of the new versus the standard treatment.

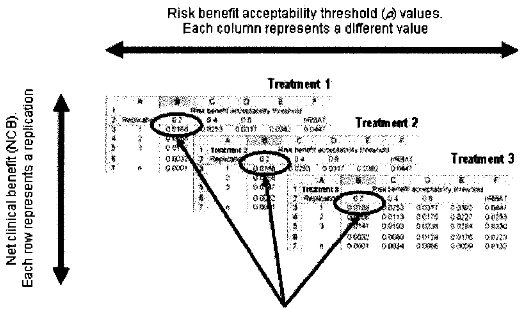
Step 4. Calculation of the net clinical benefit

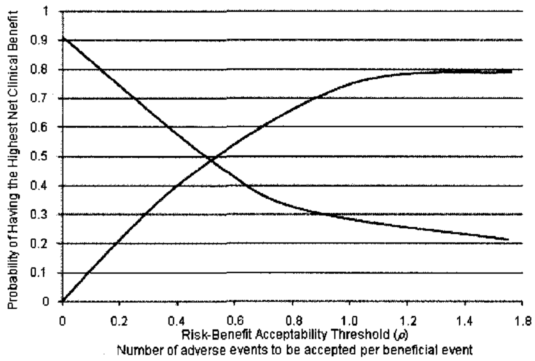


Each value of the IRBR is plotted in a risk benefit plane which incorporates a value for risk acceptance also called risk benefit acceptability threshold or ρ. This threshold represents how many adverse events are going to be accepted for each beneficial event. The IRBR is net beneficial if it is less than ρ. It can be noted that the higher the value of ρ, the greater the proportion of IRBR values that lie below it. If ρ is incorporated into the calculations the result thus obtained is called the net clinical benefit or NCB. A positive NCB means that, at a particular value of ρ, the clinical cost of the new treatment is less than the benefit obtained from it. A negative NCB means that the treatment should be rejected because the clinical cost exceeds the benefit obtained.

Box 1. Schematic representation of the clinical cost-effectiveness study (cont'd.)

Step 5. Comparison of treatment options and construction of net clinical benefit probability curves

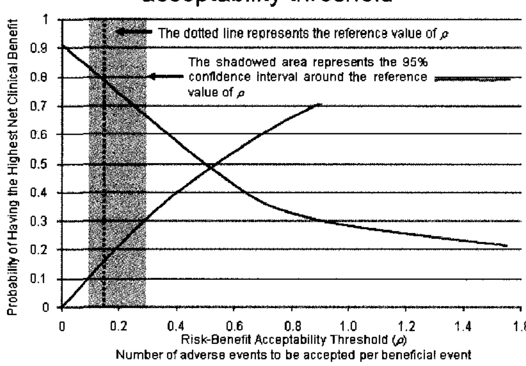




The NCB is calculated for each replication obtained in the Monte Carlo simulations. In the figure, each row represents an individual replication. The values of the NCB obtained for each treatment option at the same level of ρ are compared to determine which option has the highest value. This process is repeated for each individual replication. Then the proportion of replications for which the treatment option has the highest NCB can be calculated. This proportion indicates the probability that the treatment option has of having the highest NCB and therefore the best risk-benefit profile at each value of ρ.

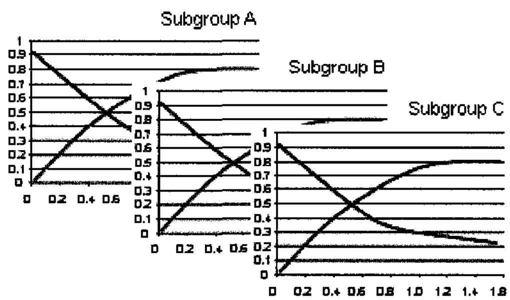
For each treatment option the probabilities of having the highest net clinical benefit are plotted in a Net Clinical Benefit Probability Curve across a range of values of ρ. This curve shows which treatment option has the highest probability of having the best risk-benefit profile, and thus be preferred, at different levels of risk acceptance. Since the latter may vary according to individual situations it is important to present the information across a range of values in order to let the clinician decide the best option for a particular clinical scenario. Note that at each value of ρ the probabilities add up to 1.

Step 6. Estimation of a reference risk benefit acceptability threshold



The next step in the analysis is to find a value of ρ that is suitable to be an appropriate reference for clinical decision making. This can be done by estimating the relative importance of the benefit-defining outcome to that of the cost-defining outcome. A possible way to do this is to estimate the ratio of the respective case fatality rates. The reference value of ρ thus obtained translates to an estimate of the risk that would be reasonable to accept based on how lethal is the event that the treatment is trying to cure or prevent compared to the adverse event produced by such treatment.

Step 7. Sensitivity analysis



Finally, to evaluate the robustness of the results, predefined subgroups of patients are studied using the same steps. The sensitivity analysis allows identifying specific groups of patients for which the treatment options might have different risk-benefit profiles.

1.3.3. Estimation of costs and benefits

A fundamental step in clinical cost-effectiveness analysis is the definition of clinical costs – a term herein considered synonym of risks– and clinical benefits, referred to as effectiveness. This will depend on the clinical problem of interest. Defining the ideal way to measure the clinical benefit derived from an intervention is usually relatively easy; however the definition of the clinical cost may not be straightforward. The clinical cost should be an adverse event directly derived from the intervention, and ideally the intervention should have only one (or very few) of them, of which the most frequent could be used to define the clinical cost. Alternatively, a composite endpoint could be used to incorporate different adverse events in one "hard" outcome, for example mortality or permanent disability. The appropriateness of the cost-defining event should be particular to the intervention being evaluated. The outcomes of interest obtained from potentially life-threatening interventions in severely ill patients (for instance, chemotherapy in cancer patients) are different from those obtained in otherwise healthy individuals undergoing for example, esthetic procedures, although all types of interventions are amenable to undergo clinical cost-effectiveness analysis.

In many cases the costs and benefits associated with an intervention can be obtained from a systematic review and meta-analysis of published evidence which, if properly conducted, should summarize the available information and reduce bias[117]. The information thus obtained can be then used to calculate pooled estimates of proportions and confidence intervals using fixed or random effects models through a simple statistical approach (see methods section 2.2.7). When analyzing randomized trials, the use of proportions – as opposed to effect sizes – for comparison purposes supposes the loss of the randomization effect, because in order to calculate proportions the study groups have to be considered independent populations. However, if properly conducted and reported, the information derived from randomized trials is usually of the highest quality[118]. Therefore, incorporating an assessment of study quality using validated scales becomes important[119,120]. On the other hand there might be a concern regarding the generalizability of the results obtained in randomized trials because they might not be conducted with a pragmatic approach as a consequence of having highly selected populations, different standards of care, specific study settings or interventions that are not widely available. However, if a sufficient number of studies are available, the pooled estimates of proportions are likely to approach the real proportion of events. However, it should be noted that prior to conducting the systematic review it is of the utmost importance to a) define all subgroup and sensitivity analyses pertinent to the intervention being evaluated, and b) pay special attention to the definition of the outcome(s) of interest used across different studies, since these issues could influence the result of the meta-analysis.

Box 2. An illustrative example of the clinical cost-effectiveness analysis. Estimation of risk and benefit

Consider the following hypothetical situation: Mrs. A is a woman who suffers from osteoarthritis requiring a total hip replacement and has a history of gastric ulcer. Her surgeon, Dr. K, has decided that she requires prophylaxis for venous thromboembolism. After a careful review of available information he learns that without the use of anticoagulant prophylaxis the proportion of venous thromboembolism after hip replacement is 24% and that this proportion would decrease to 4% with the use of the blue anticoagulant, to 7% with the red anticoagulant, and to 6% with the green anticoagulant. He also learns that the risk of bleeding complications resulting from the use of the anticoagulants is 1.6%, 0.8%, and 2.5%, respectively, and that 0.3% of the patients undergoing total hip replacement experience a major bleeding without the use of any anticoagulant. Because he was very thorough while conducting the review, he is confident that these estimates are real. Therefore, although it seems that the blue anticoagulant is the most effective for preventing clots, it also has a higher proportion of bleeding complications than the red anticoagulant. He now needs to determine which agent has the best risk-benefit profile in order to decide if the extra benefit is worth the increase in the risk.

1.3.4. Estimation of uncertainty, risk, benefit, and joint risk-benefit

Once estimates have been obtained for the proportions and their variances, uncertainty around them can be estimated using probabilistic simulation applying the method proposed by Lynd and O'Brien[103]. The proportions estimates and variances for each outcome can be used to calculate the parameters of a beta distribution using the method of moments[121] (see methods section 2.3.3). A beta distribution is bounded by 0 and 1 and can be defined in terms of the alpha and beta parameters – i.e. the number of patients experiencing and not experiencing an event, respectively – which, if unknown, can be calculated using a sample's mean and variance which can be obtained from a meta-analysis. Then these parameters can be used to run a Monte Carlo simulation usually including between 1,000 and 10,000 replications, each replication being a value randomly selected from the distribution specified by the parameters that were defined. This can be regarded as repeating the estimation of the pooled proportion as many times as replications are done. In other words, if the alpha and beta parameters are obtained from a meta-analysis of 20 studies and a simulation with 1,000 replications is conducted, the results would be equivalent to repeating a meta-analysis of 20 studies one thousand times.

Using the results of the Monte Carlo simulation, the incremental risk, the incremental benefit, and the incremental risk-benefit ratio (IRBR) are calculated for each new intervention compared to a reference intervention, the choice of which depends on each situation; we can use information on outcomes occurring in patients receiving placebo or alternatively, a standard active treatment.

The IRBR can be defined as the ratio of the difference in risk to the difference in benefit between two competing treatments; this is, $IRBR = (R_A - R_S)/(B_S - B_A)$ when a treatment is preventive, and $IRBR = (R_A - R_S)/(B_A - B_S)$ if the treatment is curative, where R_y is the true probability of an adverse event from treatment y, B_y is the true probability of an event for which therapy y is indicated, $y=S$ represents the standard treatment and $y=A$ represents the alternative treatment.

This means that the IRBR for a new therapy relative to the standard treatment is equal to the incremental probability of an adverse effect divided by the incremental probability of a beneficial effect. This is analogous to the calculation of the incremental cost-effectiveness ratio (ICER) in traditional economic cost-effectiveness analyses. The joint risk-benefit from each of the replications can be plotted in a risk-benefit plane which compares the difference in benefit versus the difference in risk obtained from the intervention. The percentage of the replications lying below the RBAT will then represent the probability of the intervention being risk-beneficial for the specified value of the threshold. If we repeat this step for a range of values and plot the results in a curve we obtain a risk-benefit acceptability curve that can be constructed for all of the interventions of interest. This curve will show the probability that the intervention(s) is (are) risk-beneficial across a range of RBAT values.

Box 3. An illustrative example of the clinical cost-effectiveness analysis. Estimation of joint risk benefit

Dr. K, who is very statistically skillful, performs a Monte Carlo simulation using the estimates of venous thromboembolism and bleeding that he had previously obtained and thus he obtains 1,000 replications of these estimates. He then calculates for each replication the difference in the proportion of bleeding between the patients receiving the blue anticoagulant and those patients not receiving any anticoagulant, and he does the same with the proportion of venous thromboembolism. He repeats these calculations for the red and green anticoagulants. Finally he calculates for each anticoagulant the ratio of the difference in bleeding to the difference in venous thromboembolism for each replication, also called the incremental risk-benefit ratio. Now he has 1,000 simulated values of the extra risk, the extra benefit and the risk benefit ratio of each one of the three anticoagulants compared to no treatment.

1.3.5. Net clinical benefit

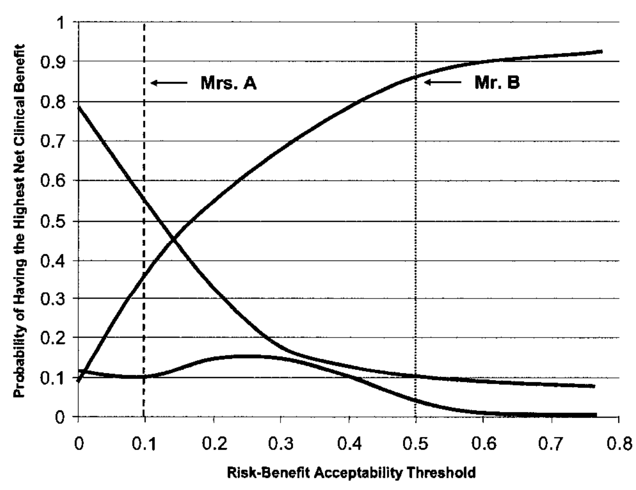
Unfortunately, the mathematical properties of ratios yield some limitations with respect to the ICER and consequently the IRBR. When the difference in effectiveness (or benefit) is small the confidence bounds may become wide, and therefore not really represent a confidence interval making it difficult to estimate the uncertainty of the ratio. In economic analyses it has been proposed the use of the net monetary benefit as an alternative to overcome the problems with the ICER[107,116,122]. The net monetary benefit is obtained by assigning a monetary value to the incremental benefit derived from a new therapy and subtracting its incremental cost. A positive net monetary benefit means that the value of the additional benefit resulting from the use of a new intervention is greater than its cost and it could be accepted. Conversely, if the net monetary benefit is negative, the new therapy should not be accepted because its cost outweighs the value of the benefit obtained. In the clinical cost-effectiveness analysis a similar approach can be used. A treatment would be cost-effective if $\Delta R / \Delta B < \rho$, where ΔR denotes the differential risk, ΔB the differential benefit and ρ is the threshold willingness-to-accept the risk or RBAT; in other words, the treatment would be cost-effective if the IRBR is less than the RBAT. To obtain the net clinical benefit (NCB) the inequality can be rearranged incorporating the RBAT as $\rho\Delta B - \Delta R > 0 = NCB$ or alternatively $NCB = \rho\Delta B - \Delta R$, where NCB represents the net clinical benefit and for *NCB* to be positive $\rho\Delta B$ has to be greater than ΔR. The differential risk ΔR is defined as $\Delta R = R_A - R_S$ and the differential benefit ΔB as $\Delta B = B_S - B_A$ when a treatment is preventive, and as $\Delta B = B_A - B_S$ if the treatment is curative where R_y

and B_y are defined as previously described. The NCB is thus obtained using a linear expression for which a variance can be easily calculated as $\mathrm{var}(NCB) = \rho^2 \times \mathrm{var}(\Delta B) + \mathrm{var}(\Delta R) - 2 \times \mathrm{cov}(\Delta B, \Delta R)$.

The NCB can then be used to conduct an overall comparison of competing interventions. The first step is to calculate the NCB for each replicated set of joint risk-benefit values obtained from the Monte Carlo simulation for each one of the interventions. By calculating the proportion of replications with the highest NCB it can be determined the probability that each intervention has of having the highest net clinical benefit for each value of the RBAT. The resulting plot would allow the clinician to easily appreciate which of the competing treatment alternatives has the highest probability of being the most clinically net risk-beneficial at a given value of the RBAT. Since the ideal RBAT is usually not known this analysis would allow incorporating the clinician's personal acceptance of risk in the decision process.

Box 4. An illustrative example of the clinical cost-effectiveness analysis.
Estimation of net clinical benefit and comparison of options

Dr. K knows that he has to trade some bleeding risk for the sake of averting a venous thrombosis and he soon learns that a treatment can be considered clinically cost-effective if the incremental risk-benefit ratio is less than the risk he is willing to take, what he learns is called the risk-benefit acceptability threshold. From his experience and readings he knows that bleeding is roughly two times as lethal as venous thrombosis and thus he decides that the maximum risk he is willing to assume is 5 bleeding episodes per each 10 thrombosis averted (a RBAT=0.5). He then proceeds to calculate the net clinical benefit by multiplying the difference in venous thromboembolism and the risk benefit acceptability threshold and then subtracting the difference in bleeding. He repeats these calculations for each anticoagulant, for each replication and for a range of values of the risk-benefit acceptability threshold. Finally he calculates for each anticoagulant how many of the 1,000 replications have the highest net clinical benefit and he plots the results in a net clinical benefit probability curve as shown below. Because of her history, in the case of Mrs. A Dr. K is concerned about provoking a bleeding episode and so he chooses to accept only 1 bleeding per 10 averted thromboses (RBAT=0.1) and he finds that at this level of risk acceptance the best anticoagulant is the red one. Consider now the hypothetical case of Mr. B, who also needs a total hip replacement but who has a history of heart and lung disease. In Mr. B's case the occurrence of a pulmonary embolism would have serious consequences; therefore Dr. K chooses to accept a higher risk of bleeding (RBAT=0.5) and opts for the blue anticoagulant.



1.4. Issues on data sources, synthesis and analysis

Information regarding the use of different therapeutic options for a determined clinical condition can be obtained from randomized clinical trials providing head-to-head comparisons of commonly used agents. Two main sources are available and depending on their nature different analytical and modeling strategies can be proposed. If data on individual patients is available the use of non-parametric bootstrapping is feasible[123]. If this information is not available an alternate strategy is the use of simulations using information on the distributions fit to the data of interest using a second-order Monte Carlo simulation[103]. The information of interest regarding the proportion of events of interest can be pooled from the available studies evaluating the agents of interest. However there is limited information on the techniques that should be used to conduct meta-analysis of single proportions. An obvious problem in this setting is the estimation of variation around the pooled estimates. Two approaches can be used depending on the homogeneity of the studies. If they are homogeneous a fixed effects model can be used or alternatively a random effects model if heterogeneity is found assessed by a χ^2 test. A detailed explanation of these models will follow in section 2.2.7. An alternate approach could be the use of generalized estimating equations to derive pooled estimates of proportions and their variances[124]. These techniques have been successfully applied in other clinical settings[125] and by using them we can obtain from the available published studies the appropriate data on clinical benefit and risk for each of the agents of interest and then incorporate it into a modeling framework using the method proposed by Lynd and O'Brien[103], as previously outlined.

1.5. Justification of the study and working hypotheses

Several anticoagulant agents are available for VTE prophylaxis in MOS patients. Each agent has a different pharmacological profile. Early studies showed that the use of an anticoagulant compared to placebo resulted in a substantial reduction of thrombotic complications. Since the use of placebo would not be ethical in newer trials, the available literature consider that if a new anticoagulant agent is better than placebo if it is equivalent or superior to an agent previously tested in placebo controlled trials. Although numerous studies have compared the available agents, they often used parallel groups and a randomized trial comparing of all the available agents has never been conducted. Such comparison is necessary in order to be able to determine if all agents are equivalent. Furthermore, the incorporation of both risk and benefit derived from the intervention should be the basis for an informed decision.

The integration of the techniques outlined in the previous sections in a clinical cost-effectiveness analysis as proposed in this work, would allow making a comparison of all the agents currently used for thromboprophylaxis in MOS in terms of their net risk-benefit and in the absence of a randomized clinical trial. Furthermore, the analysis of thromboprophylaxis in MOS by this technique would serve to show that the clinical cost effectiveness analysis is a powerful, suitable, and useful tool for clinical decision making.

The null hypothesis is that the different agents currently employed for thromboprophylaxis in patients undergoing MOS have the same risk benefit ratios. The alternate hypothesis is that the different agents currently employed for thromboprophylaxis in patients undergoing MOS have different risk benefit ratios.

1.6. Objectives

The objectives of this study were:

1.6.1. Main objectives

a) To estimate the joint risk-benefit for each agent used for thromboprophylaxis in major orthopedic surgery.
b) To estimate the probability of each intervention being clinically net-beneficial using probabilistic simulation.
c) To compare the strategies using clinical cost-effectiveness analysis.

1.6.2. Secondary objectives

a) To estimate proportions of effectiveness in the prevention of VTE and risk of bleeding for each of the agents of interest through a systematic review and meta-analysis.

2. Methods

2.1. Study design

The present study had two major components: a) A systematic review and meta-analysis of simple proportions; and b) A clinical cost-effectiveness analysis using probabilistic simulation. The information derived from the first component was used to conduct the second component.

2.2. Systematic review and meta-analysis

2.2.1. Objectives of the systematic review

The general objectives of the review were to systematically evaluate the safety and efficacy of unfractionated heparin, low molecular weight heparin, warfarin, ximelagatran, and fondaparinux for the prevention of VTE in patients undergoing MOS defined as THR, TKR or HFS using the information available from randomized clinical trials. The review aimed to obtain pooled single proportion estimates of proximal, distal and total DVT or PE and major and total bleeding episodes for each agent of interest.

2.2.2. Criteria for considering studies for review

To be considered for inclusion in the systematic review studies should have: a) indicated a randomized controlled design comparing anticoagulants head-to-head or with placebo, b) objectively assessed the diagnosis of venous thromboembolism according to the methods shown in Box 5, c) been conducted in patients undergoing total hip replacement, total knee replacement, or surgery for hip fracture, d) used prophylaxis with either ximelagatran (given at a dose of 24 mg or more twice daily) or unfractionated heparin or low molecular weight heparin (including any of the following: Ardeparin, Dalteparin, Enoxaparin, Nadroparin, Reviparin, Bemiparin, and Tinzaparin) or vitamin K antagonists (warfarin, acenocoumarol, and phenprocoumon) or fondaparinux, and e) administered the prophylactic regimen for at least five days after the surgical procedure. Studies including mechanical devices, other anticoagulants, dosing nomograms, aspirin, and low-dose warfarin were excluded from the review.

Box 5. Criteria for definition of deep venous thrombosis or pulmonary embolism

The diagnosis of deep venous thrombosis should have included:

a. A compression ultrasound showing a non-compressible area of a venous segment, or
b. A venography demonstrating a constant intraluminal filling defect in the deep veins.

The diagnosis of pulmonary embolism should have included:

a. A spiral computed tomography pulmonary angiography showing an intraluminal filling defect in a segmental or greater vessel, or
b. Ventilation perfusion scintigraphy showing an unmatched segmental or greater perfusion defect, or
c. A pulmonary angiography showing an unmatched segmental or greater perfusion defect.
d. Pulmonary embolism diagnosed at autopsy

2.2.3. Outcome measures

For the reasons outlined in the background, the main outcome measures of the analysis were: a) the occurrence of major VTE (defined as proximal DVT (either symptomatic or asymptomatic) or PE or death were PE could not be ruled out as the cause) assessed by an objective measurement technique (see Box 5)[5]; and b) the occurrence of major bleeding episodes, defined according to the criteria proposed by the International Society on Thrombosis and Haemostasis (ISTH) (see Box 6)[21]. Since these criteria were recently published and, it was considered that the definition was ISTH-like if it included at least 2 of the elements. If the ISTH criteria were not met, the definition of major bleeding provided by the authors was accepted. The secondary outcome measures were: a) the occurrence of all venous thromboembolic events defined as major venous thromboembolism plus distal venous thrombosis; and b) the occurrence of any bleeding episode as stated by the authors.

Box 6. Criteria for definition of major bleeding episodes as proposed by the International Society on Thrombosis and Haemostasis [21]

a. Fatal bleeding, and/or
b. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome, and/or
c. Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

2.2.4. Search strategy for identification of studies

The search focused on all publications describing or potentially describing a randomized controlled trial comparing any of the agents mentioned in 2.2.2 on a head-to-head comparison or with placebo, for the prevention of venous thromboembolism in patients undergoing MOS. The search screened the following electronic databases: MEDLINE (through OVID interface from January 1980 onwards), EMBASE (through OVID interface from January 1980 onwards), and The Cochrane Library (including the following databases: The Cochrane Database of Systematic Reviews, The Database of Abstracts of Reviews of Effects, The Cochrane Controlled Trials Register and The Health Technology Assessment Database). Grey literature was considered and we included the electronic versions of the abstracts of the following major international meetings: International Society on Thrombosis and Haemostasis (1999 onwards) and American Society of Hematology (1999 onwards). In addition, the references lists of the retrieved journal articles were reviewed to locate additional studies of potential interest and a search of the archive of the Thrombosis Assessment and Treatment Unit of The Ottawa Hospital which includes over 4,200 articles related to thrombosis was also conducted. The search was limited to articles published after January 1980 and no language restrictions were considered. The search strategy is outlined in Box 7. The search was conducted in July 2005 and updated in October 2005.

2.2.5. Study selection

The retrieved references were evaluated independently by 2 reviewers for possible inclusion based on the evaluation of the title and the abstract when available. Letters to the editor, review articles, editorials and commentaries were excluded. Studies were included for further review if there was an indication of the study being a randomized controlled trial, assessing the use of the aforementioned agents in the prevention of VTE in the population of interest. If any or some of these issues were not clear the study was included for further full assessment. Careful assessment of the possibility of duplicate publications was done since some of the studies were likely to be published as a meeting communication in abstract form and as a full paper. After the initial selection, the retrieved references were fully evaluated according to the aforementioned criteria for inclusion in the final review.

2.2.6. Assessment of study quality and data extraction

Quality of the included studies was assessed using the criteria proposed by Jadad and co-workers[120]. In addition, the adequacy of allocation concealment was evaluated according to the definition proposed by Schulz and Grimes[126].

Box 7. Search strategy for the Medline and EMBASE databases through OVID interface

1. orthopedic.tw
2. surgery.tw
3. 1 and 2
4. (hip adj3 (replace$ or arthroplasty)).tw
5. (knee adj3 (replace$ or arthroplasty)).tw
6. (hip adj3 surg$).tw
7. (hip adj3 fracture).tw
8. or/3-7
9. (melagatran or ximelagatran or dabigatran or exanta or "H376/95").tw
10. direct.tw
11. thrombin.tw
12. inhibitor.tw
13. oral.tw
14. and/10-13
15. or/9,14
16. warfarin.tw
17. anticoagul$.tw
18. 17 adj1 13
19. (vitamin k adj3 (antagon$ or inhibit$)).tw
20. coumadin.tw
21. coumarin.tw
22. phenprocoumon.tw
23. acenocoumarol.tw
24. or/16,18-23
25. heparin.tw
26. (unfractionated adj1 heparin).tw
27. (low molecular weight adj1 heparin).tw
28. (dalteparin or fragmin or tinzaparin or innohep or enoxaparin or clexane or lovenox or ardeparin or normiflo or nadroparin or fraxiparine or reviparin or clivarine).tw
29. (fondaparinux or arixtra).tw
30. placebo.tw
31. or/15,24-30
32. (prophylaxis or prevent$).tw
33. (venous or vein).tw
34. deep.tw
35. thrombosis.tw
36. embolism.tw
37. thromboembolism.tw
38. pulmonary.tw
39. or/32-38
40. (random$ or trial).tw
41. and/8,31, 39-40

Data was extracted by one reviewer (Alejandro Lazo-Langner) and independently verified by a second reviewer (Dr. Marc A. Rodger, Dr. Philip S. Wells, Dr. Melissa A. Forgie or Dr. Dimitrios Scarvelis) using a standard electronic form. Information was obtained on design, quality, outcome allocation, number of randomized participants, major thromboembolic events, total thromboembolic events, symptomatic thromboembolic events, major bleeding episodes, total bleeding episodes, number of evaluable patients, mortality from PE (confirmed or suspected), mortality from bleeding, total mortality, late outcomes, length of follow-up, type of definition of major bleeding, dosing, timing of initiation, duration, source of funding, and type of analysis. Mortality from confirmed pulmonary embolism was defined as deaths secondary to PE confirmed in autopsy. Mortality from probable pulmonary embolism was defined as deaths in which it was not possible to rule out PE as the cause. Discrepancies were resolved by consensus. Missing data regarding design and outcomes were requested from the authors whenever possible.

2.2.7. Statistical methods for meta-analysis of simple proportions

A meta-analysis of simple proportions was conducted to obtain pooled estimates of proportions and their variances using a fixed or random effects model as appropriate as outlined below. To determine the appropriate model to be used, heterogeneity of the proportions across individual studies was calculated using a χ^2 statistic for a $k \times 2$ table, considering as statistically significant a p<0.1.

For a collection of k studies, each i individual study giving a p proportion

$$p_i = x_i / n_i \qquad (1)$$

where x is the number of events and n the number of patients; for i=1 to k

$$n = \sum_{i=1}^{k} n_i \qquad (2)$$

and

$$x = \sum_{i=1}^{k} x_i \qquad (3)$$

if homogeneity holds, a $\hat{p}$ estimate of the true probability is

$$\hat{p} = \frac{\sum_{i=1}^{k} x_i}{\sum_{i=1}^{k} n_i} \qquad (4)$$

with variance

$$\mathrm{var}(\hat{p}) = \frac{\hat{p}(1-\hat{p})}{\sum_{i=1}^{k} n_i} \qquad (5)$$

The confidence interval can be calculated using the Wilson score method[127] as follows:

$$95\%CI = \frac{\left(2np + z^2 \pm z\sqrt{\left(z^2 + 4np(1-p)\right)}\right)}{2\left(n + z^2\right)} \qquad (6)$$

where z is the $1-\alpha/2$ point of the standard Normal distribution.

If the proportions are not homogeneous then a random effects estimator $\hat{\theta}_R$ of the true proportion may be defined as

$$\hat{\theta}_R = \frac{\sum_{i=1}^{k} w_i^* p_i}{\sum_{i=1}^{k} w_i^*} \qquad (7)$$

with variance

$$\mathrm{var}\left(\hat{\theta}_R\right) = \left(\sum_{i=1}^{k} w_i^*\right)^{-1} \qquad (8)$$

where the weights w_i^* are defined as proposed by Laird and Mosteller[128]

$$w_i^* = \frac{1}{(\overline{p}(1-\overline{p})-\hat{\tau}^2)/n_i + \hat{\tau}^2} \qquad (9)$$

where the mean proportion $\overline{p}$ for the k collection of individual i studies is

$$\overline{p} = \sum_{i=1}^{K} p_i / k \qquad (10)$$

and where the $\hat{\tau}^2$ estimate of the variance of the proportions is

$$\hat{\tau}^2 = \frac{\sum_{i=1}^{K} (p_i - \overline{p})^2}{k-1} - \frac{\sum_{i=1}^{K} p_i (1-p_i)/n_i}{k} \qquad (11)$$

Individual subgroup analyses were defined *a priori* for patients undergoing total hip replacement, hip fracture surgery and total knee replacement. To assess the robustness of the results sensitivity analyses were conducted according to:

a. Adequacy of allocation concealment

b. Source of funding (pharmaceutical industry funded versus non pharmaceutical industry funded)

c. Type of major bleeding definition used (ISTH versus non-ISTH)

d. Quality score of the study

e. Blinded adjudication of outcomes

f. Timing of initiation of anticoagulation (defined as pre-operative if drug initiated 12 – 2 hours before operation, peri-operative if drug initiated 2 hours before or up to 12 hours after surgery, and post-operative if drug initiated 12 hours or more after surgery)

g. Type of analysis (intention-to-treat versus on-treatment analysis)

In order to compare the pooled estimates of the aforementioned subgroups with the overall estimates, the difference between their respective 95% confidence limits was calculated and it was considered that the difference between the limits was significant if it was greater than the minimal clinically important difference (MCID), the values of which were 2% for major and symptomatic VTE, 5% for total (venographic) VTE and 1% for major bleeding. To show this graphically, modified forest plots were constructed displaying the pooled estimates and 95% CIs obtained from the overall and subgroup analyses. Then the MCID was added to the confidence limits of the overall estimate; and plotted in the graphs to obtain a band of clinical relevance delimiting an area around the overall estimate. It was considered that those subgroup estimates whose 95% CIs were lying outside this band were likely to have a clinically relevant difference with respect to the global estimate with and $\alpha = 0.05$. Further considerations are discussed in section 2.4.

The possibility of publication bias was explored plotting point estimates versus precision, or alternatively sample size. All the analyses were done using Excel XP version (Microsoft Corp., Redmond WA) with the statistical add-in software package Analyse-it release 1.7 (Analyse-it Software, Leeds UK).

2.3. Clinical cost-effectiveness study

2.3.1. Perspective, form of analysis and analytic horizon

A cost-effectiveness study was conducted from a clinical perspective, this is benefits and costs were clinical rather than pecuniary, namely prevention of VTE events and induction of bleeding complications. Data was incorporated using a probabilistic simulation strategy to evaluate the estimated proportion of joint risk-benefit densities lying below the risk-benefit acceptability threshold in an analogous manner to that used for the estimation of uncertainty around the incremental cost-effectiveness ratio. The analytic horizon of the study was short term since the main outcome to be obtained is usually the occurrence of VTE after a short post-surgical period that usually is no longer than 30 days.

In addition, to explore the possibility of a difference in the occurrence of VTE after completing a short course of prophylaxis, which if present, might potentially impact on benefit, pooled estimates of events occurring during the follow up period after completing prophylaxis were obtained. Data is shown in table S1 in appendix I. However, because of the fact that during follow-up only symptomatic events were recorded, it was not possible to include late events into subsequent analysis.

2.3.2. Measurement of costs (risks) and benefits

Costs (risks) and benefits were considered from a clinical standpoint in terms of the proportion of bleeding episodes induced by the agent of interest and the proportion of venous thromboembolic events presenting in the patients receiving the agent. The probabilities of bleeding and VTE episodes were obtained from the systematic review and meta-analysis of proportions outlined above. No discounting was considered for either costs or benefits since the analytic horizon was very short.

2.3.3. Estimation of benefit-risk and probabilistic analysis

In order to estimate the IRBR for each agent it was necessary to obtain incremental risks and benefits. To do this, a probabilistic analysis was conducted by means of a Monte Carlo simulation using beta distributions. The beta distribution is a continuous probability distribution with the probability density function bounded by 0 and 1 with parameters α and β, where α is the number of subjects that experience an event and β is the number of subjects that do not experience an event. The α and β parameters were calculated using the method of moments[121] as shown below.

The expected μ mean value of a beta random variable x is given by

$$\mu_x = \mu_x(\alpha,\beta) = \frac{\alpha}{\alpha+\beta} \tag{12}$$

and the σ_x^2 variance is given by

$$\sigma_x^2 = \sigma_x^2(\alpha,\beta) = \frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)} \tag{13}$$

If we know the mean and variance from a sample we can use them to estimate the α and β parameters using the method of moments[121]; therefore we have that

$$\alpha = \left[\frac{\mu_x(1-\mu_x)}{\sigma_x^2} - 1\right]\mu_x \tag{14}$$

and

$$\beta = \left[\frac{\mu_x(1-\mu_x)}{\sigma_x^2} - 1\right](1-\mu_x) \qquad (15)$$

The values thus obtained were used to parameterize a Monte Carlo simulation using a beta distribution with limits 0 and 1. The simulation was run in Excel XP version (Microsoft Corp., Redmond WA) with the add-in software package CrystalBall version 7 (Decisioneering, Denver CO) using 3,000 replications for the main analyses and 1,000 replications for the sensitivity analyses. The results were used to calculate the incremental cost and benefit for each replicated trial and were plotted in risk-benefit planes.

The benefit-risk for each individual agent was calculated according to the method of Lynd and O'Brien[103]. This method estimates an IRBR in an analogous manner to that for obtaining an ICER; this is, the IRBR is equal to the differential risk divided by the differential benefit.

The incremental risk can be defined as $R_A - R_S$ and the incremental benefit can be defined as $B_S - B_A$ when a treatment is preventive, and as $B_A - B_S$ if the treatment is curative, where R_y is the true probability of an adverse event from treatment y and B_y is the true probability of an event for which therapy y is indicated, where $y=S$ represents the standard treatment and $y=A$ represents the alternative treatment.

The true IRBR can then be defined as

$$IRBR = (R_A - R_S)/(B_S - B_A) \qquad (16)$$

when a treatment is preventive, and as

$$IRBR = (R_A - R_S)/(B_A - B_S) \qquad (17)$$

if the treatment is curative.

The IRBR can be estimated from

$$\widehat{IRBR} = (\hat{R}_A - \hat{R}_S)/(\hat{B}_S - \hat{B}_A) \qquad (18)$$

in the case of preventive treatments, or from

$$\widehat{IRBR} = (\hat{R}_A - \hat{R}_S)/(\hat{B}_A - \hat{B}_S) \qquad (19)$$

in the case of curative treatments, where $\hat{R}_y$ and $\hat{B}_y$ are the probabilities for the risks and benefits in the sample. Equations (18) and (19) can be rewritten as

$$IRBR = \Delta R / \Delta B \quad (20)$$

where ΔR denotes the differential risk and is defined as $\Delta R = R_A - R_S$ and ΔB denotes the differential benefit and is defined as $\Delta B = B_S - B_A$ when a treatment is preventive, and as $\Delta B = B_A - B_S$ if the treatment is curative.

The probability for each agent of being a net beneficial intervention was calculated by estimating the percentage of replicated trials lying below each one of the risk-benefit acceptability threshold values. The data generated was graphically represented using a risk-benefit acceptability curve across a range of threshold values.

2.3.4. Estimation of net clinical benefit

In a similar fashion to economic analyses[103,115], a treatment would be clinically cost-effective if

$$\Delta R / \Delta B < \rho \quad (21)$$

where ΔR denotes the differential risk, ΔB the differential benefit, both defined as previously described, and ρ is the threshold willingness-to-accept the risk or RBAT. The inequality can be re-arranged as

$$\rho \Delta B - \Delta R > 0 = NCB \quad (22)$$

or alternatively

$$NCB = \rho \Delta B - \Delta R \quad (23)$$

with variance equal to

$$\text{var}(NCB) = \rho^2 \times \text{var}(\Delta B) + \text{var}(\Delta R) - 2 \times \text{cov}(\Delta B, \Delta R) \quad (24)$$

where NCB represents the net clinical benefit and for NCB to be positive $\rho \Delta B$ has to be greater than ΔR.

Data from the Monte Carlo simulation was used to calculate the NCB_j for each j individual simulation trial using the equation

$$NCB_j = \rho \Delta B_j - \Delta R_j \quad (25)$$

where ΔR_j is the incremental risk and ΔB_j is the incremental benefit obtained in the j individual simulation trial and they are defined as previously described.

The variance can be used to calculate 95 percent confidence limits if we assume a normal distribution of the data, or alternatively in order to avoid an assumption of normality we can calculate these limits using the values for the 2.5 and 97.5 percentiles of the values obtained from the simulation.

The NCB_j was calculated for each simulation trial across a range of ρ values for all agents. For each trial and each value of ρ it was determined which agent had the largest NCB_j. The next step was to calculate for each agent and value of ρ the proportion of trials in which such agent had the largest NCB_j. The results were plotted in a net clinical benefit probability curve which showed the probability that each agent had of having the highest net clinical benefit across a range of ρ values.

Finally, *p*-values were calculated for each agent using the methodology proposed by Indurkhya and coworkers[122]. According to these authors a *p*-value for the comparison of the new treatment versus the standard treatment can be calculated for each value of ρ using

$$p_\rho = \Phi\left(NCB_\rho / \sigma_{NCB_\rho}\right) \quad (26)$$

Where p_ρ is the *p*-value for a given value of ρ, Φ is the distribution function of the normal distribution with mean 0 and unit variance, NCB_ρ is the net clinical benefit for a given value of ρ, and σ_{NCB_ρ} is the estimated standard deviation of the NCB[122].

For the null hypothesis

H_0: $\mathrm{NCB}(\rho) \leq 0$

with an alternative hypothesis

H_1: $\mathrm{NCB}(\rho) > 0$

if $p_\rho > 0.95$ for all the values of $\rho > \rho^*$ we reject H_0 for all values $\rho > \rho^*$ (i.e. for all values of $\rho > \rho^*$ the new treatment is preferred at the 5 percent level of significance).

This alternative method provided another way to plot risk-benefit acceptability curves. Since the results were essentially identical to the ones obtained with the original method, it was decided to adhere to the latter.

2.4. Subgroup and sensitivity analyses

The robustness of the results was assessed using sensitivity analyses for allocation concealment, funding source, type of major bleeding definition, quality of the study, adjudication of outcomes, timing of initiation of anticoagulation, and type of analysis, as depicted in 2.2.7. Also, separate analyses were conducted for the TKR, THR, and HFS groups and for all patients. Point estimates and 95% confidence intervals for all the analyses were depicted in modified forest plots. To determine if there was a significant difference between the global estimates and the estimates of the subgroup analyses, the difference between the confidence limits of such estimates was determined. This difference was considered significant if it was greater than the minimal clinically important difference (MCID), the values of which were 2% for major and symptomatic VTE, 5% for total (venographic) VTE and 1% for major bleeding episodes. These values were determined by a panel of experts and have been used in the design of recent trials[65,66,68]. The differences were then integrated in the forest plots as a band (the band of clinical relevance) that defines the limits beyond which the difference between the point estimates is clinically relevant with a confidence of 95% (see supplemental figures S1-S24 in appendix II).

During the analysis of the data the possibility of secular trends was observed. In order to explore this issue a cumulative meta-analysis was conducted by obtaining point estimates according to year of publication. Data on the significantly different variables in the systematic review was included in the sensitivity analyses of the cost-effectiveness analysis. In addition to this, IRBRs were calculated for major, total, and symptomatic VTE, as well as for major bleeding episodes. Finally, since ximelagatran was withdrawn from all markets during the conduct of the study, analyses were conducted as previously described, including all sensitivity sub-analyses, with and without that drug. The analysis after excluding ximelagatran is shown in appendix III.

3. Results

3.1. Systematic review

3.1.1. Literature search results

The search of the literature identified 1,583 potentially relevant citations of which 203 were fully assessed and 55 were included in the final review. The reasons for exclusion and a flow diagram of the review according to the recommendations of the QUOROM statement[117] is shown in figure 5. The reasons for exclusion are shown in figure 5 and box 7.

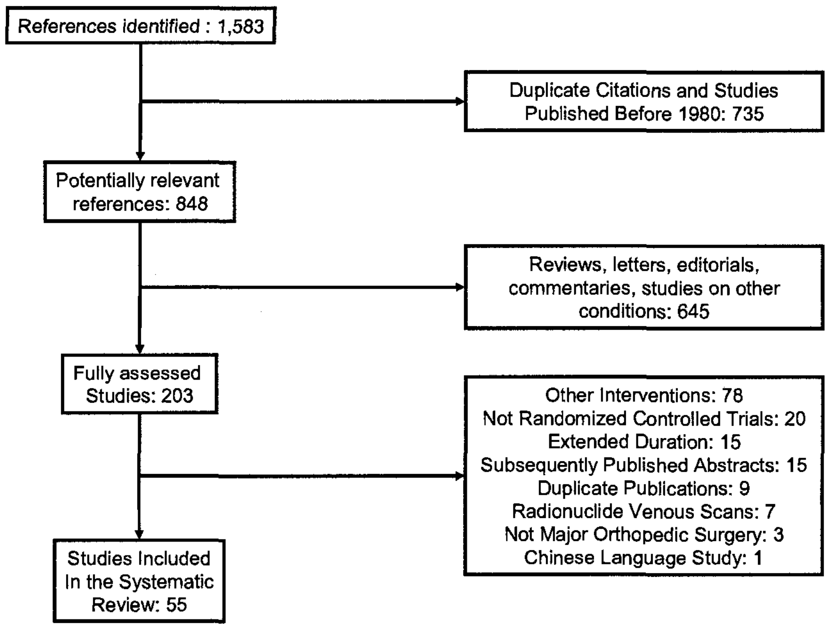


Figure 5. Flow diagram showing the progress of the systematic review.

Box 8. Excluded interventions identified during the systematic review

Hirudin
Danaparoid
Dextran
Dermatan sulphate
Defibrotide
Dihydroergotamine/heparin
Dabigatran
Antithrombin
Warfarin nomograms
Low-dose warfarin
Aspirin
Foot pumps
Pneumatic compression devices

The studies including the interventions pointed in Box 7 were excluded because such interventions are not standard of care, are not available anymore, the

Table 4. Characteristics of the studies included in the systematic review

Year / Author / Reference	*Jadad Score*	*Allocation Concealment*	*Funding*	*Outcome Allocation*	*Follow up (days)*	*Type of Procedure*	*No. of Randomized Patients*	*Interventions*
1983 Leyvraz[a 129]	3	Adequate	Pharmaceutical	Blinded	≤15	THR	96	UFH 3,500 IU TID Pre.
1986 Turpie[51]	5	Inadequate / Unclear	Non Pharmaceutical / Unclear	Blinded	≤15	THR	100	Enoxaparin 30 mg BID Post. Placebo
1988 Planes[130]	4	Inadequate / Unclear	Non Pharmaceutical / Unclear	Blinded	≤15	THR	237	Enoxaparin 40 mg OD Pre. UFH 5,000 IU TID Peri.
1989 Monreal[131]	4	Adequate	Non Pharmaceutical / Unclear	Not Blinded / Unclear	≤15	HFS	90	Dalteparin 5,000 IU anti-Xa OD Peri. UFH 5,000 IU TID Peri.
1991 Eriksson[132]	4	Adequate	Non Pharmaceutical / Unclear	Blinded	≤15	THR	136	Dalteparin 5,000 IU anti-Xa OD Pre. UFH 5,000 IU TID Peri.
1991 Lassen[47]	4	Inadequate / Unclear	Non Pharmaceutical / Unclear	Blinded	≤15	THR	210	Tinzaparin 50 IU anti-Xa /Kg OD Pre. Placebo
1991 Levine[133]	5	Inadequate / Unclear	Non Pharmaceutical / Unclear	Blinded	≤15	THR	665	Enoxaparin 30 mg BID Post. UFH 7,500 IU BID Post.
1991 Leyvraz[b c 83]	3	Adequate	Pharmaceutical	Blinded	≤15	THR	409	Nadroparin 62 IU anti-Xa/Kg Pre. UFH Approx. 4,000 IU TID Pre.
1991 Torholm[50]	4	Inadequate / Unclear	Non Pharmaceutical / Unclear	Not Blinded / Unclear	42	THR	112	Dalteparin 5,000 IU anti-Xa OD Peri. Placebo
1992 GHAT[82]	5	Adequate	Pharmaceutical	Blinded	42	THR	335	Nadroparin 10,000 IU anti-Xa OD Pre. UFH 5,000 IU TID Pre.
1992 Leclerc[48]	5	Adequate	Pharmaceutical	Blinded	42	TKR	131	Enoxaparin 30 mg BID Post. Placebo
1993 Hull[81]	5	Adequate	Pharmaceutical	Blinded	90	THR TKR	1436	Tinzaparin 75 IU anti-Xa/Kg OD Post. Warfarin Target INR 2-3 Peri.
1993 Platz[134]	2	Inadequate / Unclear	Non Pharmaceutical / Unclear	Not Blinded / Unclear	≤15	HFS	68	Certoparin 3,000 IU anti-Xa Pre. UFH 5,000 IU TID Pre.
1994 Colwell[135]	2	Adequate	Pharmaceutical	Not Blinded / Unclear	≤15	THR	610	Enoxaparin 40 mg OD Post. Enoxaparin 30 mg BID Post. UFH 5,000 IU TID Post.
1994 Fauno[79]	2	Adequate	Pharmaceutical	Blinded	≤15	TKR	224	Enoxaparin 40 mg OD Pre. UFH 5,000 IU TID Pre.
1994 Friedman[136]	3	Inadequate / Unclear	Pharmaceutical	Blinded	≤15	THR TKR	1173	Ardeparin 50 IU anti-Xa/Kg BID Peri. Ardeparin 90 IU anti-Xa/Kg OD Peri. Warfarin Target INR 1.5-3.0 Pre.
1994 Spiro[80]	4	Adequate	Pharmaceutical	Blinded	≤15	THR	572	Enoxaparin 10 mg OD Post. Enoxaparin 40 mg OD Post. Enoxaparin 30 mg BID Post.
1995 Avikainen[137]	1	Inadequate / Unclear	Non Pharmaceutical / Unclear	Not Blinded / Unclear	≤15	THR	167	Enoxaparin 40 mg OD Pre. UFH 5,000 IU BID Peri.
1995 Colwell[138]	2	Inadequate / Unclear	Pharmaceutical	Blinded	≤15	TKR	453	Enoxaparin 30 mg BID Peri. UFH 5,000 IU TID Peri.
1995 Hamulyak[139]	3	Adequate	Pharmaceutical	Blinded	≤15	THR TKR	672	Nadroparin 60 IU anti-Xa/Kg OD Pre. Acenocoumarol Target INR 2-3 Pre.

Table 4. *Characteristics of the studies included in the systematic review (continued)*

Year / Author / Reference	*Jadad Score*	*Allocation Concealment*	*Funding*	*Outcome Allocation*	*Follow up (days)*	*Type of Procedure*	*No. of Randomized Patients*	*Interventions*
1995 Lee[140]	1	Inadequate / Unclear	Non Pharmaceutical / Unclear	Not Blinded / Unclear	≤15	THR	72	Dalteparin 5,000 IU anti-Xa OD Peri. Warfarin Target INR 2.5 Pre.
1995 Warwick[52]	2	Inadequate / Unclear	Non Pharmaceutical / Unclear	Blinded	≤15	THR	156	Enoxaparin 40 mg OD Pre. Placebo
1996 Kalodiki[d 46]	5	Inadequate / Unclear	Pharmaceutical	Blinded	≤15	THR	93	Enoxaparin 40 mg OD Pre. Placebo
1996 Leclerc[78]	5	Adequate	Pharmaceutical	Blinded	180	TKR	670	Enoxaparin 30 mg BID Post. Warfarin Target INR 2-3 Peri.
1996 Levine[e 49]	5	Adequate	Non Pharmaceutical / Unclear	Blinded	≤15	TKR	246	Ardeparin 50 IU anti-Xa/Kg BID Post. Placebo
1996 Schwartsmann[141]	1	Inadequate / Unclear	Non Pharmaceutical / Unclear	Not Blinded / Unclear	≤15	THR	99	Enoxaparin 40 mg OD Peri. UFH 5,000 IU TID Peri.
1997 Francis[142]	2	Inadequate / Unclear	Non Pharmaceutical / Unclear	Blinded	≤15	THR	580	Dalteparin 5,000 IU anti-Xa OD Peri. Warfarin Target INR 2.5 Pre.
1997 Heit[143]	5	Adequate	Pharmaceutical	Blinded	≤15	TKR	833	Ardeparin 25 IU anti-Xa/Kg BID Peri. Ardeparin 35 IU anti-Xa/Kg BID Peri. Ardeparin 50 IU anti-Xa/Kg BID Peri. Warfarin Target INR 2-3 Pre.
1997 Yoo[b 53]	1	Inadequate / Unclear	Pharmaceutical	Not Blinded / Unclear	≤15	THR	100	Nadroparin 62 IU anti-Xa Kg OD Pre. Placebo
1998 Planes[144]	4	Adequate	Non Pharmaceutical / Unclear	Blinded	≤15	THR	498	Reviparin 4,200 IU anti-Xa OD Pre. Enoxaparin 40 mg OD Pre.
1999 Adolf[145]	4	Inadequate / Unclear	Pharmaceutical	Blinded	≤15	THR	341	Certoparin 3,000 IU anti-Xa OD Pre. Certoparin 5,000 IU anti-Xa OD Pre.
1999 Colwell[77]	2	Inadequate / Unclear	Pharmaceutical	Blinded	90	THR	3011	Enoxaparin 30 mg BID Post. Warfarin Target INR 2-3 Post.
1999 Planes[146]	5	Adequate	Pharmaceutical	Blinded	≤15	THR	499	Enoxaparin 40 mg OD Pre. Tinzaparin 4,500 IU anti-Xa OD Pre.
1999 TIFDED[f 64]	2	Inadequate / Unclear	Pharmaceutical	Blinded	56	HFS	132	Enoxaparin 40 mg OD Peri. Dalteparin 5,000 IU anti-Xa OD Peri.
2000 Hull[g 98]	5	Adequate	Pharmaceutical	Blinded	≤15	THR	1472	Dalteparin 5,000 IU anti-Xa OD Peri. Warfarin Target INR 2-3 Peri.
2000 Kakkar[76]	4	Adequate	Pharmaceutical	Blinded	56	THR	298	Bemiparin 3,500 IU anti-Xa OD Peri. UFH 5,000 IU BID Peri.
2000 Lassen[147]	4	Adequate	Non Pharmaceutical / Unclear	Blinded	70	THR	250	Tinzaparin 75 IU anti-Xa/Kg OD Pre. Tinzaparin 50 IU anti-Xa Kg OD Peri.
2001 Bauer[85]	5	Adequate	Pharmaceutical	Blinded	49	TKR	1049	Enoxaparin 30 mg BID Post. Fondaparinux 2.5 mg OD Peri.
2001 Eriksson[73]	5	Adequate	Pharmaceutical	Blinded	≤15	HFS	1711	Enoxaparin 40 mg OD Post. Fondaparinux 2.5 mg OD Peri.
2001 Fitzgerald[148]	3	Adequate	Pharmaceutical	Blinded	≤15	TKR	349	Enoxaparin 30 mg BID Peri. Warfarin Target INR 2-3 Peri.
2001 Haas[149]	4	Adequate	Pharmaceutical	Blinded	≤15	THR TKR	2021	Reviparin 4,200 IU anti-Xa OD Pre. UFH 7,500 IU BID Pre.

***Table 4**. Characteristics of the studies included in the systematic review (continued)*

Year / Author / Reference	*Jadad Score*	*Allocation Concealment*	*Funding*	*Outcome Allocation*	*Follow up (days)*	*Type of Procedure*	*No. of Randomized Patients*	*Interventions*
2001 Heit[74]	3	Adequate	Pharmaceutical	Blinded	28	TKR	255	Ximelagatran 24 mg BID Post. Enoxaparin 30 mg BID Post.
2001 Turpie[75]	5	Adequate	Pharmaceutical	Blinded	42	THR	933	Enoxaparin 30 mg BID Post. Fondaparinux 0.75, 1.5, 3, 6, and 8 mg OD Peri.
2002 Eriksson[h 69]	5	Adequate	Pharmaceutical	Blinded	≤15	THR TKR	760	Ximelagatran 24 mg BID Peri. Dalteparin 5,000 IU anti-Xa OD Pre.
2002 Eriksson[h 150]	2	Inadequate / Unclear	Pharmaceutical	Blinded	49	THR TKR	67	Ximelagatran 24 mg BID Peri. Dalteparin 5,000 IU anti-Xa OD Pre.
2002 Francis[70]	5	Adequate	Pharmaceutical	Blinded	≤15	TKR	680	Ximelagatran 24 mg BID Post. Warfarin Target INR 2.5 Peri.
2002 Lassen[72]	5	Adequate	Pharmaceutical	Blinded	49	THR	2309	Enoxaparin 40 mg OD Pre. Fondaparinux 2.5 mg OD Peri.
2002 Turpie[71]	5	Adequate	Pharmaceutical	Blinded	≤15	THR	2275	Enoxaparin 30 mg BID Post. Fondaparinux 2.5 mg OD Peri.
2003 Colwell[66]	5	Adequate	Pharmaceutical	Blinded	≤15	THR	1838	Ximelagatran 24 mg BID Pre. Enoxaparin 30 mg BID Post.
2003 Eriksson[h 65]	5	Adequate	Pharmaceutical	Blinded	42	THR TKR	2764	Ximelagatran 24 mg BID Peri. Enoxaparin 40 mg OD Pre.
2003 Eriksson[h 68]	5	Adequate	Pharmaceutical	Blinded	≤15	THR TKR	2788	Ximelagatran 24 mg BID Peri. Enoxaparin 40 mg OD Pre.
2003 Francis[151]	5	Adequate	Pharmaceutical	Blinded	≤15	TKR	2301	Ximelagatran 24 mg BID Post. Ximelagatran 36 mg BID Post. Warfarin Target INR 2.5 Peri.
2003 Navarro-Quilis[67]	5	Adequate	Pharmaceutical	Blinded	42	TKR	381	Bemiparin 3,500 IU anti-Xa OD Peri. Enoxaparin 40 mg OD Pre.
2004 Wang[i 54]	0	Inadequate / Unclear	Non Pharmaceutical / Unclear	Blinded	≤15	TKR	101	Nadroparin 1,900-3,800 IU anti-Xa OD Pre. Placebo
2005 Colwell[84]	5	Adequate	Pharmaceutical	Blinded	42	TKR	2303	Ximelagatran 36 mg BID Post. Warfarin Target INR 2.5 Peri.

GHAT German hip arthroplasty trial group; TIFDED Thromboprophylaxis in Fracture Surgery: Danaparoid, Enoxaparin, Dalteparin Study Group; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery; IU anti-Xa International units anti-activated factor X; OD Once daily; BID Twice daily; TID Three times daily; UFH Unfractionated heparin; Pre Preoperative timing of initiation; Peri Perioperative timing of initiation; Post Postoperative timing of initiation; INR International normalized ratio

[a] This trial included two arms using the same initial dose; one arm had dosing adjustments according to activated partial thromboplastin time.
[b] The initial dose of nadroparin was 41 IU anti-Xa/Kg OD during the first 3 days.
[c] The unfractionated heparin arm was adjusted according to activated thromboplastin time.
[d] This trial included two enoxaparin groups one of which used graduate compression stockings.
[e] In this trial both groups used graduate compression stockings.
[f] This trial included a danaparoid arm.
[g] This trial included two dalteparin arms starting at 2 hours pre- and 4 hours postoperatively.
[h] These trials used initial subcutaneous melagatran in the ximelagatran arm.
[i] This trial included an indomethacin arm.

number of available studies was very small, there is a general consensus advising against their use, or the groups included more than one intervention.

3.1.2. Characteristics of included studies and methodological quality

The characteristics of the 55 included studies are shown in table 4. The included studies comprised 123 intervention arms 2 of which were excluded. One study included a danaparoid arm in addition to the tinzaparin and dalteparin arms; the other study included an indomethacin arm together with a nadroparin and a placebo arms. In total 121 patient groups enrolling 42,131 patients were included in the review. Of these, 24,630 underwent THR, 13,318 underwent TKR, 2,001 underwent HFS, and in 2,182 the type of surgery was not specified. The numbers of groups and patients included for each drug and placebo are shown in table 5.

Table 5. Number of patient groups and randomized patients included in the systematic review

Drug	*No. of Patient groups*	*No. of Randomized Patients*
Ximelagatran	9	7,274
LMWH	65	20,213
UFH	16	2,897
Warfarin	13	6,813
Fondaparinux	9	4,341
Placebo	9	593
Total	121	42,131

LMWH Low molecular weight heparin; UFH Unfractionated heparin.

The percentages of patients evaluable for major outcomes are shown in table 6. The majority of the randomized patients were evaluable for major bleeding. On the contrary, information on symptomatic VTE was often missing from the studies.

Table 6. Number and percentage of patients evaluable for major outcomes

Drug	*Major VTE*		*Total VTE*		*Symptomatic VTE*		*Major Bleeding*	
	No.	*%[a]*	*No.*	*%[a]*	*No.*	*%[a]*	*No.*	*%[a]*
Ximelagatran	5,956	81.9	5,975	82.1	6,801	93.5	7,245	99.6
LMWH	16,493	81.6	14,430	71.4	11,239	55.6	19,493	96.4
UFH	2,407	83.1	1,672	57.7	339	11.7	2,803	96.8
Warfarin	5,677	83.3	4,203	61.7	4,146	60.9	6,751	99.1
Fondaparinux	3,135	72.2	3,104	71.5	3,603	83.0	4,289	98.8
Placebo	541	91.2	541	91.2	198	33.4	394	66.4
Total	34,209	81.2	29,925	71.0	26,326	62.5	40,975	97.3

VTE Venous thromboembolism; LMWH Low molecular weight heparin; UFH Unfractionated heparin.
[a] Represents percentage of evaluable patients out of the total number of randomized patients.

The methodological characteristics of the studies are shown in table 7. In general the methodological quality of the reports was acceptable. Allocation concealment was appropriate in approximately two thirds of the studies. The majority of the studies were funded by the pharmaceutical industry, and most of them used a blinded process to adjudicate outcomes. Only about one half of the studies used a similar definition for major bleeding events. Particularly important is the fact that the definition of minor bleeding events was extremely heterogeneous which prevented its inclusion in the final analysis.

Table 7. Methodological characteristics of the studies included in the systematic review

Characteristic	*Number*	*Percentage*
Jadad score		
0	1	1.8
1	4	7.3
2	9	16.4
3	6	10.9
4	11	20.0
5	24	43.6
Allocation concealment		
Adequate	35	63.6
Inadequate	4	7.3
Unclear / Not stated	16	29.1
Type of analysis		
Intention to treat	46	83.6
As treated	9	16.4
Funding source		
Pharmaceutical	38	69.1
Non pharmaceutical	8	14.5
Unclear / not stated	9	16.4
Blinded adjudication of outcomes		
Yes	47	85.5
No	5	9.1
Not stated	3	5.5
ISTH-like definition of major bleeding		
Yes	31	56.4
No	20	36.4
Not stated	4	7.3

ISTH International Society on Thrombosis and Haemostasis

3.1.3. Estimates of venous thromboembolism

The pooled estimates of VTE for all studies are shown in table 8 and in figures 6-8. The agent that resulted in the lowest proportion of major, total and sym-

Table 8. Pooled estimates of proportion for main outcomes in all studies

Drug	*Major VTE* % (95% CI)	*Total VTE* % (95% CI)	*Symptomatic VTE* % (95% CI)	*Major Bleeding* % (95% CI)
Ximelagatran	3.274 (3.175, 3.372)	19.396 (19.001, 19.790)	1.059 (1.034, 1.083)	1.804 (1.722, 1.885)
LMWH	6.528 (6.357, 6.699)	20.412 (20.138, 20.687)	1.433 (1.365, 1.501)	2.208 (2.156, 2.260)
UFH	13.394 (12.862, 13.926)	23.464 (22.904, 24.023)	3.245 (3.056, 3.433)	2.494 (2.363, 2.625)
Warfarin	6.278 (6.092, 6.463)	31.049 (30.439, 31.659)	1.955 (1.830, 2.080)	1.778 (1.690, 1.867)
Fondaparinux	2.051 (1.957, 2.146)	6.707 (6.425, 6.988)	0.611 (0.585, 0.636)	5.113 (4.690, 5.536)
Placebo	21.019 (19.978, 22.060)	52.307 (50.886, 53.729)	12.019 (10.317, 13.721)	1.781 (1.651, 1.912)

VTE Venous thromboembolism; CI Confidence interval; LMWH Low molecular weight heparin; UFH Unfractionated heparin.

ptomatic VTE was fondaparinux. The drugs associated with the highest proportion of events were unfractionated heparin for major and symptomatic VTE, and warfarin for total VTE. The pooled estimates were obtained using a random effects model because of the presence of heterogeneity in the analyses.

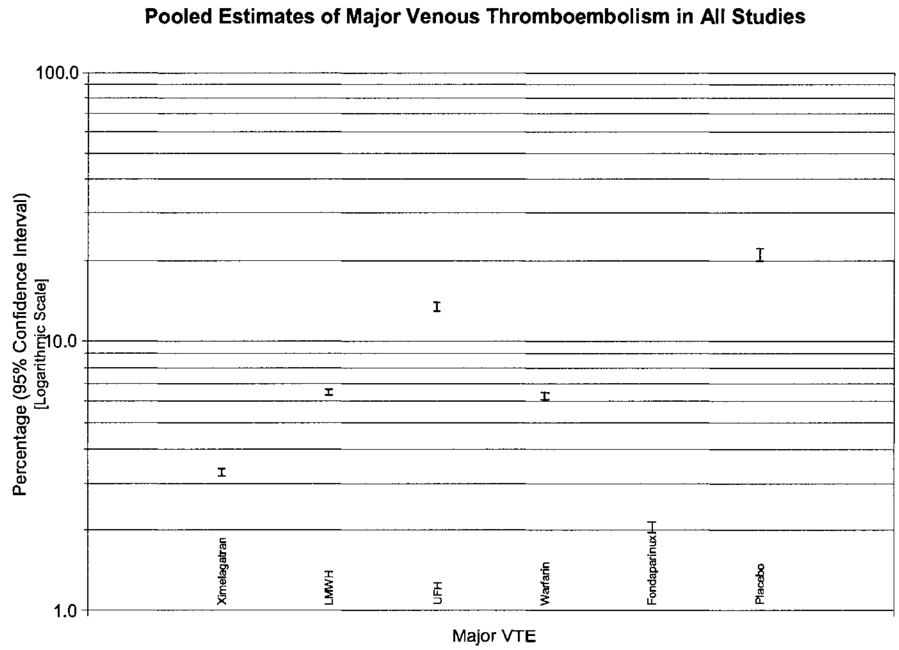


Figure 6. Pooled estimates of major venous thromboembolism in all studies. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. VTE Venous thromboembolism; LMWH Low molecular weight heparin; UFH Unfractionated heparin.

Pooled Estimates of Total Venous Thromboembolism in All Studies

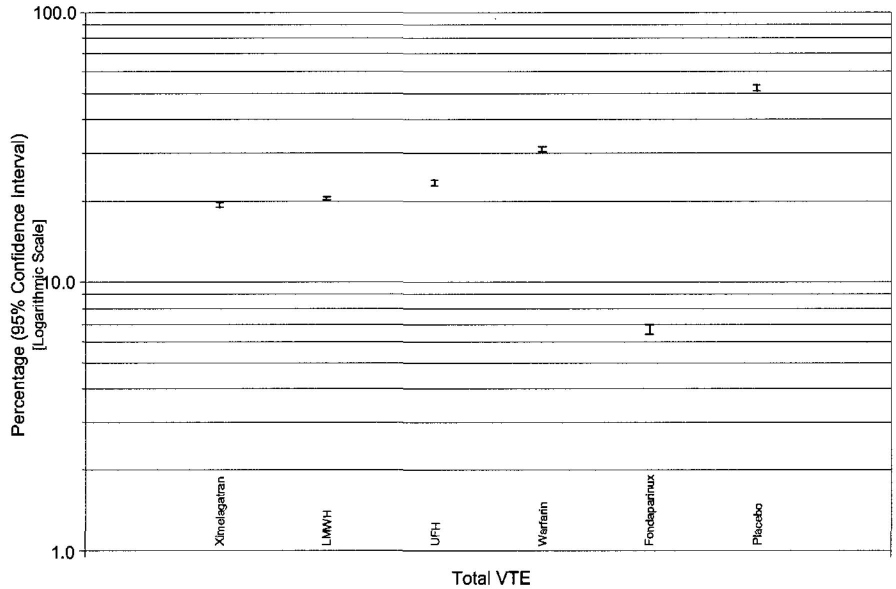


Figure 7. Pooled estimates of total venous thromboembolism in all studies. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. VTE Venous thromboembolism; LMWH Low molecular weight heparin; UFH Unfractionated heparin.

Pooled Estimates of Symptomatic Venous Thromboembolism in All Studies

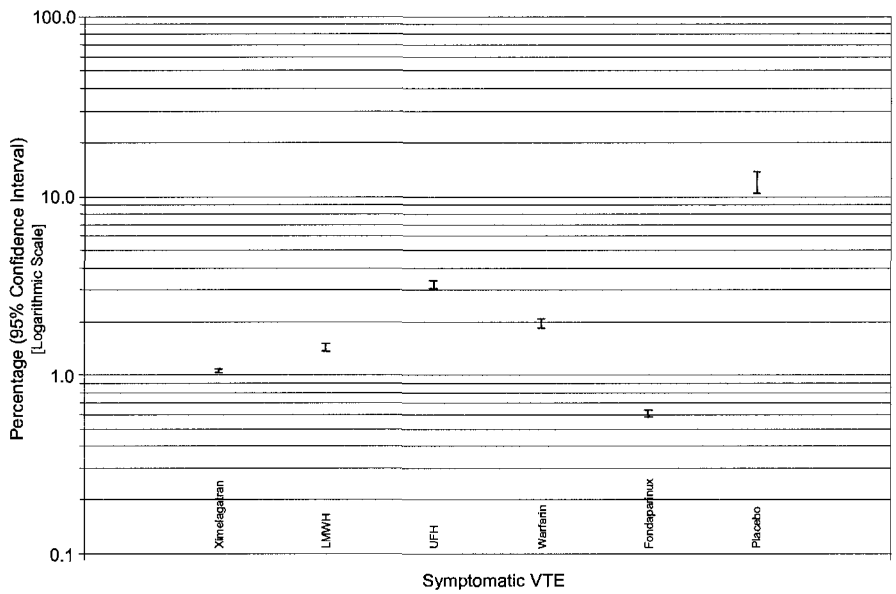


Figure 8. Pooled estimates of symptomatic venous thromboembolism in all studies. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. VTE Venous thromboembolism; LMWH Low molecular weight heparin; UFH Unfractionated heparin.

3.1.4. Estimates of major bleeding episodes

After pooling the results of all studies the drug associated with the highest proportion of major bleeding events was fondaparinux whereas warfarin had the lowest proportion (see table 8 and figure 9). As with VTE, the estimates represent the results of a random effects model because of the presence of heterogeneity among the studies.

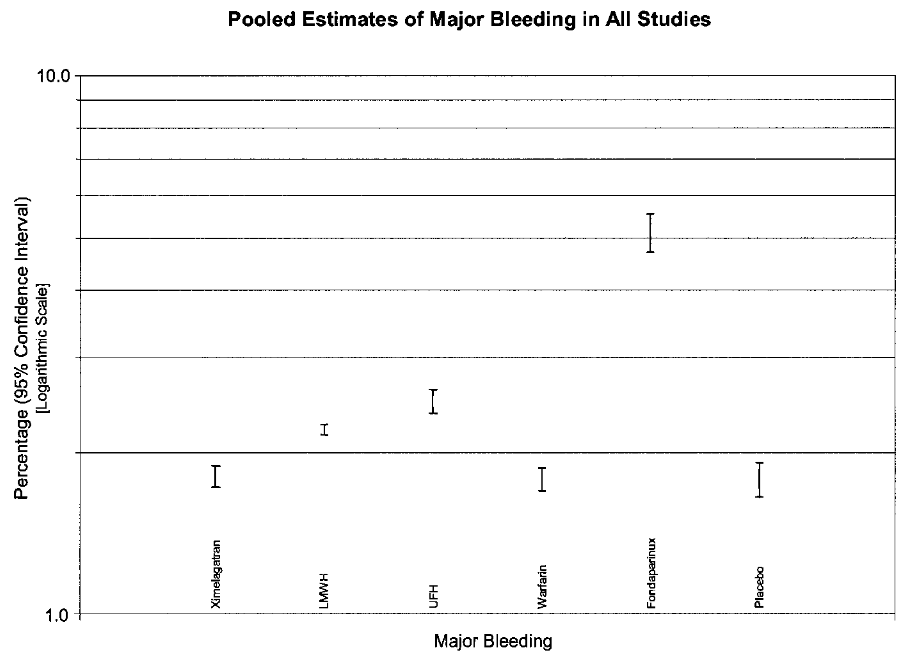


Figure 9. Pooled estimates of major bleeding events in all studies. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

3.1.5. Subgroup and sensitivity analyses

As mentioned in the methods section, in order to explore heterogeneity, several subgroup and sensitivity analyses were conducted because of a concern regarding their possible influence on the estimates of the outcomes. The analysis was done using modified forest plots for each agent and outcome; these plots depicted the pooled estimates and 95% CIs obtained from the overall and subgroup analyses, together with the band of clinical relevance. It was considered that subgroup estimates whose 95% CIs were lying outside of it were likely to have a statistically significant and clinically relevant difference with respect to the global estimate. The plots showing the analyses for major, total, and symptomatic VTE, and major bleeding are shown in supplemental figures S1 – S6, S7 – S12, S13 – S18, and S19 – S24 in appendix II, respectively.

The subgroup and sensitivity analyses showed that the features that were unlikely to influence the results of the estimates of major, total, and symptomatic VTE as well as major bleeding were: adequacy of allocation concealment, type of analysis, and Jadad score, and therefore no further analyses were conducted. The potential influence of blinded outcome adjudication could not be further explored because the vast majority of studies used this method. Other sub-analyses are detailed below.

Major bleeding definition. The estimates of major bleeding events according to the type of definition used are shown in table 9 and are graphically presented in figure S25 in appendix II. The number of patients and study groups contributing information for these analyses are shown in table 10. All studies evaluating fondaparinux and ximelagatran used an ISTH-like definition. A significant difference was only found for the studies evaluating UFH and using an ISTH-like definition when compared to the global estimates. The global pooled estimates were deemed to be adequate because: a) no systematic clinically relevant difference was found when compared to the estimates from studies using both types of definitions, and b) although in studies using a non ISTH-like definition the criteria to define a major bleeding episode were heterogeneous, they incorporated the surgeons assessment of bleeding.

Table 9. Estimates of major bleeding episodes according to type of definition

Drug	*ISTH-Like Definition % (95% CI)*	*Non ISTH-Like Definition % (95% CI)*	*All Definitions % (95% CI)*
Ximelagatran	1.804 (1.722, 1.885)	NE	1.804 (1.722, 1.885)
LMWH	2.304 (2.244, 2.364)	1.996 (1.892, 2.099)	2.208 (2.156, 2.260)
UFH	4.893 (4.728, 5.058)	1.939 (1.810, 2.067)	2.494 (2.363, 2.625)
Warfarin	1.562 (1.480, 1.644)	2.717 (2.614, 2.820)	1.778 (1.690, 1.867)
Fondaparinux	5.113(4.690, 5.536)	NE	5.113 (4.690, 5.536)
Placebo	2.414 (2.215, 2.612)	0.644 (0.518, 0.770)	1.781 (1.651, 1.912)

ISTH International Society on Thrombosis and Haemostasis; CI Confidence interval; LMWH Low molecular weight heparin; UFH Unfractionated heparin

Type of surgery. It was of special interest to explore possible differences according to the type of surgery. Results of the subgroup analyses are shown in table 11 and graphically in figures S26-S29 in appendix II.

Table 10. Number of patients and study groups that were included in the calculation of the major bleeding estimates according to the type of major bleeding definition

	ISTH-Like Definition		*Non ISTH-Like Definition*		*All Definitions*	
	NS	*Pts.*	*NS*	*Pts.*	*NS*	*Pts.*
Ximelagatran	9	7245	–	–	9	7245
LMWH	37	15492	19	4001	56	19493
UFH	3	654	12	2149	15	2803
Warfarin	9	5794	3	957	12	6751
Fondaparinux	9	4289	–	–	9	4289
Placebo	3	239	2	155	5	394

ISTH international Society on Thrombosis and Haemostasis; NS Number of study groups; Pts. Number of patients; LMWH Low molecular weight heparin; UFH Unfractionated heparin; – no information available
[a] This study included only patients undergoing total hip replacement

Table 11. Pooled estimates of main outcomes according to type of surgery

Drug	*Total Hip Replacement*	*Total Knee Replacement*	*Hip Fracture Surgery*
	% (95% CI)	*% (95% CI)*	*% (95% CI)*
Major venous thromboembolism			
Ximelagatran	3.401 (3.181, 3.621)	3.100 (3.042, 3.158)	NE
LMWH	6.472 (6.293, 6.651)	5.143 (5.010, 5.277)	12.797 (11.101, 14.492)
UFH	15.154 (14.446, 15.862)	9.119 (8.803, 9.436)	16.667 (15.333, 18.000)
Warfarin	4.280 (4.083, 4.477)	8.100 (7.879, 8.322)	NE
Fondaparinux	2.138 (2.009, 2.267)	2.446 (2.288, 2.603)	1.595 (1.497, 1.693)
Placebo	24.726 (23.268, 26.184)	14.833 (14.351, 15.314)	NE
Total venous thromboembolism			
Ximelagatran	12.762 (11.915, 13.610)	26.693 (26.078, 27.309)	NE
LMWH	15.546 (15.291, 15.801)	32.197 (31.860, 32.535)	20.745 (19.518, 21.972)
UFH	21.843 (21.116, 22.570)	32.075 (31.562, 32.589)	25.397 (24.322, 26.472)
Warfarin	19.831 (19.384, 20.277)	39.356 (38.693, 40.020)	NE
Fondaparinux	5.394 (5.106, 5.682)	12.465 (12.125, 12.806)	8.307 (8.091, 8.523)
Placebo	46.291 (44.295, 48.287)	63.158 (62.504, 63.812)	NE
Symptomatic venous thromboembolism			
Ximelagatran	0.756 (0.713, 0.798)	1.388 (1.349, 1.427)	NE
LMWH	1.172 (1.109, 1.235)	2.110 (2.035, 2.184)	0.421 (0.380, 0.463)
UFH	4.472 (4.213, 4.730)	NE	NE
Warfarin	2.692 (2.374, 3.009)	1.897 (1.838, 1.956)	NE
Fondaparinux	0.665 (0.632, 0.699)	0.580 (0.515, 0.646)	0.481 (0.434, 0.528)
Placebo	2.721 (2.458, 2.984)	29.412 (28.161, 30.662)	NE
Major bleeding episodes			
Ximelagatran	2.892 (2.683, 3.101)	1.127 (1.095, 1.159)	NE
LMWH	2.151 (2.085, 2.216)	1.605 (1.566, 1.644)	2.559 (2.464, 2.655)
UFH	2.813 (2.625, 3.001)	0.943 (0.837, 1.050)	3.896 (3.464, 4.328)
Warfarin	2.229 (2.088, 2.371)	0.822 (0.792, 0.852)	NE
Fondaparinux	6.033 (5.501, 6.566)	2.128 (2.003, 2.252)	2.166 (2.067, 2.265)
Placebo	1.463 (1.299, 1.628)	2.116 (1.911, 2.322)	NE

CI Confidence interval; LMWH Low molecular weight heparin; UFH Unfractionated heparin; NE not estimable

The number of patients and study groups contributing information for these analyses are shown in table 12.

Table 12. Number of study groups and patients that were included in the calculation of the estimates according to type of surgery and timing of administration

	All Patients								*THR*		*TKR*		*HFS*	
	All Timing		*Pre*		*Peri*		*Post*							
	NS	*Pts.*	*NS*	*Pts.*	*NS*	*Pts.*	*NS*	*Pts.*	*NS*	*Pts.*	*NS*	*Pts.*	*NS*	*Pts.*
Major Venous Thromboembolism														
Ximelagatran	9	5956	1[a]	782	4	2594	4	2580	5	2569	8	3387	–	–
LMWH	60	16493	27	6967	15	2946	18	6580	42	11547	19	3335	4	768
UFH	14	2407	6	1124	6	638	2	645	10	1244	2	318	1	30
Warfarin	12	5677	4	990	7	3192	1[a]	1495	6	2758	9	2919	–	–
Fondaparinux	9	3135	–	–	9	3135	–	–	7	2140	1	368	1	627
Placebo	9	541	–	–	–	–	–	–	6	332	3	209	–	–
Total Venous Thromboembolism														
Ximelagatran	9	5975	1[a]	782	4	2597	4	2596	5	2561	8	3414	–	–
LMWH	63	14430	27	6187	19	3222	17	5021	44	10035	22	3591	5	801
UFH	15	1672	6	342	7	685	2	645	11	1291	2	318	2	63
Warfarin	12	4203	5	1025	7	3178	–	–	6	1273	9	2930	–	–
Fondaparinux	9	3104	–	–	9	3104	–	–	7	2117	1	361	1	626
Placebo	9	541	–	–	–	–	–	–	6	332	3	209	–	–
Symptomatic Venous Thromboembolism														
Ximelagatran	8	6801	1[a]	782	3	2902	4	3117	2	1588	5	3457	–	–
LMWH	26	11239	14	5367	6	999	6	4873	14	6840	7	1422	3	949
UFH	4	339	2	230	2	109	–	0	3	246	1	93	–	–
Warfarin	6	4146	1	257	4	2394	1[a]	1495	2	1833	3	2056	–	–
Fondaparinux	4	3603	–	–	4	3603	–	–	2	2255	1	517	1	831
Placebo	3	198	–	–	–	–	–	–	2	147	1	51	–	–
Major Bleeding														
Ximelagatran	9	7245	1[a]	906	4	3190	4	3149	4	3041	7	4170	–	–
LMWH	56	19493	23	7913	15	3693	18	7887	35	12596	19	3988	5	1055
UFH	15	2803	7	1380	6	683	2	541	10	1401	2	318	2	77
Warfarin	12	6751	4	1299	7	3957	1[a]	1495	5	2856	8	3407	–	–
Fondaparinux	9	4289	–	–	9	4289	–	–	7	2941	1	517	1	831
Placebo	5	394	–	–	–	–	–	–	3	205	2	189	–	–

Pre Preoperative (up 2 hours before surgery) ; Peri Perioperative (within 2 hours before and up to 12 hours after surgery); Post Postoperative (12 hours or more after surgery); THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery; NS number of study groups; Pts. Number of patients; LMWH Low molecular weight heparin; UFH Unfractionated heparin; – no information available

[a] This study included only patients undergoing total hip replacement

There were no systematic differences between groups for the estimates of major and symptomatic VTE, although TKR patients receiving UFH and THR patients receiving warfarin had less major VTE than the other groups. Of note THR patients receiving placebo had more major VTE than TKR patients but less total VTE. An important finding was that TKR patients had systematically more total VTE episodes than THR of HFS patients independently of the prophylactic agent used. These differences were statistically significant. No difference was found in the proportion of symptomatic VTE between types of surgery, except for those patients receiving placebo. These patients had a much higher proportion of events if they had undergone TKR rather than THR. A higher proportion of major bleeding events was observed in THR patients receiving ximelagatran, UFH, warfarin, and fondaparinux, compared to TKR patients. No difference was observed in patients receiving LMWH or placebo.

Timing of initiation. The results of the analyses according to timing of initiation of the prophylactic agent are shown in table 13 and graphically in figures S30 – S33 in appendix II. The number of patients and study groups contributing information for these analyses are shown in table 12. Although no systematic differences were found for any outcome, those patients starting UFH or LMWH postoperatively had less major VTE events than those starting pre- or perioperatively. Regarding total VTE, more episodes were seen in patients receiving preoperative UFH than in those receiving it peri- or postoperatively; on the contrary, less VTE events were seen in patients receiving preoperative warfarin compared to those receiving it perioperatively. No clinically relevant differences (i.e. >2%) were seen between estimates of symptomatic VTE.

Table 13. Pooled estimates of main outcomes according to timing of initiation

Drug	*Preoperative*[a] *% (95% CI)*	*Perioperative*[b] *% (95% CI)*	*Postoperative*[c] *% (95% CI)*
Major venous thromboembolism			
Ximelagatran	NE	3.129 (2.879, 3.379)	2.946 (2.880, 3.011)
LMWH	7.749 (7.496, 8.002)	7.398 (6.945, 7.850)	4.179 (4.035, 4.323)
UFH	13.561 (12.509, 14.613)	16.220 (15.345, 17.095)	7.752 (7.546, 7.958)
Warfarin	7.374 (7.211, 7.537)	6.587 (6.311, 6.863)	NE
Fondaparinux	NE	2.051 (1.957, 2.146)	NE
Placebo	21.019 (19.978, 22.060)	21.019 (19.978, 22.060)	21.019 (19.978, 22.060)
Total venous thromboembolism			
Ximelagatran	NE	21.596 (20.920, 22.272)	21.764 (21.606, 21.923)
LMWH	21.572 (21.136, 22.007)	20.874 (20.339, 21.410)	18.185 (17.724, 18.646)
UFH	30.117 (29.631, 30.603)	22.853 (21.892, 23.814)	17.519 (17.226, 17.813)
Warfarin	25.811 (25.018, 26.603)	34.586 (33.805, 35.367)	NE
Fondaparinux	NE	6.707 (6.425, 6.988)	NE
Placebo	52.307 (50.886, 53.729)	52.307 (50.886, 53.729)	52.307 (50.886, 53.729)
Symptomatic venous thromboembolism			
Ximelagatran	NE	1.055 (1.002, 1.107)	1.219 (1.181, 1.258)
LMWH	1.230 (1.200, 1.259)	2.002 (1.915, 2.089)	0.493 (0.473, 0.512)
UFH	2.609 (2.403, 2.815)	4.587 (4.194, 4.980)	NE
Warfarin	NE	2.256 (2.196, 2.315)	NE
Fondaparinux	NE	0.611 (0.585, 0.636)	NE
Placebo	12.019 (10.317, 13.721)	12.019 (10.317, 13.721)	12.019 (10.317, 13.721)
Major bleeding episodes			
Ximelagatran	NE	2.665 (2.604, 2.725)	0.953 (0.919, 0.987)
LMWH	1.453 (1.427, 1.480)	4.360 (4.294, 4.425)	1.788 (1.759, 1.817)
UFH	1.159 (1.103, 1.216)	2.196 (2.086, 2.306)	4.730 (4.577, 4.883)
Warfarin	2.617 (2.531, 2.704)	1.639 (1.538, 1.740)	NE
Fondaparinux	NE	5.113 (4.690, 5.536)	NE
Placebo	1.781 (1.651, 1.912)	1.781 (1.651, 1.912)	1.781 (1.651, 1.912)

CI Confidence interval; LMWH Low molecular weight heparin; UFH Unfractionated heparin; NE not estimable
[a] up 2 hours before surgery
[b] within 2 hours before and up to 12 hours after surgery
[c] *12 hours or more after surgery*

The analysis of major bleeding episodes showed that the proportion of events was higher in those patients receiving perioperative ximelagatran or LMWH, preoperative warfarin, and postoperative UFH. All studies evaluating fondaparinux used perioperative administration.

It is particularly important to mention that the sub-analyses according to type of surgery and timing of initiation were of an exploratory nature, and because of that, some estimates are based on only 1 or 2 available studies, as can be seen in table 12. Therefore the interpretation of this information should be done cautiously.

Table 14. Pooled estimates of main outcomes according to funding source

Drug	*Industry funded % (95% CI)*	*Not industry funded % (95% CI)*
Major venous thromboembolism		
Ximelagatran	3.274 (3.175, 3.372)	NE
LMWH	5.237 (5.100, 5.373)	10.155 (9.663, 10.647)
UFH	11.623 (11.037, 12.210)	16.748 (15.659, 17.838)
Warfarin	6.126 (5.926, 6.327)	8.421 (8.026, 8.816)
Fondaparinux	2.051 (1.957, 2.146)	NE
Placebo	28.557 (27.820, 29.294)	18.183 (17.266, 19.099)
Total venous thromboembolism		
Ximelagatran	19.396 (19.001, 19.790)	NE
LMWH	20.341 (20.036, 20.646)	20.632 (20.041, 21.222)
UFH	24.102 (23.363, 24.841)	22.668 (21.758, 23.579)
Warfarin	32.697 (32.065, 33.329)	24.000 (23.442, 24.558)
Fondaparinux	6.707 (6.425, 6.988)	NE
Placebo	59.383 (55.343, 63.422)	49.770 (48.647, 50.893)
Symptomatic venous thromboembolism		
Ximelagatran	1.059 (1.034, 1.083)	NE
LMWH	1.153 (1.106, 1.201)	3.462 (3.239, 3.684)
UFH	2.609 (2.403, 2.815)	4.587 (4.194, 4.980)
Warfarin	1.955 (1.830, 2.080)	NE
Fondaparinux	0.611 (0.585, 0.636)	NE
Placebo	NE	15.070 (12.314, 17.826)
Major bleeding episodes		
Ximelagatran	1.804 (1.722, 1.885)	NE
LMWH	2.256 (2.196, 2.317)	1.845 (1.782, 1.909)
UFH	1.919 (1.774, 2.063)	4.006 (3.858, 4.154)
Warfarin	1.810 (1.713, 1.906)	1.434 (1.294, 1.573)
Fondaparinux	5.113 (4.690, 5.536)	NE
Placebo	0.868 (0.699, 1.038)	2.065 (1.894, 2.235)

CI Confidence interval; LMWH Low molecular weight heparin; UFH Unfractionated heparin; NE not estimable

Funding source. Since there is some evidence that the funding source of a study might influence the outcomes resulting in publication bias[152-154] it was of interest to explore this issue. A sub-analysis according to the funding source was conducted and the results are shown in table 14 and graphically in figure S34 in appendix II. All the studies evaluating ximelagatran and fondaparinux were funded by the pharmaceutical industry. For the remaining agents, it was found that for major VTE the industry funded studies reported less events than the not industry funded studies in the groups receiving LMWH, UFH or warfarin. The contrary was found in the placebo group. However, in patients receiving warfarin or placebo more total VTE events were reported in the industry funded studies whereas no difference was observed for total VTE in the LMWH or UFH groups. In regard to symptomatic VTE a slightly higher proportion of events was reported in the LMWH and UFH groups, although such difference was marginally relevant only for LMWH. No difference was observed regarding major bleeding events, except in the UFH group.

Secular trends. Finally, during the conduct of the systematic review and meta-analysis it was observed the possibility of a trend towards a lower frequency of major and total VTE in the more recent trials. Such trend could be explained by differences in surgical techniques or post-surgical care practices. This issue would be relevant if due to the influence of earlier studies, the estimates obtained from all studies (1980 – 2004) were significantly different from the estimates obtained from the most recent studies (1994 – 2004), which likely reflect the current clinical practice. To explore this issue and determine if the differences were significant, a cumulative meta-analysis was conducted. Since studies evaluating ximelagatran and fondaparinux are very recent, only LMWH, UFH, warfarin, and placebo were analyzed. The results are shown in table 15 and graphically presented in figures S35 – S48 in appendix II.

The evaluation of the forest plots suggested that studies published after 1994 might have reported a lower frequency of VTE. Therefore a second cumulative meta-analysis was done after excluding studies published prior to that year. It was found that compared to studies published between 1994 and 2004, the studies published between 1980 and 1993 reported higher proportions of major and total VTE in patients receiving UFH and LMWH. However, when the estimates of all studies (published between 1980 and 2004) were compared to the estimates of the studies published between 1994 and 2004, only the estimate of major VTE in patients receiving UFH showed a statistically significant difference whereas the rest of the estimates did not show differences.

Table 15. Cumulative pooled estimates of venous thromboembolism according to year of publication

Drug	*1980 – 1993* % (95% CI)	*NS*	*1994 – 2004* % (95% CI)	*NS*	*1980 – 2004* % (95% CI)	*NS*
Major venous thromboembolism						
LMWH	11.55 (10.87, 12.23)	11	5.41 (5.28, 5.55)	49	6.53 (6.36, 6.70)	60
UFH	18.52 (17.75, 19.29)	8	6.93 (6.75, 7.11)	6	13.39 (12.86, 13.93)	14
Warfarin	NE	1	6.17 (5.96, 6.37)	11	6.28 (6.09, 6.46)	12
Placebo	22.33 (21.14, 23.53)	4	20.72 (18.97, 22.46)	5	21.02 (19.98, 22.06)	9
Total venous thromboembolism						
LMWH	23.2 (22.59, 23.82)	12	19.80 (19.50, 20.11)	51	20.41 (20.14, 20.69)	63
UFH	27.06 (26.4, 27.73)	9	18.37 (17.51, 19.23)	6	23.46 (22.90, 24.02)	15
Warfarin	NE	1	30.41 (29.76, 31.07)	11	31.05 (30.44, 31.66)	12
Placebo	47.93 (46.51, 49.35)	4	56.44 (54.06, 58.82)	5	52.31 (50.89, 53.73)	9

CI Confidence interval; NS Number of study groups; LMWH Low molecular weight heparin; UFH Unfractionated heparin; NE Not estimable

This means that except in the case of UFH, earlier studies did not influence the overall estimates and therefore the results of all studies were included in the subsequent analyses although separate exploratory analyses were done using both estimates of major VTE in patients receiving UFH. The previous findings are most likely due to the fact that, except in the case of UFH, the majority of the included studies were published after 1994. The fact that the different placebo cumulative estimates did not show a statistically significant difference suggests that changes in surgical or anesthetic techniques probably do not influence the occurrence of VTE after orthopedic surgery.

In addition, a cumulative meta-analysis was also done for major bleeding episodes. Results are shown in table 16 and are presented graphically in figures S49 – S52 in appendix II. No significant variations depending on publication date were found.

Table 16. Cumulative pooled estimates of major bleeding episodes obtained using a random effects model and divided according to year of publication

Drug	1980 – 1993		1994 – 2004		1980 – 2004	
	% (95% CI)	NS	% (95% CI)	NS	% (95% CI)	NS
Major bleeding episodes						
LMWH	2.07 (1.95, 2.2)	11	2.23 (2.17, 2.29)	45	2.21 (2.16, 2.26)	56
UFH	2.72 (2.54, 2.9)	9	2.22 (2.01, 2.42)	6	2.49 (2.36, 2.62)	15
Warfarin	NE	1	1.83 (1.74, 1.93)	11	1.78 (1.69, 1.87)	12
Placebo	1.64 (1.49, 1.79)	3	1.44 (1.18, 1.7)	2	1.78 (1.66, 1.9)	5

CI Confidence interval; NS Number of studies; LMWH Low molecular weight heparin; UFH Unfractionated heparin; NE Not estimable

3.1.6. Case fatality rates

The pooled estimates of the proportion of fatal events are shown in table 17 and in figure S53 in appendix II. Not surprisingly, the lowest case fatality from VTE was for total events whereas the highest was for symptomatic.

Table 17. Pooled proportions of fatal events (case fatality rates) in all studies

Drug	n	N	p-value [a]	% (95% CI)
Major venous thromboembolism				
Confirmed PE deaths	13	1366	0.423	0.952 (0.557, 1.621)
Probable PE deaths	6	1340	0.988	0.448 (0.205, 0.973)
Confirmed and probable PE deaths	19	1366	0.747	1.391 (0.892, 2.162)
Total venous thromboembolism				
Confirmed PE deaths	13	6250	0.243	0.208 (0.122, 0.356)
Probable PE deaths	6	6250	0.890	0.096 (0.044, 0.209)
Confirmed and probable PE deaths[b]	19	6250	0.030	0.364 (0.344, 0.383)
Confirmed and probable PE deaths[c]	19	6250	—	0.304 (0.195, 0.474)
Symptomatic venous thromboembolism				
Confirmed and probable PE deaths[b,d]	11	228	<0.001	7.401 (6.681, 8.122)
Confirmed and probable PE deaths[c,d]	11	228	—	4.825 (2.715, 8.431)
Major Bleeding				
All major bleeding definitions[b]	11	808	<0.001	3.557 (3.203, 3.911)
All major bleeding definitions[d]	11	808	—	1.361 (0.762, 2.421)
ISTH major bleeding definition	7	687	0.744	1.019 (0.494, 2.088)
Non ISTH major bleeding definition	4	121	>0.999	3.306 (1.293, 8.192)

n Number of deaths; N Number of events; CI Confidence interval; PE Pulmonary embolism; ISTH International Society on Thrombosis and Haemostasis

[a] χ^2 *p*-value for heterogeneity of the pooled estimate

[b] Estimate obtained using a random effects model

[c] Estimate obtained using a fixed effects model

[d] All deaths but one were confirmed to be due to PE

The confirmed and suspected deaths from PE were analyzed separately, however because of the low number of events, the overall estimate was the one used in subsequent analysis. Regarding fatal bleeding events, the estimate obtained using all definitions of major bleeding was statistically heterogeneous; this issue was explored by analyzing the estimates according to the type of major bleeding definition (ISTH-like or non ISTH-like). The latter estimates were homogeneous and no clinically relevant difference was found between them tested using the band of clinical relevance; however there was a clinically relevant difference between the pooled estimate for all major bleeding definitions and the pooled estimate from studies using an ISTH-like major bleeding definition and this issue was considered in subsequent analyses.

A potential concern with the weighting method proposed by Laird and Mosteller is that it uses a normal approximation to proportions which might be inappropriate if the proportions are very small[128] and similarly, the use of a χ^2 test to determine heterogeneity might not be ideal. Because of this, pooled estimates were calculated using both the fixed and random effects models if the difference between them was considered to be of concern, as shown in table 17, and used in subsequent calculations.

Table 18. Pooled proportions of fatal thromboembolic events (case fatality rates) according to prophylaxis use status

	n	*N*	*p-value* [a]	% (95% CI)
Major venous thromboembolism				
Any prophylaxis	18	1272	0.851	1.415 (0.897, 2.226)
No prophylaxis	1	94	0.802	1.064 (0.188, 5.782)
Total venous thromboembolism				
Any prophylaxis	18	6139	0.050	0.350 (0.331, 0.370)
No prophylaxis	1	270	0.904	0.370 (0.065, 2.068)

n Number of deaths; N Number of events; CI Confidence interval
[a] χ^2 *p*-value for heterogeneity of the pooled estimate

To evaluate if the case fatality rates were influenced by the use of prophylaxis and consequently if the use of pooled estimates was appropriate, the case fatality rates were also analyzed according to the use or not of prophylaxis. No differences were found between groups (table18, figure S54 in appendix II).

Finally, the ratios of the case fatality rates of major, total, and symptomatic VTE to the case fatality rates of major bleeding were calculated. These ratios indicate the relative importance of VTE to bleeding, in other words they inform how lethal is a thrombotic event compared to a bleeding event. To obtain the 95% CI for each ratio, a Monte Carlo simulation was conducted using 1,000 replications of the case fatality rates and ratios were calculated for each replication and the 2.5th and

97.5th percentile values of the replications were used to define the 95% confidence interval. Results are shown in table 19.

Table 19. Case fatality rate-ratios of venous thromboembolism to major bleeding

Major Bleeding Definition	*Major VTE [Ratio (95% CI)]*	*Total VTE[a] [Ratio (95% CI])*	*Total VTE[b] [Ratio (95% CI])*	*Symptomatic VTE [Ratio (95% CI])*
All Definitions[a]	**0.391 (0.158, 1.579)**	**0.102 (0.039, 0.435)**	0.085 (0.034, 0.346)	**2.081 (0.559, 9.037)**
All Definitions[b]	1.022 (0.505, 2.264)	0.267 (0.119, 0.580)	0.223 (0.114, 0.483)	5.438 (1.238, 14.685)
ISTH-Like	1.365 (0.643, 3.483)	0.357 (0.149, 0.884)	0.298 (0.138, 0.741)	7.264 (1.751, 22.975)
Non ISTH-Like	0.421 (0.169, 1.409)	0.110 (0.040, 0.361)	0.092 (0.037, 0.312)	2.239 (0.522, 9.855)

VTE Venous thromboembolism; CI Confidence interval; ISTH International Society on Thrombosis and Haemostasis
[a] Estimate obtained using a random effects model
[b] Estimate obtained using a fixed effects model
Numbers on bold type indicate the case-fatality rate ratios that were used as reference in subsequent analyses

Case fatality rate-ratios were calculated for all bleeding definitions and total VTE using the estimates obtained by both the fixed and the random effects models. However, since the ratio obtained using the fixed effects model was contained within the 95% CI of the ratio that was obtained using the random effects model, it was decided to use the random effects model in subsequent analyses.

3.2. Clinical cost-effectiveness analysis

3.2.1. Risk-benefit planes and risk-benefit acceptability curves

Values of cost (risk) and benefit were obtained from the Monte Carlo simulations. Benefit was estimated as the proportion of major, total, or symptomatic VTE and cost (risk) as the proportion of major bleeding events. Incremental risk and benefit were then calculated and paired observations of the replications were plotted in risk-benefit planes for each drug and each pair of observations. The reference values were those obtained for placebo patients (Figures S55 – S59 in appendix II). The proportion of paired observations lying below the risk-benefit acceptability threshold was calculated across a range of values and plotted in risk-benefit acceptability curves for each agent and combination of outcomes as shown in figures S60 – S62 in appendix II. These curves represent the probability that an agent has of being net-beneficial relative to placebo across a range of values for the risk-benefit acceptability threshold. From these curves it became evident that the choice of the outcome defining costs and benefits influenced the proportion of net beneficial interventions for each agent. Because the optimal RBAT is not known, a reference value was calculated based on 'hard' outcomes. The clinical relevance of VTE relative to that of major bleeding was estimated using the values of the case fatality rate-ratios. These ratios and their 95% CI were then plotted in the curves to provide an estimate of the approximate level of risk acceptance (RBAT) that should be considered for each VTE outcome.

3.2.2. Comparison of therapeutic options for thromboembolism prophylaxis in orthopedic surgery

Agents were compared with each other by estimating the probability of having the highest NCB for each value of the RBAT. Comparisons were done separately for major, total and symptomatic VTE. The net clinical benefit probability curves thus obtained are shown in figures 10 – 12.

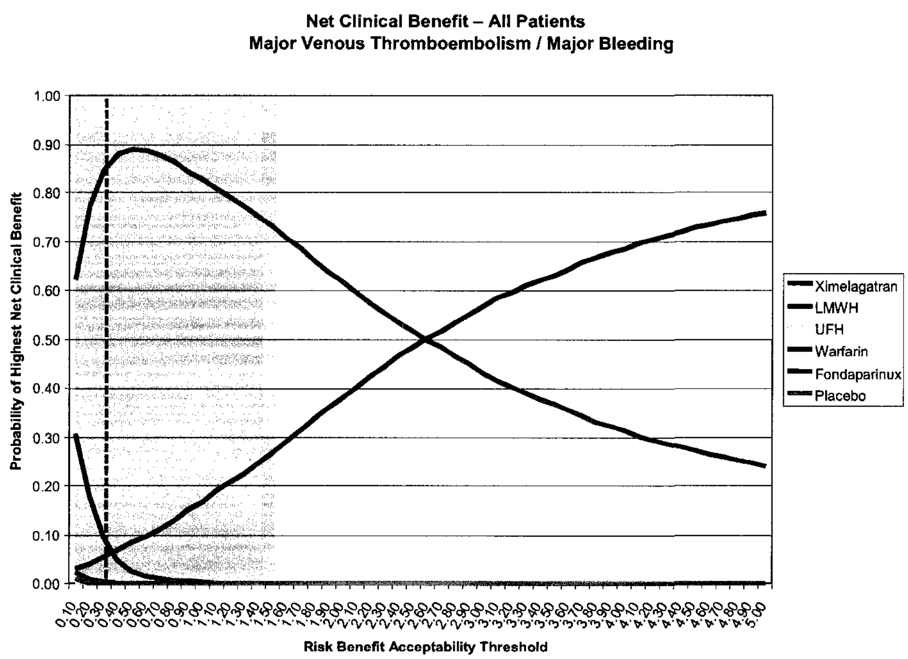


Figure 10. Net clinical benefit probability curves for major venous thromboembolism and major bleeding (all definitions) in all patients. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

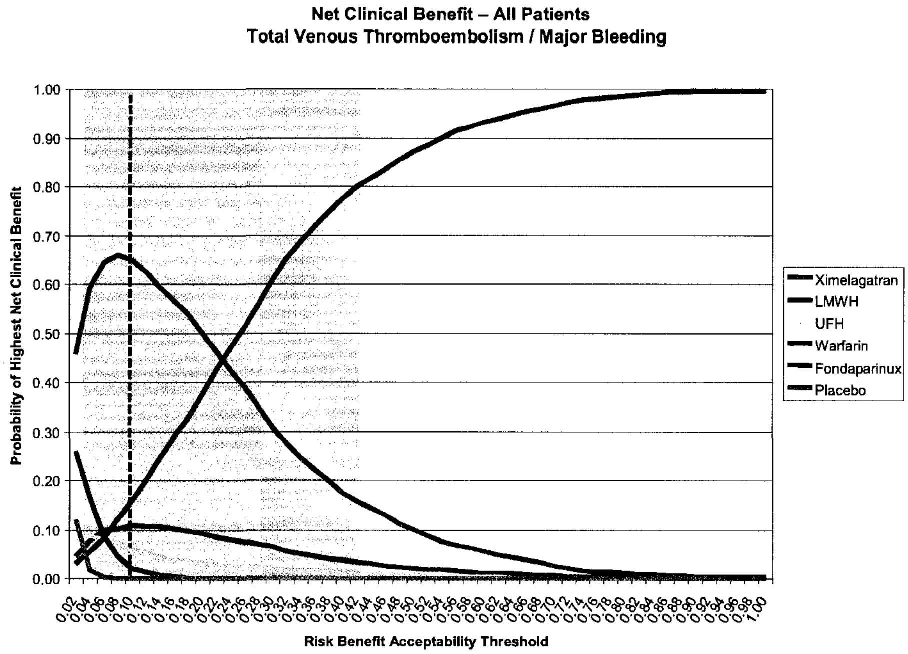


Figure 11. Net clinical benefit probability curves for total venous thromboembolism and major bleeding (all definitions) in all patients. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

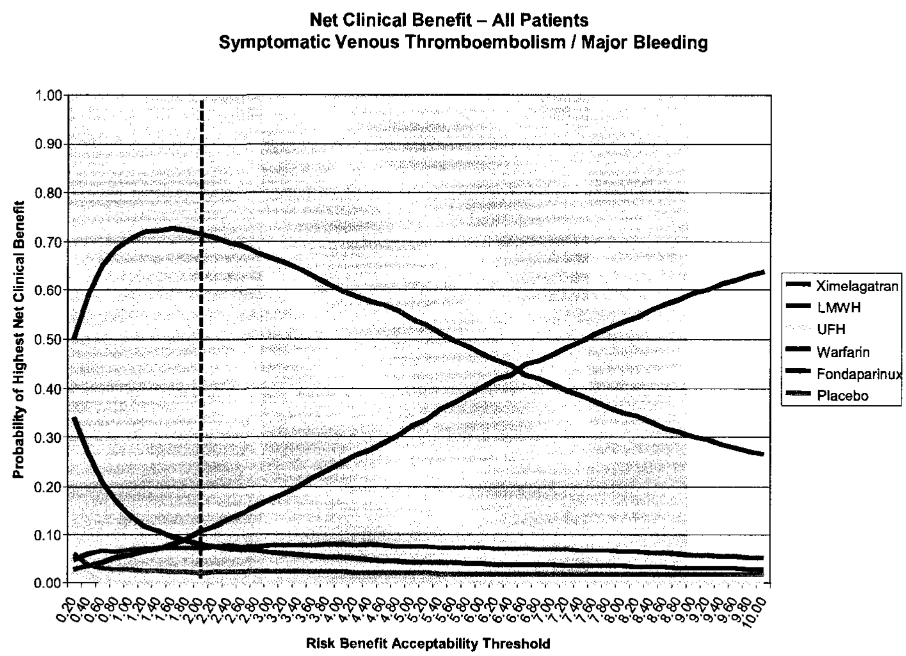


Figure 12. Net clinical benefit probability curves for symptomatic venous thromboembolism and major bleeding (all definitions) in all patients. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

Because ximelagatran was withdrawn from the market by the manufacturer during the conduct of this study due to unforeseen liver toxicity, a sub-analysis was done after excluding this agent. The results of this analysis are shown separately in Appendix III. It can be argued that the inclusion of ximelagatran might be irrelevant, since it is no longer available, however, because the exclusion of ximelagatran was not planned during the design of this study, and because there are new agents of the same pharmacological class currently being tested, it was decided to keep the original analysis as planned and present the sub-analysis as a separate study.

Values were obtained for the probability of achieving the highest net clinical benefit using as reference for the RBAT the values of the case fatality rate ratios appropriate to the outcome evaluated. The results are shown in table 20. The figures in this table represent the probability for each drug of having the highest net clinical benefit when considering different outcomes, namely major, total, and symptomatic VTE. The value for the RBAT used for these comparisons was the reference obtained from the case fatality rate–ratios of major, total and symptomatic VTE to major bleeding (all bleeding definitions), respectively. In addition, as part of the sensitivity analysis, further analyses were done using the case fatality rate-ratio obtained using ISTH-like bleeding definitions. The numbers in bold type in the table represent the probability of having the highest net clinical benefit using as reference RBAT the case fatality rate – ratio that is appropriate for the particular outcome (major, total or symptomatic VTE). The case fatality rate–ratios calculated using all bleeding definitions are shown graphically in figures 10 – 12 as dashed vertical lines with the surrounding shadowed area representing the 95% CI of the ratio.

It can be appreciated that for the analysis of all patients the dominant drug at the reference RBAT is ximelagatran in all analyses. However the agent of choice, that is, the one with the probability of having the highest net clinical benefit, varied depending on the level of risk acceptance. The analysis using different outcomes to define the benefit (i.e. major, total, or symptomatic VTE) showed that the agent of choice varied, and results were not always concordant between them.

Table 20. Probability (%) of obtaining the highest net clinical benefit for each agent used for venous thromboembolism prophylaxis in patients undergoing major orthopedic surgery according to different risk-benefit acceptability thresholds estimated from case fatality rate-ratios [a]

Outcome / Anticoagulant	Case Fatality Rate – Ratio of: *Major Venous Thromboembolism to Major Bleeding*		*Total Venous Thromboembolism to Major Bleeding*		*Symptomatic Venous Thromboembolism to Major Bleeding*	
	All bleeding definitions	*ISTH-like bleeding definition*	*All bleeding definitions*	*ISTH-like bleeding definition*	*All bleeding definitions*	*ISTH-like bleeding definition*
Major Venous Thromboembolism						
Placebo	**0.0**	**0.0**	1.0	0.0	0.0	0.0
Ximelagatran	**87.8**	**75.9**	62.6	87.3	60.0	15.7
LMWH	**0.2**	**0.0**	2.3	0.2	0.0	0.0
UFH	**0.0**	**0.0**	0.5	0.0	0.0	0.0
Warfarin	**5.1**	**0.2**	30.5	6.3	0.0	0.0
Fondaparinux	**6.9**	**23.9**	3.1	6.2	39.9	84.3
Total Venous Thromboembolism						
Placebo	0.0	0.0	**0.0**	**0.0**	0.0	0.0
Ximelagatran	18.4	0.0	**64.7**	**22.1**	0.0	0.0
LMWH	3.8	0.0	**11.1**	**4.6**	0.0	0.0
UFH	1.4	0.0	**5.8**	**1.5**	0.0	0.0
Warfarin	0.0	0.0	**2.1**	**0.0**	0.0	0.0
Fondaparinux	76.4	99.9	**16.3**	**71.8**	100.0	100.0
Symptomatic Venous Thromboembolism						
Placebo	3.7	2.4	10.4	3.9	**2.1**	**1.8**
Ximelagatran	58.6	72.2	42.4	57.3	**71.2**	**39.1**
LMWH	5.8	7.3	3.7	5.6	**7.5**	**6.8**
UFH	1.2	0.1	4.5	1.3	**0.1**	**0.1**
Warfarin	27.3	11.1	36.9	28.6	**8.0**	**3.6**
Fondaparinux	3.4	7.0	2.1	3.2	**11.0**	**48.7**

ISTH International Society on Thrombosis and Haemostasis; LMWH Low molecular weight heparin; UFH Unfractionated heparin
[a] Bold numbers indicate the results of the ideal combination of outcome and risk-benefit acceptability threshold. The box indicates the results of the primary analysis

3.2.3. Sub-analysis according to type of surgery

Because the meta-analysis suggested that type of surgery influenced the results of the estimates, further exploratory analyses were conducted separately for patients undergoing total hip and knee replacement. However, the number of studies providing information was limited for some agents, and therefore results are to be interpreted with caution. The number of studies providing information is shown in table 12. No analysis was done for patients undergoing hip fracture surgery because of the scarce information available.

Total hip replacement. The analysis of the patients undergoing total hip replacement is shown in figures 13 – 15 and in table 21.

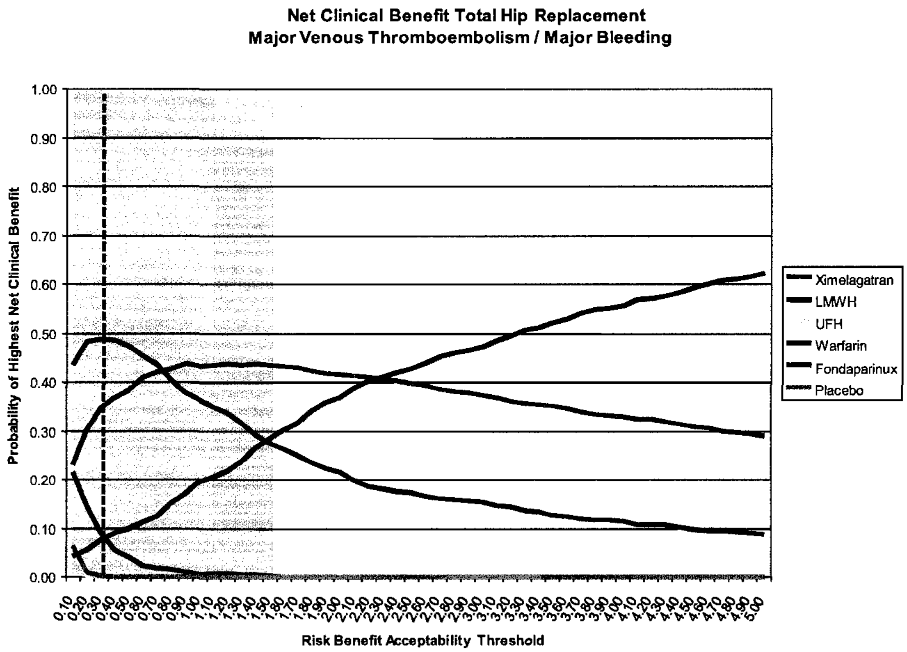


Figure 13. Net clinical benefit probability curves for major venous thromboembolism and major bleeding in patients undergoing total hip replacement. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

In contrast with the analysis in all MOS patients, it can be seen that when analyzing major VTE in patients undergoing total hip replacement, the choice between ximelagatran and warfarin is probably indifferent at low values of the RBAT (i.e. risk aversion). When using the reference RBAT calculated from the case fatality rate–ratio of major VTE to major bleeding using all definitions, the preferred agent would be warfarin; however, when the ratio used was that calculated from the studies using an ISTH-like definition of major bleeding, the agent of choice was ximelagatran.

In contrast, when analyzing total VTE the choice was indifferent between low molecular weight heparin and ximelagatran at the reference RBAT calculated using all definitions of major bleeding, but at the RBAT calculated using only the ISTH-like definitions, the choice became indifferent between ximelagatran and fondaparinux (Fig. 14, Table 21).

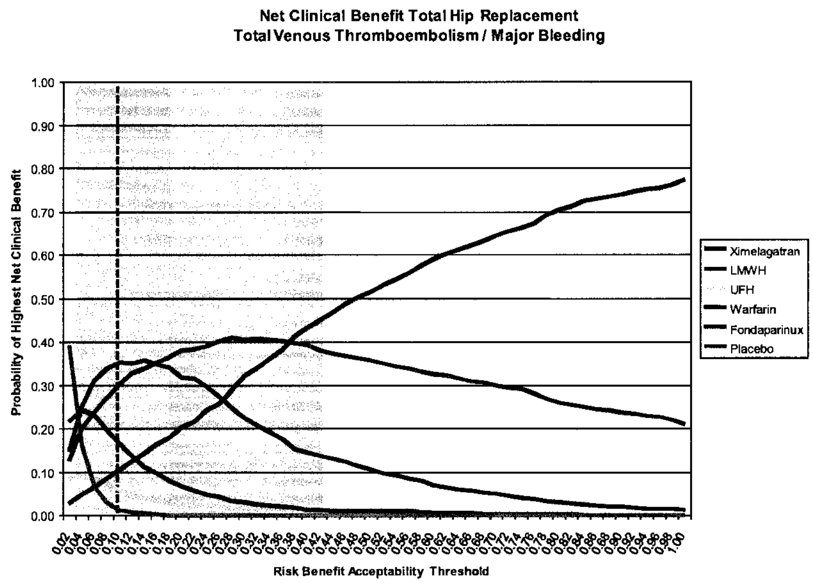


Figure 14. Net clinical benefit probability curves for total venous thromboembolism and major bleeding in patients undergoing total hip replacement. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

In addition, when analyzing symptomatic VTE (Fig. 15), the choice was indifferent between ximelagatran and low molecular weight heparin at almost any RBAT.

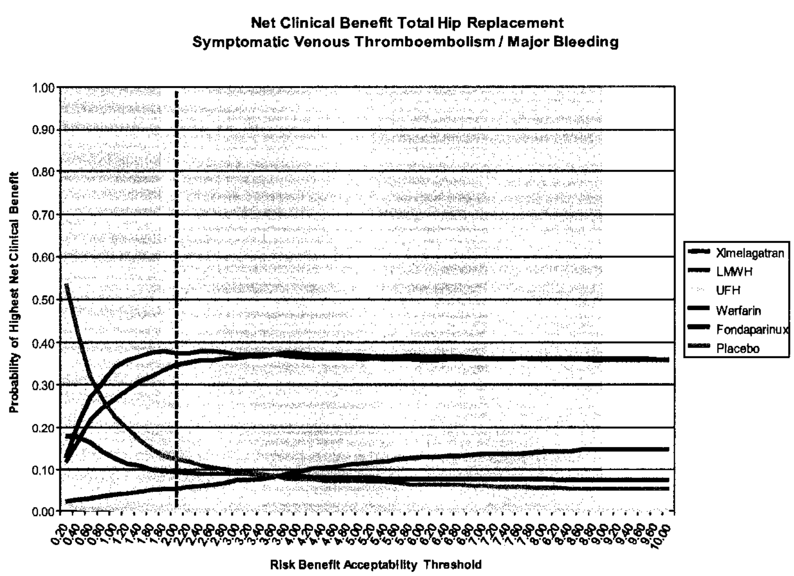


Figure 15. Net clinical benefit probability curves for symptomatic venous thromboembolism and major bleeding in patients undergoing total hip replacement. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

Table 21. *Probability (%) of obtaining the highest net clinical benefit for each agent according to different risk-benefit acceptability thresholds estimated from case fatality rate-ratios. Sub-analysis in patients undergoing total hip replacement* [a]

Outcome / Anticoagulant	*Case Fatality Rate – Ratio of* Major Venous Thromboembolism to Major Bleeding: *All bleeding definitions*	Major Venous Thromboembolism to Major Bleeding: *ISTH-like bleeding definition*	Total Venous Thromboembolism to Major Bleeding: *All bleeding definitions*	Total Venous Thromboembolism to Major Bleeding: *ISTH-like bleeding definition*	Symptomatic Venous Thromboembolism to Major Bleeding: *All bleeding definitions*	Symptomatic Venous Thromboembolism to Major Bleeding: *ISTH-like bleeding definition*
Major Venous Thromboembolism						
Placebo	**0.2**	**0.0**	6.1	0.2	0.0	0.0
Ximelagatran	**36.7**	**43.6**	23.2	35.7	41.6	25.1
LMWH	**5.7**	**0.6**	21.3	6.8	0.0	0.0
UFH	**0.0**	**0.0**	1.4	0.0	0.0	0.0
Warfarin	**48.6**	**30.2**	43.8	48.9	20.1	6.5
Fondaparinux	**8.8**	**25.6**	4.2	8.4	38.3	68.4
Total Venous Thromboembolism						
Placebo	0.0	0.0	**1.3**	**0.0**	0.0	0.0
Ximelagatran	39.8	15.5	**30.6**	**40.5**	11.1	5.1
LMWH	15.0	0.7	**35.3**	**18.0**	0.0	0.0
UFH	1.5	0.0	**5.8**	**1.6**	0.0	0.0
Warfarin	1.4	0.0	**16.2**	**2.1**	0.0	0.0
Fondaparinux	42.3	83.8	**10.8**	**37.8**	88.9	94.9
Symptomatic Venous Thromboembolism						
Placebo	42.4	17.6	60.0	44.6	**12.5**	**6.0**
Ximelagatran	16.4	30.4	9.0	15.2	**34.8**	**36.3**
LMWH	20.4	36.3	9.4	19.2	**37.4**	**35.9**
UFH	0.4	0.1	3.4	0.4	**0.1**	**0.1**
Warfarin	17.7	11.0	16.3	18.0	**9.6**	**7.8**
Fondaparinux	2.7	4.6	1.9	2.6	**5.6**	**13.9**

ISTH International Society on Thrombosis and Haemostasis; LMWH Low molecular weight heparin; UFH Unfractionated heparin
[a] Bold numbers indicate the results of the ideal combination of outcome and risk-benefit acceptability threshold. The box indicates the results of the primary analysis

It is worth noting that the last analysis showed that at very low RBAT values the choice would be placebo, which is what would be expected if very little or no risk was to be accepted. A careful observation of the net clinical benefit probability curves shows that the point of inflexion at which placebo reached a consistently very low or zero probability of being the preferred treatment varied depending on the outcome analyzed but it coincided with the reference value of the RBAT. This suggests that case-fatality rate ratios provide an appropriate reference value for the RBAT that can be used in clinical decision making. It is evident that conclusions are different when analyzing major, total or symptomatic VTE.

Total knee replacement. The analysis of the patients undergoing total knee replacement is shown in figures 16 – 18 and in table 22. When analyzing major VTE it was observed that ximelagatran was preferred at the reference value of the RBAT (all bleeding definitions); however, at higher values fondaparinux would be preferred.

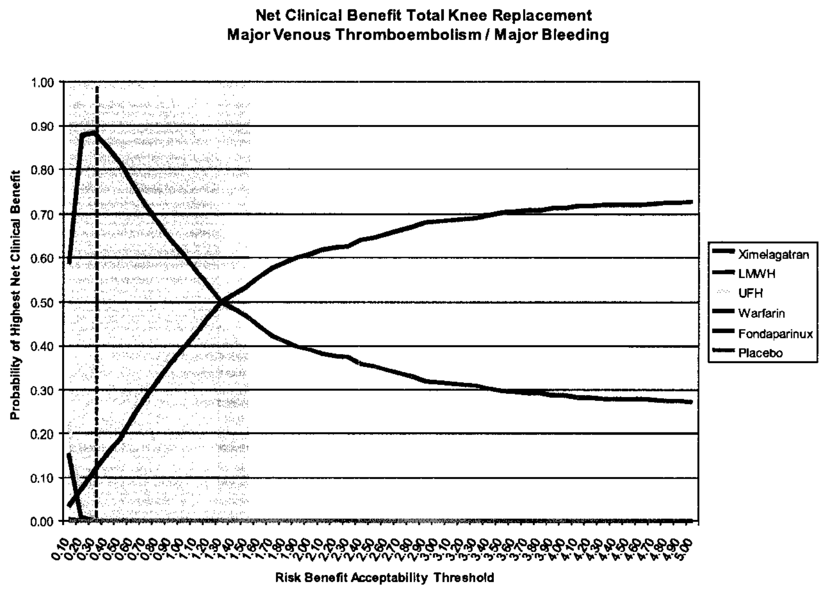


Figure 16. Net clinical benefit probability curves for major venous thromboembolism and major bleeding in patients undergoing total knee replacement. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

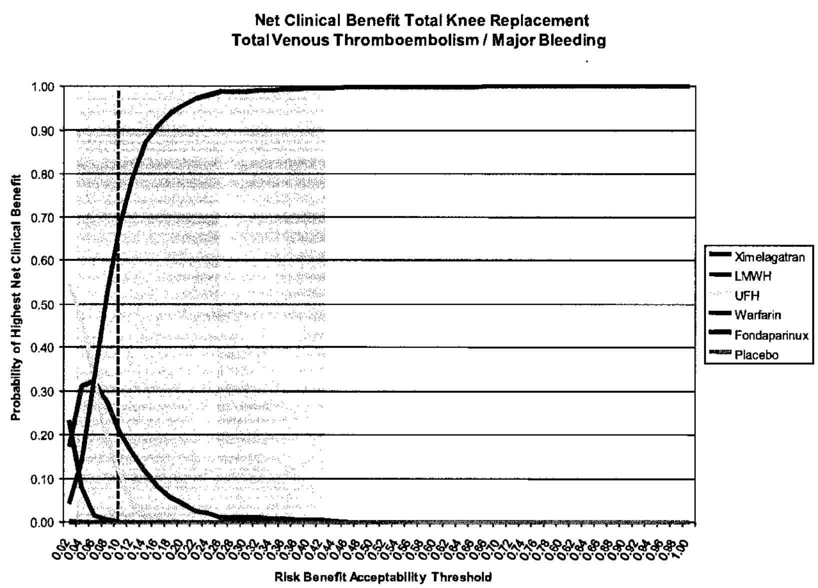


Figure 17. Net clinical benefit probability curves for total venous thromboembolism and major bleeding in patients undergoing total knee replacement. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

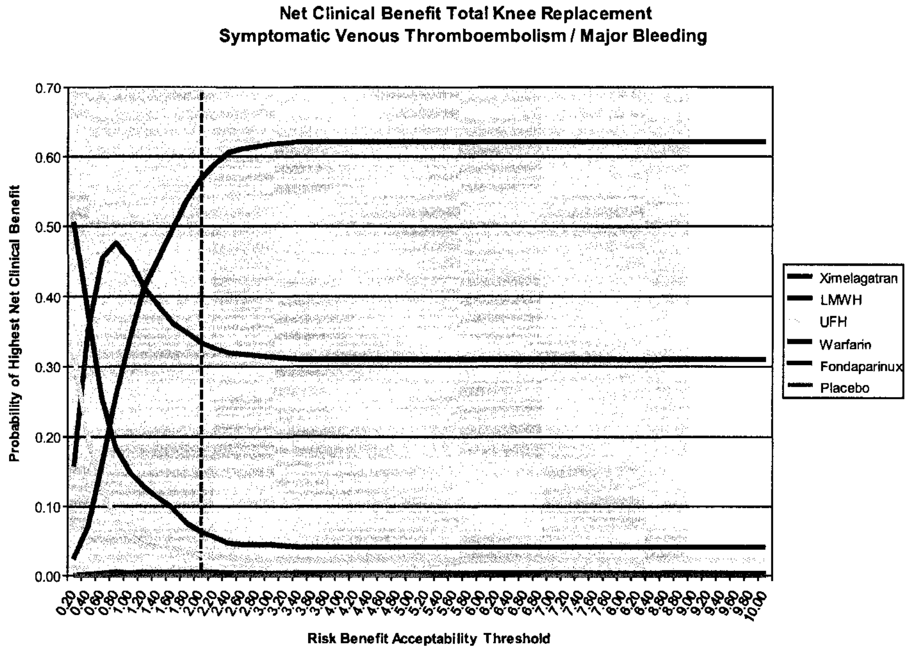


Figure 18. Net clinical benefit probability curves for symptomatic venous thromboembolism and major bleeding in patients undergoing total knee replacement. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

At the RBAT value calculated using the ISTH-like definition the choice between both agents was indifferent. In contrast, the analysis of total VTE showed that the agent of choice would be fondaparinux at almost any RBAT value including the reference ones, and this observation was concordant with the analysis of symptomatic VTE.

A consistent finding in TKR patients was that warfarin, low molecular weight heparin and unfractionated heparin were never the agent of choice and that fondaparinux was the agent of choice at higher levels or the RBAT.

However some facts should be noted. For the analysis of this sub-group there was only 1 study providing information regarding fondaparinux and only 2 providing information regarding unfractionated heparin. It was decided that they should be included for exploratory purposes, but the conclusions should be considered cautiously. In addition, the study evaluating fondaparinux used only a perioperative timing of administration, which might have also influenced the results as it will be shown in the next section.

Table 22. Probability (%) of obtaining the highest net clinical benefit for each agent according to different risk-benefit acceptability thresholds estimated from case fatality rate-ratios. Sub-analysis in patients undergoing total knee replacement [a]

Outcome / Anticoagulant	*Case Fatality Rate – Ratio of* Major Venous Thromboembolism to Major Bleeding		Total Venous Thromboembolism to Major Bleeding		Symptomatic Venous Thromboembolism to Major Bleeding	
	All bleeding definitions	*ISTH-like bleeding definition*	*All bleeding definitions*	*ISTH-like bleeding definition*	*All bleeding definitions*	*ISTH-like bleeding definition*
Major Venous Thromboembolism						
Placebo	**0.0**	**0.0**	0.1	0.0	0.0	0.0
Ximelagatran	**85.2**	**48.9**	59.3	86.5	38.3	25.3
LMWH	**0.0**	**0.0**	0.3	0.0	0.1	0.1
UFH	**0.0**	**0.0**	22.1	0.1	0.0	0.0
Warfarin	**0.0**	**0.0**	15.0	0.1	0.0	0.0
Fondaparinux	**14.8**	**51.1**	3.2	13.3	61.6	74.6
Total Venous Thromboembolism						
Placebo	0.0	0.0	**0.0**	**0.0**	0.0	0.0
Ximelagatran	0.7	0.0	**20.3**	**0.9**	0.0	0.0
LMWH	0.0	0.0	**0.0**	**0.0**	0.0	0.0
UFH	0.0	0.0	**10.3**	**0.0**	0.0	0.0
Warfarin	0.0	0.0	**0.2**	**0.0**	0.0	0.0
Fondaparinux	99.3	100.0	**69.2**	**99.1**	100.0	100.0
Symptomatic Venous Thromboembolism						
Placebo	0.0	0.0	0.0	0.0	**0.0**	**0.0**
Ximelagatran	34.2	39.1	8.2	31.7	**33.0**	**31.1**
LMWH	0.1	0.5	0.0	0.1	**0.5**	**0.4**
UFH	20.7	4.2	40.4	21.9	**2.7**	**2.2**
Warfarin	38.2	11.6	50.5	40.7	**5.9**	**4.2**
Fondaparinux	6.8	44.6	0.9	5.6	**57.9**	**62.1**

ISTH International Society on Thrombosis and Haemostasis; LMWH Low molecular weight heparin; UFH Unfractionated heparin
[a] Bold numbers indicate the results of the ideal combination of outcome and risk-benefit acceptability threshold. The box indicates the results of the primary analysis

3.2.4. Sub-analysis according to timing of administration

Since the meta-analysis also suggested that the time of the initial administration of the anticoagulant might affect the results, an exploratory sub-analysis according to this was done, the results of which are shown in figures 19 and 20 and in table 23.

The analysis showed that when analyzing major VTE the agent of choice at both reference values for RBAT was ximelagatran administered postoperatively (initiated 12 hours or more after surgery), whereas perioperatively administered (initiated 2 hours before surgery and up to 12 hours after) ximelagatran and fondaparinux had similar behaviors and the choice between them would be indifferent and only at very high values of the RBAT.

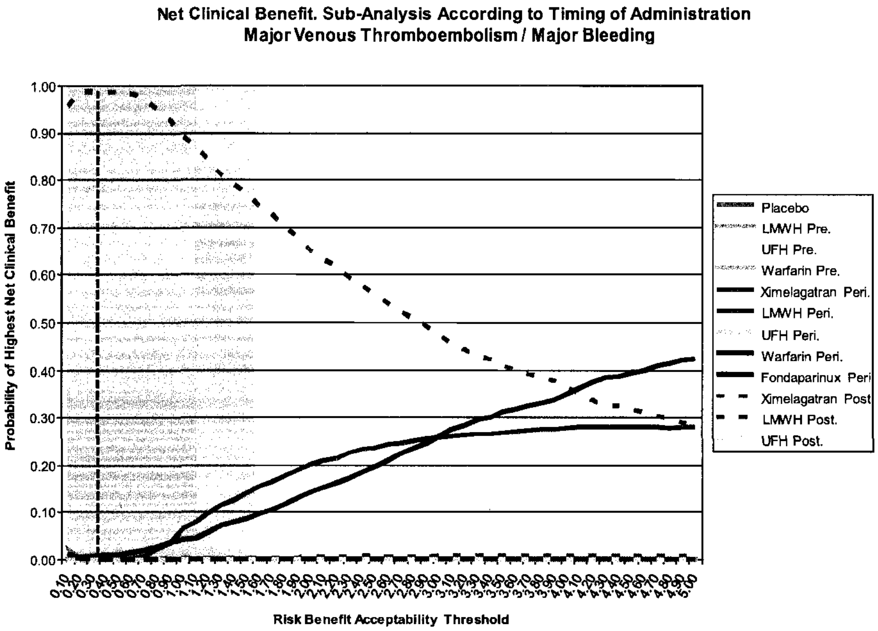


Figure 19. Net clinical benefit probability curves for major venous thromboembolism and major bleeding analyzed according to timing of administration in all patients. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin; Pre Preoperative (up 2 hours before surgery); Peri Perioperative (within 2 hours before and up to 12 hours after surgery); Post Postoperative (12 hours or more after surgery).

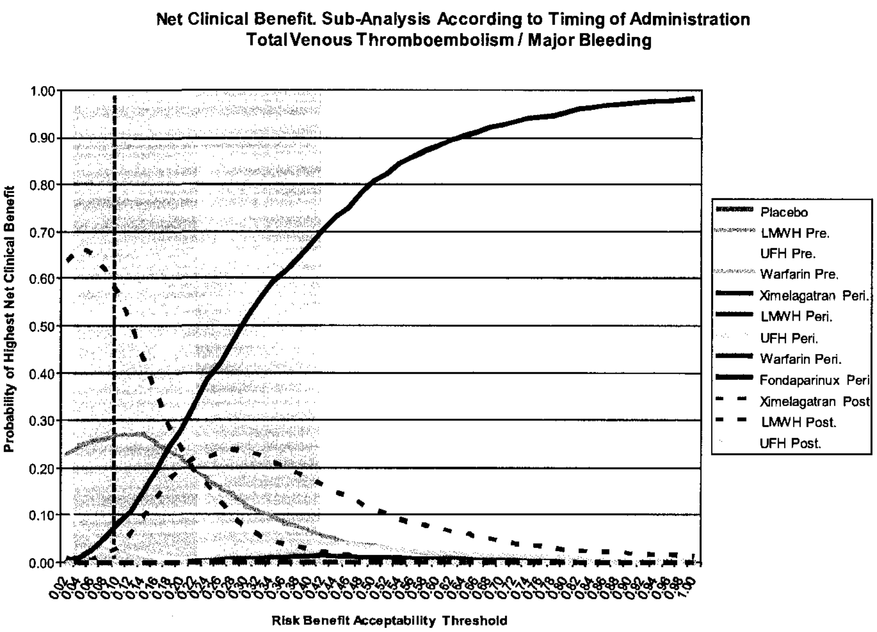


Figure 20. Net clinical benefit probability curves for total venous thromboembolism and major bleeding analyzed according to timing of administration in all patients. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin; Pre Preoperative (up 2 hours before surgery); Peri Perioperative (within 2 hours before and up to 12 hours after surgery); Post Postoperative (12 hours or more after surgery).

When analyzing total VTE it was also observed that postoperative ximelagatran was the agent of choice at low levels of RBAT including the reference value calculated using all the bleeding definitions.

Table 23. Probability (%) of obtaining the highest net clinical benefit for each agent according to different risk-benefit acceptability thresholds estimated from case fatality rate-ratios. Sub-analysis according to timing of administration [a]

Outcome / Anticoagulant / Timing		Case Fatality Rate – Ratio of: Major Venous Thromboembolism to Major Bleeding		Total Venous Thromboembolism to Major Bleeding		Symptomatic Venous Thromboembolism to Major Bleeding	
		All bleeding definitions	*ISTH-like bleeding definition*	*All bleeding definitions*	*ISTH-like bleeding definition*	*All bleeding definitions*	*ISTH-like bleeding definition*
Major Venous Thromboembolism							
	Placebo	**0**	**0**	0	0	0	0
Pre	LMWH	**0.2**	**0**	2.3	0.3	0	0
Pre	UFH	**0**	**0**	0.3	0	0	0
Pre	Warfarin	**0**	**0**	0	0	0	0
Peri	Ximelagatran	**0**	**12.3**	0	0	20.9	27.1
Peri	LMWH	**0**	**0**	0	0	0	0.1
Peri	UFH	**0**	**0**	0	0	0	0
Peri	Warfarin	**0.1**	**0**	1.2	0.1	0	0
Peri	Fondaparinux	**1.1**	**7.9**	0.3	0.9	15.2	53.3
Post	Ximelagatran	**98.6**	**79.4**	95.9	98.7	63.4	18.9
Post	LMWH	**0**	**0.4**	0	0	0.5	0.6
Post	UFH	**0**	**0**	0	0	0	0
Total Venous Thromboembolism							
	Placebo	0	0	**0**	**0**	0	0
Pre	LMWH	8.3	0.1	**57.3**	**10.2**	0	0
Pre	UFH	0.4	0	**10.3**	**0.5**	0	0
Pre	Warfarin	0	0	**0**	**0**	0	0
Peri	Ximelagatran	1.4	0	**0**	**1.2**	0	0
Peri	LMWH	0	0	**0**	**0**	0	0
Peri	UFH	4.5	0	**5.1**	**4.8**	0	0
Peri	Warfarin	0	0	**0**	**0**	0	0
Peri	Fondaparinux	65.8	99.6	**10.4**	**61.5**	99.9	99.9
Post	Ximelagatran	0	0	**0**	**0**	0	0
Post	LMWH	19.6	0.3	**16.9**	**21.8**	0.1	0.1
Post	UFH	0	0	**0**	**0**	0	0

ISTH International Society on Thrombosis and Haemostasis; LMWH Low molecular weight heparin; UFH Unfractionated heparin; Pre Preoperative (up 2 hours before surgery) ; Peri Perioperative (within 2 hours before and up to 12 hours after surgery); Post Postoperative (12 hours or more after surgery)

[a] Bold numbers indicate the results of the ideal combination of outcome and risk-benefit acceptability threshold. The box indicates the results of the primary analysis

However at higher values of the RBAT, including the reference RBAT calculated from ISTH-like definitions of bleeding, the preferred choice would be fondaparinux. It can be seen that again there was no concordance between the results obtained in the analyses of major and total VTE.

It is worth noting that in all of the studies evaluating fondaparinux it was administered in close proximity to surgery and also that none of the studies in the group of perioperative administration started the administration of the anticoagulants beyond 6 ± 2 hours after surgery.

It is necessary to comment that similar to the sub-analysis according to type of surgery, in the analysis according to timing of administration there were few studies providing information for some of the groups (table 12) and therefore the results should be considered with caution. In addition, although one study[77] did use warfarin administered postoperatively and one study[66] used ximelagatran preoperatively they were excluded from the sub-analysis according to timing of administration because such studies only included patients undergoing total hip replacement.

Finally, a sensitivity analysis was done by calculating the net clinical benefit using the incremental risk obtained only from the studies with an ISTH-like definition of major bleeding. The figures are shown in appendix IV. The analysis showed that there were no major differences between the calculations when using all major bleeding definitions or only the ISTH-like major bleeding definitions.

There were differences when we compared all major bleeding definitions with the non-ISTH-like ones; however, only a small number of studies was included none of which evaluated ximelagatran or fondaparinux, therefore the results are difficult to interpret because they are not really comparable.

4. Discussion

The present study introduces the clinical cost-effectiveness study, a new approach to clinical decision making that might help to guide clinical decisions in areas where tension between risk and benefit exist and there are multiple therapeutic options. It also provides new insights in the clinical cost-effectiveness of different anticoagulant options for thromboprophylaxis in orthopedic surgery, a clinical situation that was used as an example of this new method. Several major findings, which I discuss in the following sections, have resulted from my work.

4.1. Clinical cost-effectiveness study: methodological considerations

When confronted with the clinical disjunctive of using a potentially harmful intervention, the clinician decides whether to use it or not based on weighing the pros and cons inherent to it. In other words, the decision is based on whether the perceived risk is outweighed by the perceived benefit. This perception depends on the clinician's experience, knowledge and expertise among other factors and the decision of using an intervention ultimately represents a personal choice. There has been an increasing interest in methods for the assessment of risk and benefit and some work has been done in this area[105,106,155-157]. These techniques are conceptually difficult to interpret and they have the disadvantage that they do not allow a comparison between multiple agents when these are available for the same indication.

The present work illustrates an innovative method designed to compare competing interventions using a concurrent evaluation of clinical benefits and risks and it is elaborated on an extension of a technique that has been recently proposed[103]. This technique is based on an economic cost-effectiveness approach and in contrast to randomized controlled trials it concurrently takes into account the risk and benefit components of the interventions being evaluated. It also recognizes that the optimal cutoff value for the tradeoff between risks and benefits is usually not known and thus it presents the information through a range of plausible values in order to facilitate the clinicians to decide according to their personal preference for risk acceptance. The extension that I propose in this work allows comparing multiple interventions in order to determine the one with the best risk-benefit profile. In addition, my work also provides a novel way to estimate a plausible reference value for the tradeoff based on the case fatality rate – ratios of the events defining the risks and benefits.

If for a clinical situation there are numerous therapeutic options it is unlikely that all options will be compared in a randomized trial usually because of sample size and research cost constraints. The method described herein provides a way to indirectly compare several interventions by incorporating the information available from randomized trials comparing some of the options to estimate costs and benefits, although information from non-randomized studies could also be used. However I prefer the former because information derived from randomized trials is usually of higher quality.

The present method does not allow the estimation of effect sizes such as odds ratios or relative risks, rather it provides the clinician with information regarding the probability that certain intervention will have of being net risk-beneficial compared to the reference treatment(s) at a given value of risk acceptance. Proven that risks and benefits can be measured in equivalent terms for all the treatment options, the preferred choice should be that conferring the probability of having the highest net clinical benefit at the chosen value for risk acceptance.

As it can be inferred, some conditions are necessary to conduct a clinical cost-effectiveness study. First, the outcomes used to derive clinical costs and benefits must be defined similarly across all studies. Incorporation of studies using different outcome definitions would result in a heterogeneous result difficult to interpret. It is particularly important to test for secular trends since outcome definitions might change over time as a result of new knowledge, which might represent a problem for older therapies still in use. Second, if clinically acceptable, costs and benefits should ideally be defined by a single outcome; if this is not possible then a composite outcome could be used proven that the first condition is met. Third, it is assumed that events defining costs and benefits are relevant from a clinical standpoint. Fourth, as previously pointed out if the systematic review spans several years, it is important to explore the influence of publication time since changes in medical or surgical techniques or in health policy are likely to influence the results and therefore populations might not be similar.

If the aforementioned conditions are met, it can be argued that a clinical cost-effectiveness study provides a pragmatic panorama by incorporating all the available information that is regarded to be properly collected and reported. It can also be appreciated that the systematic review must be stringently rigorous and adhere to standardized requirements such as the QUOROM statement[117] in spite of which it is possible to find heterogeneity, thus requiring the use of a random effects model to appropriately deal with the uncertainty around the point estimates. Hence exploring heterogeneity becomes essential and a thorough sensitivity analysis should be conducted prior to incorporating the information into the Monte Carlo simulation, to assure to the maximum extent that studies include comparable populations. In this sense, this work also provides a new and rather simple approach to explore differences of proportions in sensitivity analysis by using the band of clinical relevance. This simple calculation allows exploring if the difference between the confidence limits of two estimates is greater than the minimal clinically important difference. Since the method proposed in the present study relies on proportions of events, rather than on effect sizes, the sensitivity analysis should explore whether proportions are different in sub-analyses of groups of interest and if such difference is clinically relevant. Consider, for example, the main efficacy outcome in this work, major VTE. It is of interest to know if there is a significant difference in the proportion of major VTE between the overall estimate for all patients, for patients undergoing TKR and for patients undergoing THR, and also if such difference is clinically relevant. If it is assumed that a 2% difference in the proportion of major VTE is clinically relevant, the band of clinical relevance can be calculated by adding 2% to the upper and lower 95% confidence limits of the overall estimate. If the 95%CI around the estimates of the proportions of major VTE in the THR and TKR subgroups lie beyond this band, it can be reasonably argued that the difference between the estimates is clinically relevant at the 0.05 level of significance, and thus it deserves further analysis.

A final consideration is that the present study presents a novel way to estimate a reference value for the RBAT by calculating the case-fatality rate ratio of VTE to major bleeding. This simple calculation allows estimating the relative importance of the benefit-defining event to the risk-defining one and it can be modified to incorporate other measures such as disability rate, that are appropriate for the clinical situation under study. Alternatively, a reference RBAT can be obtained from expert consensus or surveys, if a rate ratio is not suitable or appropriate. In any case a reference RBAT should be a guideline for the clinician to be applied on an individual basis.

4.2. Considerations for thromboprophylaxis in orthopedic surgery

The present study has shown several important issues. When analyzing all patients undergoing major orthopedic surgery, either by major, total or symptomatic VTE, it was observed that ximelagatran was the agent most likely to derive the highest net clinical benefit at low levels of risk acceptance, such as the RBAT reference value, but at higher levels of risk acceptance fondaparinux was almost consistently the agent of choice. However, the sensitivity analysis depicted several major findings that need further discussion. Firstly, the results were influenced by the type of surgery. In second place, the results were sensitive to the initial timing of administration of the anticoagulant agent. Third, the results varied depending on the event used to define the benefit, that is different results were found for major, total or symptomatic VTE. It is worth noting here that case fatality rate ratios were used as the reference value of the RBAT because they represent the relative importance of VTE to major bleeding with respect to mortality. In other words, they represent how lethal is a VTE event with respect to a bleeding event. Since the optimal RBAT is not known, this value provides a reasonable reference for risk acceptance. The considerations that follow are based on this assumption.

4.2.1. Influence of type of surgery on the agent of choice

When patients were analyzed according to type of surgery it was observed that in patients undergoing THR, the choice of the preferred agent at the reference value for the RBAT was indifferent between warfarin and ximelagatran if analyzed by major VTE, and was also indifferent between ximelagatran and LMWH if analyzed by total or symptomatic VTE. In the case of the patients undergoing TKR the agent of choice at the reference value for the RBAT was almost consistently ximelagatran if analyzed by major VTE, however, if analyzed by total or symptomatic VTE, the choice was fondaparinux. In any case fondaparinux was preferred at higher levels of risk acceptance (higher than the reference RBAT). In regard to patients undergoing HFS no analyses were conducted because of the paucity of studies. The previous results suggest that pooling of patients undergoing major orthopedic surgery is probably not appropriate since proportions of VTE seem to be different between THR, TKR, and HFS patients. As a result the choice of preferred agents would be different according to the type of surgery. The consequence to this is that different recommendations should be made for patients undergoing different procedures. In this regard it is particularly worrisome the paucity of well conducted studies evaluating thromboprophylaxis in patients undergoing HFS. These results also suggest that adjustments should be done when estimating the sample size in the planning phase of a trial including patients undergoing both TKR and THR, something that as far as I know, has not been done. Although in my systematic review there were only 8 studies including patients undergoing both types of surgery[65,68,69,81,136,139,149,150], such studies included 11,681 patients representing 27.73% of all the patients included. None of these studies reported adjustments to the sample size calculation according to surgery type, and it is thus possible that some of them might have been overpowered in one of the groups, a situation that is inappropriate due to ethical reasons and might result in increased research costs[158-160].

An additional finding of the systematic review is that a higher proportion of bleeding events was observed in THR patients receiving ximelagatran, UFH, warfarin or fondaparinux when compared to TKR, and although no significant differences were observed in patients receiving LMWH there was also a similar trend. However, placebo patients experienced less major bleeding episodes if they had undergone THR than TKR. This suggests that there might be a slightly higher increase in the risk of bleeding associated with prophylactic anticoagulants in patients undergoing THR, which could be related to differences in the surgical procedure itself.

4.2.2. Influence of timing of initiation on the agent of choice

A second major finding of the present study was that timing of administration influenced the choice of the preferred agents by modifying their risk-benefit profile. In the analysis according to initial timing of administration of the prophylactic anticoagulant it was found that, at the reference value for the RBAT, the preferred agent would be ximelagatran administered postoperatively (beginning twelve or more hours after surgery). This finding was consistent if analyzed by major or total VTE. Again, at higher levels of risk acceptance the preferred agent was found to be fondaparinux. Interestingly, perioperatively administered ximelagatran had a similar behavior to that of fondaparinux – which was administered perioperatively in all studies – if analyzed by major VTE, but if analyzed by total VTE it was never the agent of choice. Further analyses divided by type of surgery and timing of administration were not conducted because of the paucity of studies found within the different categories when this was explored. The optimal timing for starting prophylaxis after orthopedic surgery is a matter of debate and has been the subject of several publications[161-167]. There is evidence suggesting that thrombi often begin intraoperatively[11] which has led to hypothesize that administering prophylaxis closer to the time of surgery would result in a decreased frequency of VTE. However, it is physiologically plausible that administering an anticoagulant close to surgery prevents small clinically irrelevant distal thromboses but starting prophylaxis at a later time prevents the occurrence of a clinically relevant proximal clot. Previous studies have shown that perioperative initiation of prophylaxis (between 2 hours pre- and 6 ± 2 hours postoperatively) indeed leads to a decreased occurrence of VTE[161,167]; however although somewhat controversial, there is also evidence suggesting that if the anticoagulant is started closer to the surgery there is an increased risk of bleeding[163,166,167]. This is supported by the findings of my systematic review showing a higher frequency of major bleeding episodes in patients receiving perioperative ximelagatran, LMWH, and fondaparinux (although the last agent was always administered perioperatively). In the case of the patients receiving warfarin the highest proportion was observed among those starting it preoperatively, which is not surprising given the fact that it is very likely that a therapeutic effect had been achieved shortly after surgery thus increasing the bleeding risk. However in the case of UFH, the highest proportion of bleeding was observed among those starting it postoperatively. I believe that this might be due to the fact that the information was obtained from a reduced number of patients participating in 2 studies.

It is therefore conceivable that the benefit-risk ratio is modified by the timing of initial administration, as it has been suggested[166]. This is also supported by the finding that a lower number of major VTE events were observed in patients receiving postoperative ximelagatran, LMWH and UFH than in those starting pre- or perioperatively. This could be reflecting the fact that when a patient develops a bleeding episode the anticoagulant drug has to be stopped thus increasing the thrombotic risk. The present study is the first one demonstrating that timing of initial administration influences the risk-benefit profile, meaning that whereas efficacy is improved by administering the prophylactic drug closer to surgery, this improvement is overpowered by an increase in the risk, resulting in a lower net clinical benefit. In support of the previous notion, although the lowest proportion of VTE was observed with fondaparinux, this is almost certainly due to the fact that it was given closer to surgery. However, the fact that fondaparinux consistently became the agent of choice only at higher levels of risk acceptance, is reflecting that it was also associated with the highest proportion of bleeding complications which undermined its efficacy. As a consequence, at higher levels of risk acceptance fondaparinux became net clinically beneficial compared to the other agents. This leads to wonder if the studies evaluating thromboprophylaxis in major orthopedic surgery might have inadvertently used high values of risk acceptance, since they were designed based on VTE outcomes rather than bleeding ones. The consequence of this would be that if lower values of risk acceptance had been used the conclusions would have probably changed.

4.2.3. Influence of the outcomes on the agent of choice

The third very important finding is that this is the first study demonstrating that in trials evaluating thromboprophylaxis after orthopedic surgery the use of different outcomes leads to different conclusions. This can be easily appreciated in the net clinical benefit probability curves (Figs. 10 – 18) where the agent of choice would be different if analyzed either by major, total or symptomatic VTE. This is a particularly important issue because almost all of the included studies used venographic events (e.g. total VTE) as the primary efficacy outcome. Venography is usually considered a valid surrogate outcome in VTE prevention studies[27] and it is used due to the low frequency of symptomatic VTE events occurring after orthopedic surgery[31,32,39,56,168] which, if used for sample size calculation would result in exceedingly large sample sizes. However, the appropriateness of venographic outcomes has been questioned by some authors emphasizing the difficulty to obtain clinically relevant conclusions based on such data[26,169]. In spite of the use of standardized radiological techniques and interpretation criteria[24,28,30] and a good inter-observer agreement[29], it has been demonstrated that there are large variations in the proportion of events reported by different adjudication committees[33].

Furthermore, there are no uniform criteria to determine the clinical relevance of the radiological findings. This issue is especially hampered by the fact that for obvious reasons, data regarding the natural history of venographically demonstrated asymptomatic VTE is very limited because such patients are usually treated. One study including 40 postoperative patients with an untreated venographically demonstrated VTE showed that symptomatic PE developed in 4 out 9 patients with proximal DVT but in none of those with clots confined to the calf[13]. Another study included 48 patients with calf thrombosis after TKR, 24 of which were symptomatic and received anticoagulation for up to 7 days followed by analgesics. The other 24 patients were asymptomatic and received no treatment. None of the 48 patients had developed a recurrence, proximal extension or PE at 42 months of follow up[170]. In general, approximately one sixth of patients with symptomatic calf thromboses will eventually extend into the proximal system; unfortunately there is still no way to identify them, although additional risk factors such as thrombophilia might influence the progression of the clot[11,171].

Considering that the present study found that the proportion of total VTE events was roughly between 2 and 4-fold that of major VTE events which in turn was also between 2 and 4-fold that of symptomatic events, it can be appreciated why venographic events are used as surrogate outcome. However the proportion of total VTE events in TKR patients was twice as high as that in THR, but the proportion of major and symptomatic VTE was similar between surgery types except in the placebo group (which included a reduced number of patients). Thus it can be argued that venographic events might not be an appropriate surrogate measure because the relative proportions of total and symptomatic thrombosis differ between surgery types (i.e. the relation between total and symptomatic VTE is inconsistent) and also because venographic events do not necessarily reflect a clinically relevant outcome. In this regard other findings from the systematic review should be noted. There were systematically more total VTE events in TKR patients when compared to THR. However, although differences were observed for patients receiving UFH and warfarin, no systematic difference was observed regarding major and symptomatic VTE. This suggests that TKR patients experience distal thrombosis more frequently than patients undergoing THR. Moreover, since there was no information regarding which patients experiencing a symptomatic thrombosis had clots confined to the calf, it is difficult to estimate which symptomatic events were clinically meaningful.

The findings of my study challenge two of the three postulates proposed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use for considering a surrogate endpoint as appropriate[35]. My results suggest that total VTE is not prognostic of symptomatic VTE and more importantly, they show that the use of anticoagulants for VTE prophylaxis after orthopedic surgery have different effects when evaluating total and symptomatic VTE events.

As previously mentioned, the use of symptomatic thrombosis as an outcome, although ideal, is not feasible from a design standpoint and it is further complicated by the lack of a standard definition of what constitutes a clinically relevant symptomatic VTE, since distal thromboses might be symptomatic but not necessarily clinically relevant. For these reasons I believe that there is an urgent need to develop standardized operational definitions of what constitutes a clinically relevant thrombotic event, either symptomatic or not, in patients undergoing orthopedic surgery. A reasonable alternate endpoint would be what in this study was defined as major VTE (proximal VTE –venographically demonstrated– plus PE plus death when PE cannot be excluded as the cause). Such an outcome definition would include all of the patients that are usually accepted to require therapy[5,8] and would resemble more closely the usual clinical practice, since there is no consensus regarding which patients with isolated calf thrombosis must be treated and in many centers such patients are followed to evaluate progression, on the basis of which a therapeutic decision is made. This definition also assumes that all asymptomatic proximal thromboses found by venography require treatment, something that is difficult to prove but it is usually accepted[5,8]. For these reasons it was considered that the analysis using major VTE should be the primary strategy in the present study.

4.2.4. Other considerations and potential limitations

Other important findings deserve further comment. It is important to note that no study was adequately powered to detect differences in risk and only some of them included bleeding events in a composite outcome. The usual practice is to compare bleeding events separately from thrombotic events; however, they should be considered together because their occurrence is inter-related. In this regard, the present study adds to the previous knowledge on the issue by estimating the net benefit derived from the use of thromboprophylaxis after orthopedic surgery. An important advantage of this technique is that it allows larger sample sizes; hence more power to detect differences in less common, more clinically meaningful outcomes.

An important issue that was shown by the systematic review was the lack of a uniform definition of bleeding events. Whereas the majority of the studies used some set of criteria established *a priori* including clinical judgment, in some the judgment about the relevance of a bleeding event was entirely left to the discretion of the researcher or the treating physician. Because the estimation of risk is crucial to the technique used in this work, an attempt was made to homogenize the results by conducting a sub-analysis in only those studies using a major bleeding definition that was similar to a standardized definition that was recently proposed by the International Society on Thrombosis and Haemostasis[21]. When only such studies were analyzed, the behavior and shape of the net clinical probability curves were very similar to those obtained using all definitions of major bleeding. A potential drawback of this analysis is that the aforementioned definition was intended for use in non-surgical trials, however almost all trials included some clinical judgment among the criteria. For the previous two reasons it was decided that the use of all major bleeding definitions was appropriate for the analysis.

Another finding was that although the majority of patients were evaluable for major bleeding events, this was not always the case regarding VTE events. For example, the average percentage of patients evaluable for symptomatic VTE was 62.5% and for some agents, such as UFH was as low as 12%. This lack of information availability certainly makes further analysis of the studies difficult and might compromise the conclusions. However, information on major VTE was available for more than 80% of the included patients which makes the latter situation unlikely. For the aforementioned reasons I believe that it is highly desirable the development of minimal standards of design and reporting for trials exploring thromboprophylaxis in surgical settings in general, and in orthopedic surgery in particular, with a particular emphasis on the development of standard definitions of symptomatic VTE events, and major bleeding events.

An interesting finding was that in studies evaluating LMWH, UFH and warfarin there were less major VTE reported in the studies funded by the pharmaceutical industry than in those that were not. A similar finding was made for studies evaluating LMWH and UFH regarding symptomatic VTE. On the contrary, in patients receiving placebo there was a higher proportion of major and total VTE in industry funded studies. In addition there were more total VTE events among patients receiving warfarin, but not LMWH or UFH, if the studies were industry funded. Regarding bleeding events the only difference was observed among patients receiving UFH in whom a higher frequency was reported in non-industry funded studies. Although certainly these differences might be related to bias, it is also possible that they are a reflection of better funding among industry funded studies allowing for better logistic support. Sub-analyses were not conducted in the clinical cost-effectiveness study because 70% of studies were industry funded, and I considered that if the difference in the estimates was a result of bias, the inclusion of all studies would likely result in a more pragmatic panorama.

Since a probable trend towards a lower frequency of major and total VTE in more recent trials was observed, a cumulative meta-analysis was conducted. The results suggested that except in the case of major VTE in patients receiving UFH, earlier studies (1980 – 1994) did not influence the overall estimates. An exploratory analysis was done using both estimates of major VTE in patients receiving UFH, but conclusions did not change and therefore the results of all studies were included in the subsequent clinical cost-effectiveness study. These findings are most likely due to the fact that, except for UFH, the majority of the studies were published after 1994. The fact that the cumulative estimates in patients receiving placebo did not show a statistically significant difference suggests that changes in surgical or anesthetic techniques probably do not influence the occurrence of VTE after orthopedic surgery.

The limitations of the study arise from three issues: 1) the fact that the information was obtained retrospectively from a systematic review and meta-analysis with their inherent caveats; 2) the methodological aspects regarding the pooling of single proportions; and 3) the limitations regarding modeling techniques and their application to clinical risk-benefit ratio and incremental risk-benefit ratio analysis. With respect to the first point it was considered that the ample sensitivity analysis that was conducted sufficed to establish the robustness of the conclusions of the study. As mentioned before, this was a thoroughly analyzed and conducted systematic review, with well defined inclusion and exclusion criteria and I believe that it reflects the *status quo* on the matter until the time of the review. In regard to the second potential limitation there are examples of the application of the proposed pooling techniques[125] and a major strength of this study is the fact that the estimates were the result of a comprehensive review and meta-analysis including all the major, well conducted studies. A potential problem with the weighting method of Laird and Mosteller is that it uses a normal approximation to proportions which might result inappropriate if the proportions are very small because they might not have a normal distribution anymore[128]. In a similar fashion, the use of a χ^2 test to determine heterogeneity might not be totally appropriate when proportions are very small. These issues are reflected by the fact that the estimate of the case fatality rate of major bleeding events differed when it was calculated using a weighted and a non weighted method. The consequence is that the case fatality rate – ratio of VTE to bleeding is different if both estimates are used. However, the ratio obtained using the non weighted method was contained within the 95% CI of the ratio that was obtained using the weighted estimate and so it was decided to use the latter. Finally, the modeling techniques used in this study although frequent in the economic literature, are not commonly found in clinical medicine and in fact, their application to clinical decision making was described only very recently[103]. The present study is the first to use these techniques to conduct indirect comparisons of multiple therapeutic options in the absence of randomized trials, for which it was necessary to further elaborate on several methodological issues. It is my belief that this method will prove useful for clinical decision making, however its performance compared to other methods of risk-benefit assessment still remains to be tested. This will be the matter of future research projects.

In summary, I consider that in the case of VTE prophylaxis after orthopedic surgery, the best outcome measure is major VTE and major bleeding together with their corresponding case-fatality rate ratio as reference value for risk acceptance. Under these conditions the best prophylactic agents for patients undergoing THR are warfarin and ximelagatran and for patients undergoing TKR are ximelagatran and less likely fondaparinux. The clinical cost-effectiveness study provides the clinician with a useful tool for clinical decision making that incorporates three key elements in the decision process (the risk, the benefit, and the willingness-to-accept the risk) in a user-friendly manner and might prove to be a valuable aid in order to facilitate the implementation and practice of evidence-based medicine. Finally, by adding new drugs to an ongoing clinical cost-effectiveness analysis, it might be used by regulatory agencies to estimate the risk benefit profiles of new interventions compared to the already existing ones, in order to decide if they should be accepted.

5. Conclusions

The results of the present study allow for several important conclusions:

a. When considering VTE prophylaxis in patients undergoing major orthopedic surgery, separate recommendations should be made for patients undergoing THR or TKR.

b. If it is accepted that the case fatality rate – ratios provide a valid reference value for risk acceptance, in patients undergoing THR the agents most likely to provide the highest net clinical benefit are warfarin and ximelagatran whereas in patients undergoing TKR they were ximelagatran and probably fondaparinux. When ximelagatran was excluded from the analysis then warfarin was the agent of choice in patients undergoing THR and fondaparinux in patients undergoing TKR. In no case was unfractionated heparin the agent of choice.

c. The timing of initiation of the prophylactic drug influences its risk-benefit profile. Although perioperative (2 hours before and up to 12 hours after surgery) administration leads to a decreased occurrence of thrombosis, this benefit is undermined by an increase in bleeding risk. The optimal timing of administration is postoperative (starting 12 hours or more after surgery).

d. The use of different outcomes – namely major, total or symptomatic VTE – to define benefit leads to different conclusions regarding the agent of choice. This calls into question the validity of total (venographic) VTE as a surrogate endpoint in trials evaluating thromboprophylaxis in MOS.

e. Major VTE (defined as proximal VTE –venographically demonstrated– plus PE plus death when PE cannot be excluded as the cause) is the best endpoint because it identifies the patients that require anticoagulant treatment. In contrast, the identification of patients with an isolated distal DVT in venography does not allow identifying which patients will eventually require treatment, since the majority of patients with distal DVT will not extend into the proximal veins. Furthermore, although symptomatic VTE is the ideal endpoint in this clinical situation, its low frequency and the lack of a standard definition of what constitutes a relevant symptomatic DVT hamper its use; in this regard major VTE allows a more standard definition of outcomes and it would also result in smaller sample sizes than symptomatic events when designing clinical trials.

f. In the absence of randomized trials directly comparing multiple competing interventions, the clinical cost-effectiveness analysis introduced herein is a tool to indirectly compare those interventions. It has the advantage of incorporating all the key elements of a decision providing a way to determine which intervention has the best risk-benefit profile and it is a useful aid for clinical decision making.

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Appendices

Appendix I. Supplemental Table

Table S1. Pooled estimates of the prevalence of late venous thromboembolic events occurring after completing a course of short-term prophylaxis in patients undergoing major orthopedic surgery

Drug	*Symptomatic VTE % (95% CI)*	*Fatal Pulmonary Embolism % (95% CI)*
Ximelagatran	0.54 (0.51, 0.56)	0.14 (0.12, 0.15)
LMWH	0.87 (0.84, 0.90)	0.12 (0.11, 0.13)
UFH	1.63 (1.53, 1.73)	0.19 (0.15, 0.23)
Warfarin	0.52 (0.47, 0.58)	0.05 (0.04, 0.05)
Fondaparinux	1.26 (1.22, 1.30)	0.21 (0.20, 0.22)

VTE Venous thromboembolism; CI Confidence interval; LMWH Low molecular weight heparin; UFH Unfractionated heparin.

Appendix II. Supplemental Figures

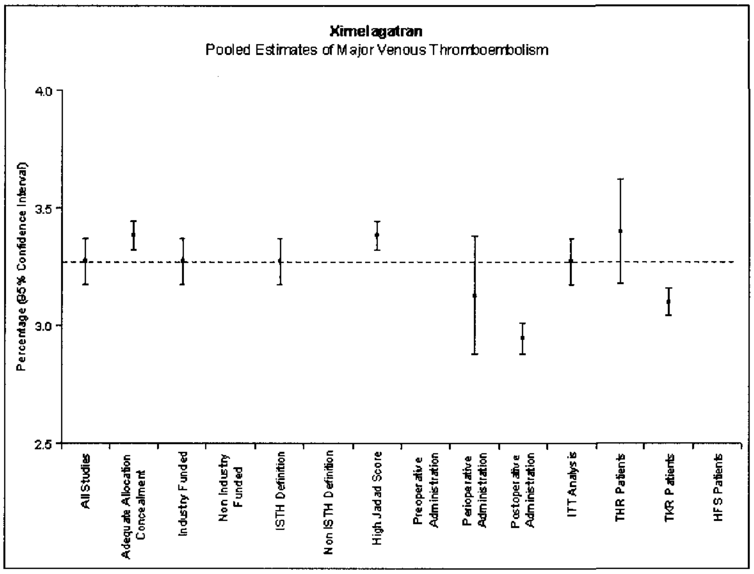

Figure S1. Subgroup and sensitivity analyses. Major venous thromboembolism in patients receiving ximelagatran. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

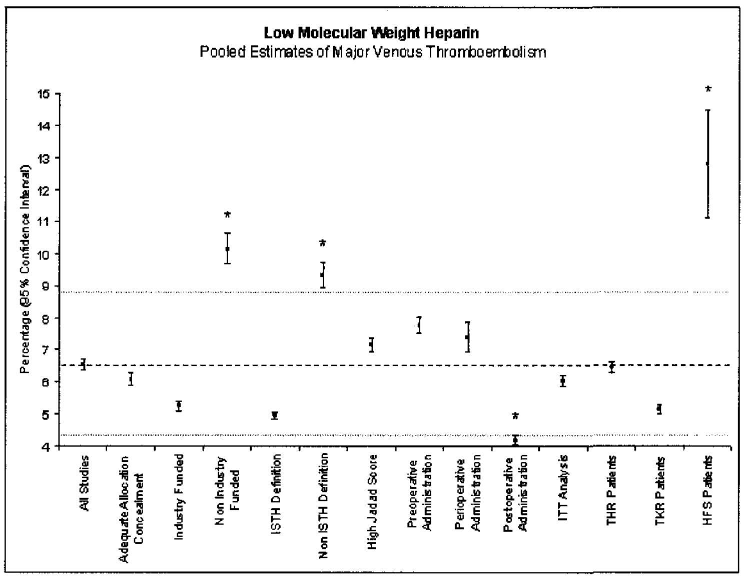

Figure S2. Subgroup and sensitivity analyses. Major venous thromboembolism in patients receiving low molecular weight heparin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

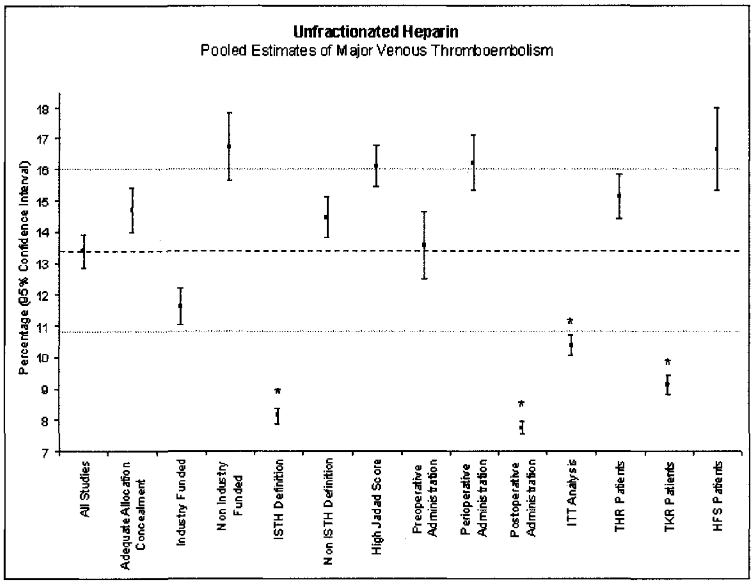

Figure S3. Subgroup and sensitivity analyses. Major venous thromboembolism in patients receiving unfractionated heparin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

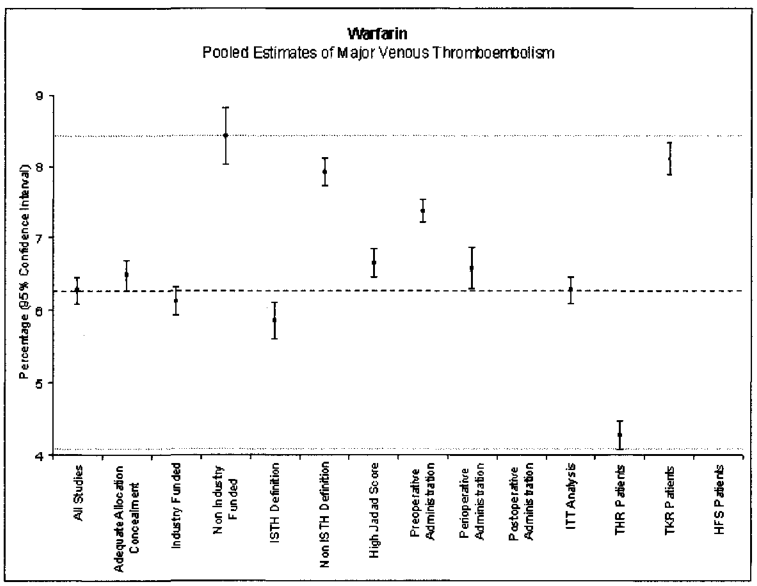

Figure S4. Subgroup and sensitivity analyses. Major venous thromboembolism in patients receiving warfarin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

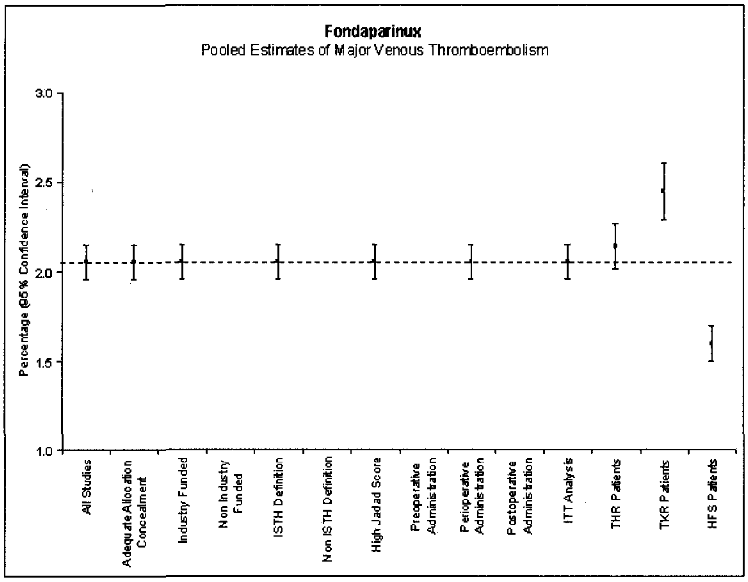

Figure S5. Subgroup and sensitivity analyses. Major venous thromboembolism in patients receiving fondaparinux. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

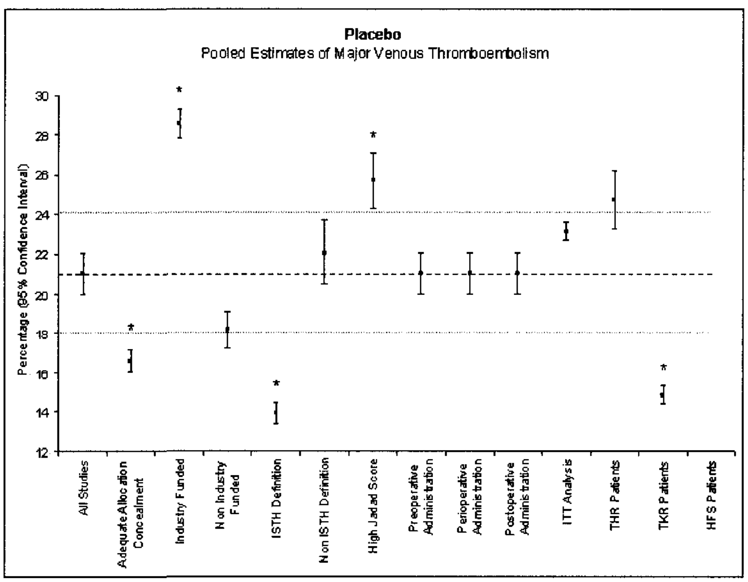

Figure S6. Subgroup and sensitivity analyses. Major venous thromboembolism in patients receiving placebo. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

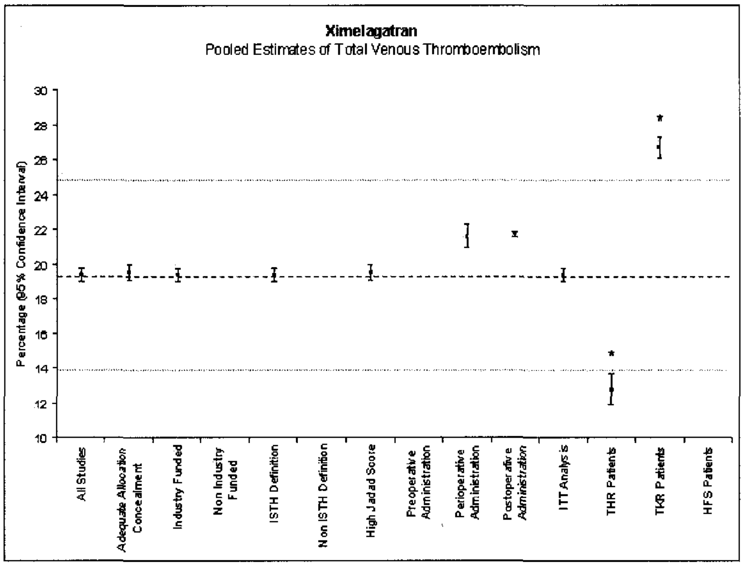

Figure S7. Subgroup and sensitivity analyses. Total venous thromboembolism in patients receiving ximelagatran. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

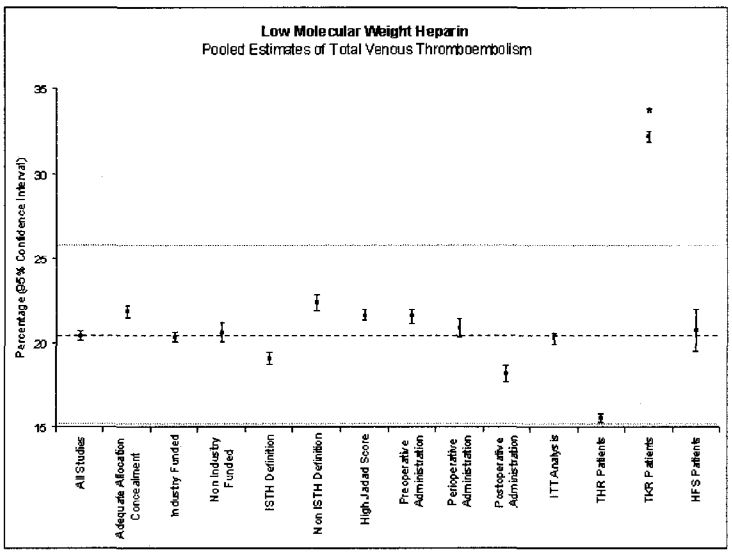

Figure S8. Subgroup and sensitivity analyses. Total venous thromboembolism in patients receiving low molecular weight heparin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

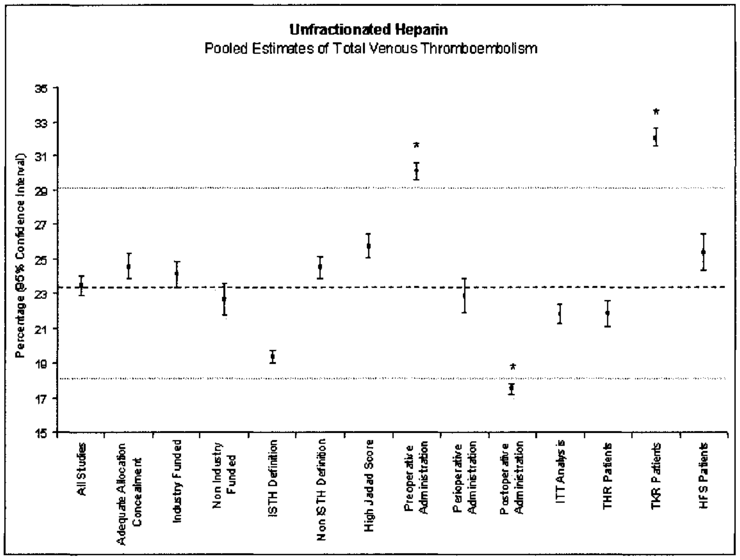

Figure S9. Subgroup and sensitivity analyses. Total venous thromboembolism in patients receiving unfractionated heparin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

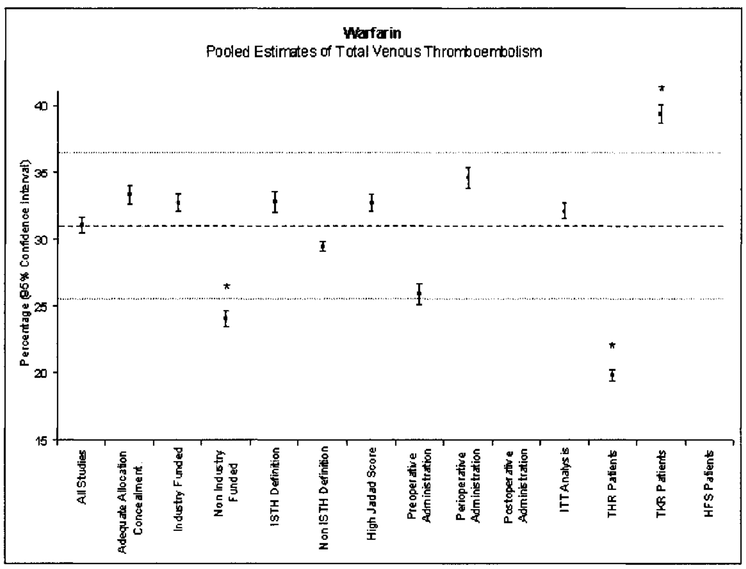

Figure S10. Subgroup and sensitivity analyses. Total venous thromboembolism in patients receiving warfarin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

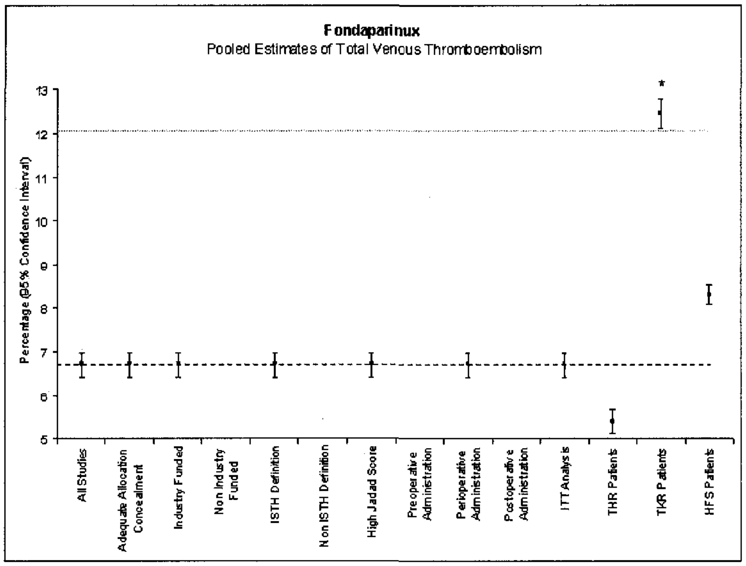

Figure S11. Subgroup and sensitivity analyses. Total venous thromboembolism in patients receiving fondaparinux. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

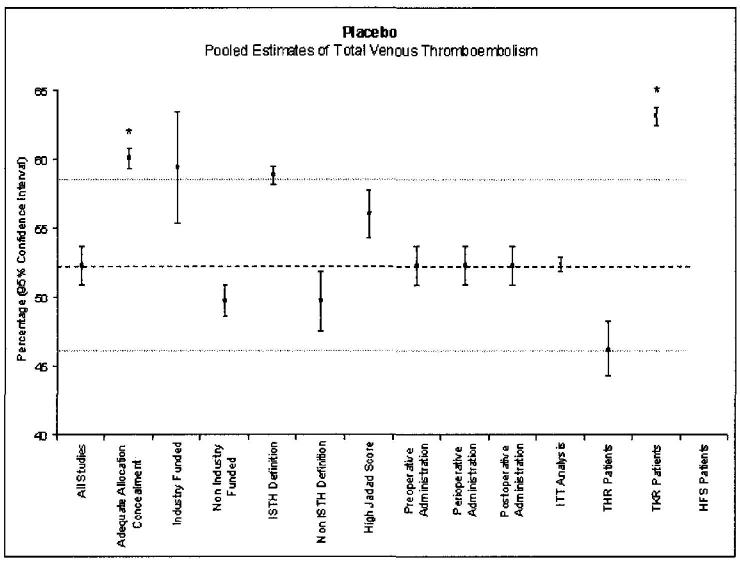

Figure S12. Subgroup and sensitivity analyses. Total venous thromboembolism in patients receiving placebo. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

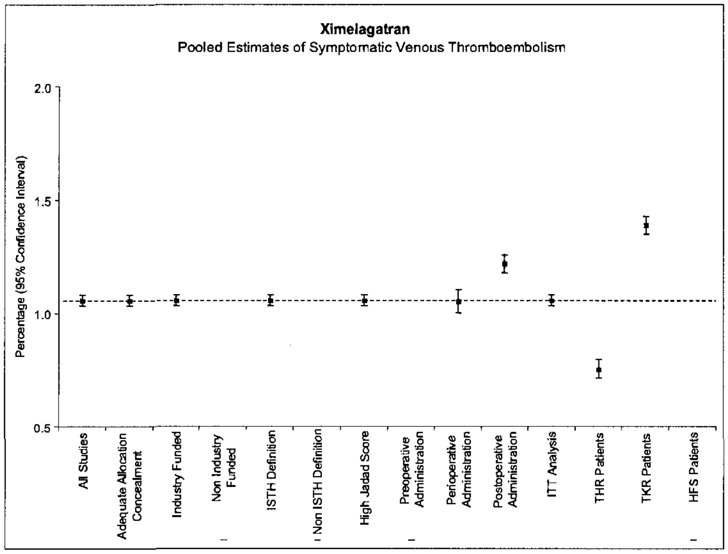

Figure S13. Subgroup and sensitivity analyses. Symptomatic venous thromboembolism in patients receiving ximelagatran. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

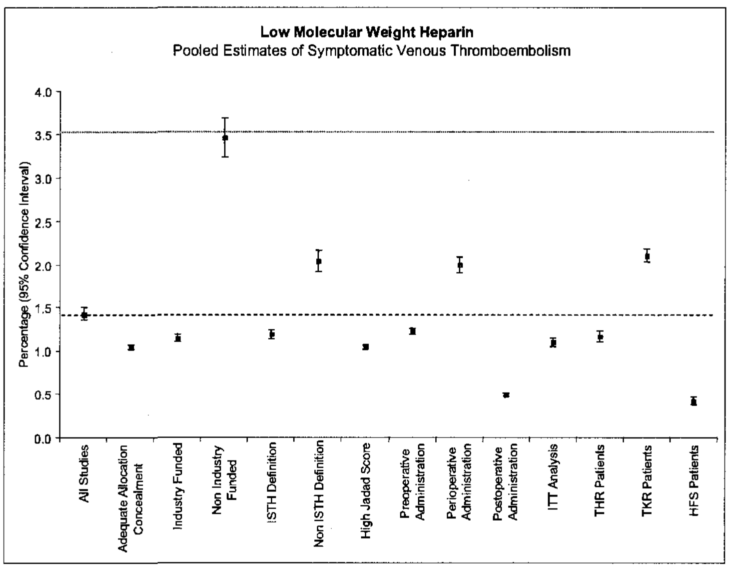

Figure S14. Subgroup and sensitivity analyses. Symptomatic venous thromboembolism in patients receiving low molecular weight heparin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

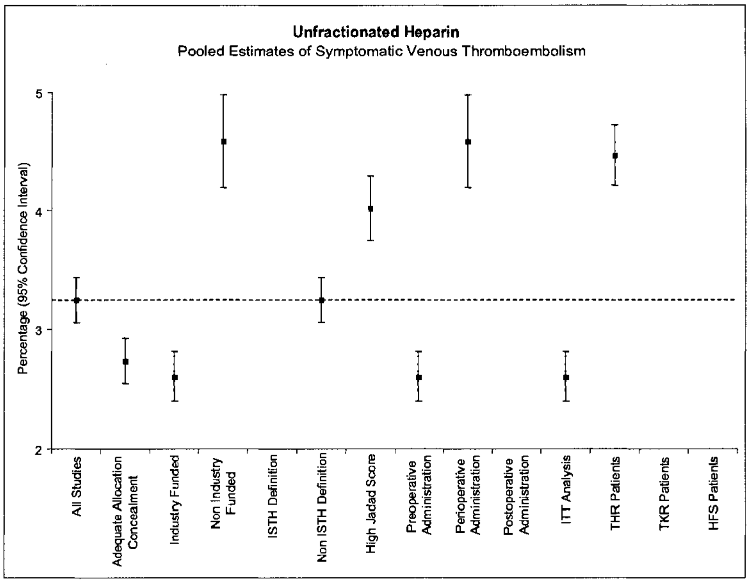

Figure S15. Subgroup and sensitivity analyses. Symptomatic venous thromboembolism in patients receiving unfractionated heparin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

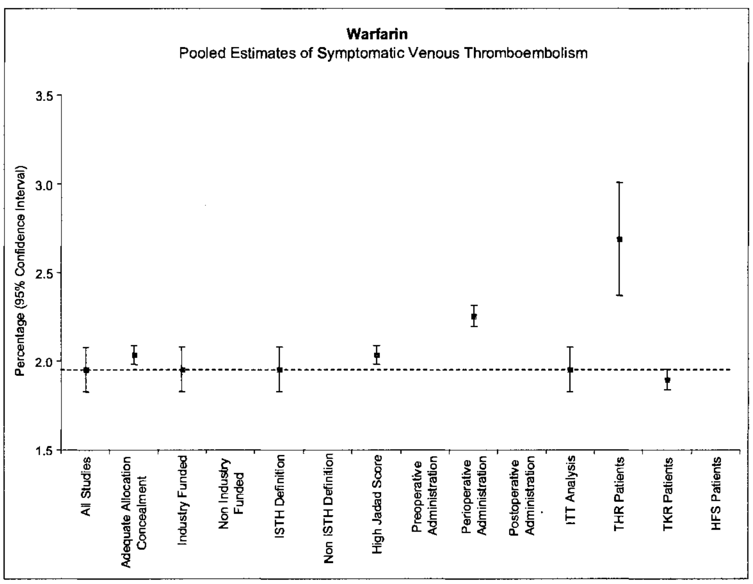

Figure S16. Subgroup and sensitivity analyses. Symptomatic venous thromboembolism in patients receiving warfarin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

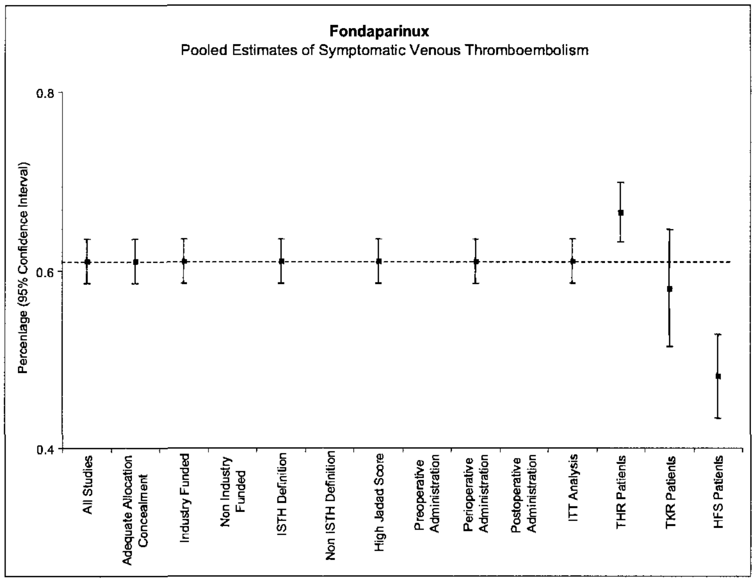

Figure S17. Subgroup and sensitivity analyses. Symptomatic venous thromboembolism in patients receiving fondaparinux. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

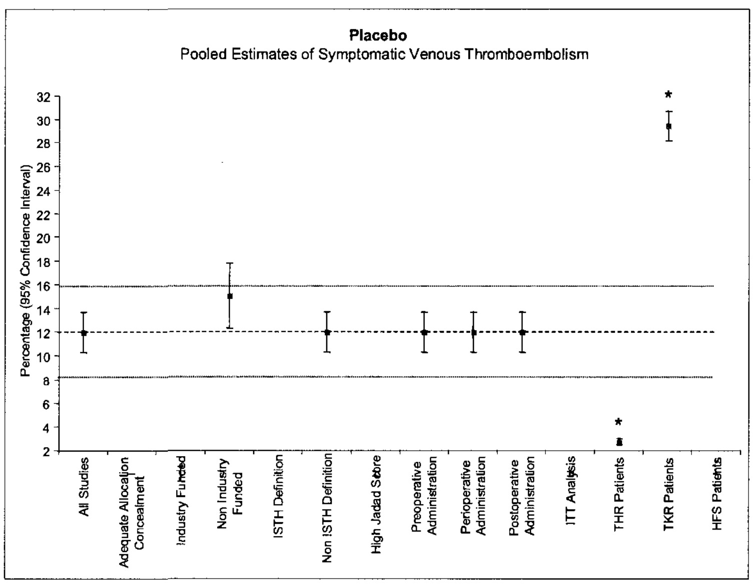

Figure S18. Subgroup and sensitivity analyses. Symptomatic venous thromboembolism in patients receiving placebo. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

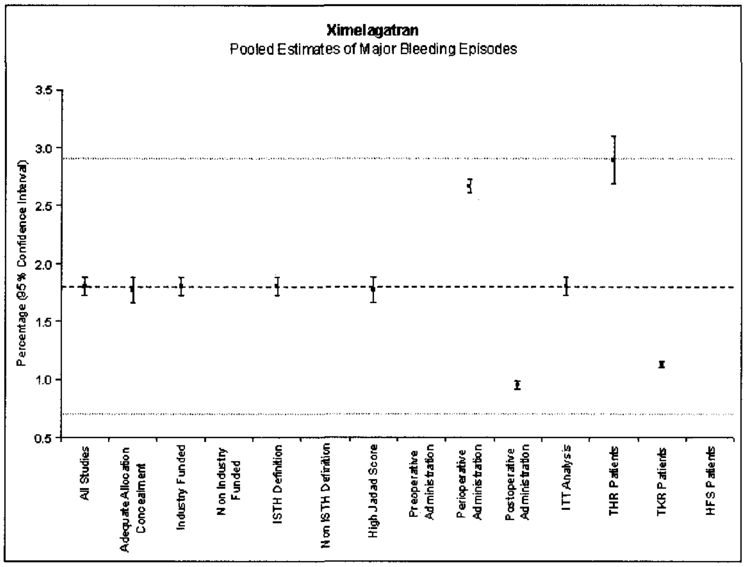

Figure S19. Subgroup and sensitivity analyses. Major bleeding events in patients receiving ximelagatran. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

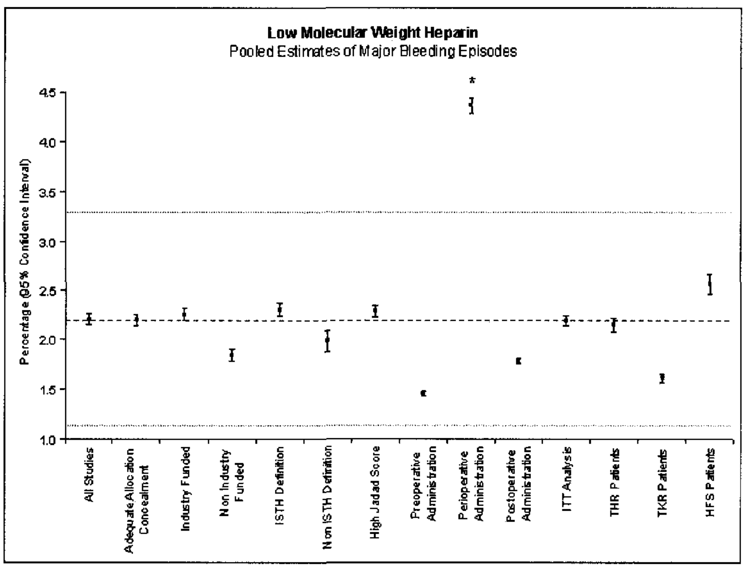

Figure S20. Subgroup and sensitivity analyses. Major bleeding events in patients receiving low molecular weight heparin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

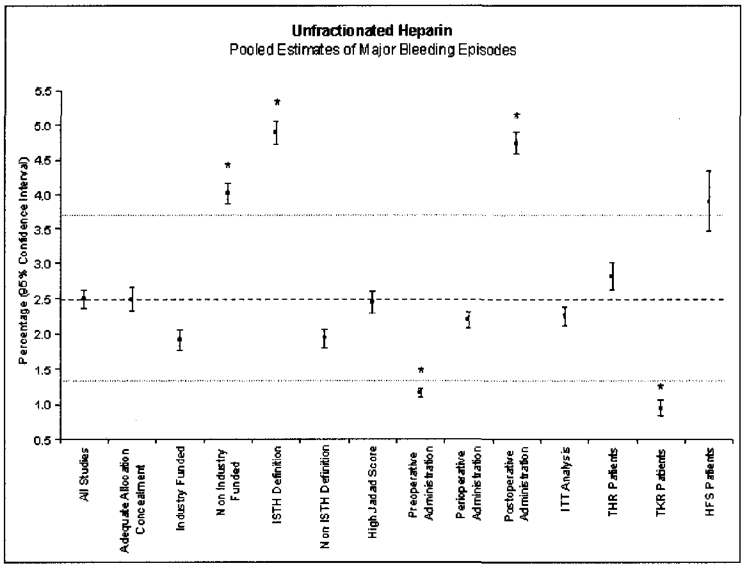

Figure S21. Subgroup and sensitivity analyses. Major bleeding events in patients receiving unfractionated heparin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

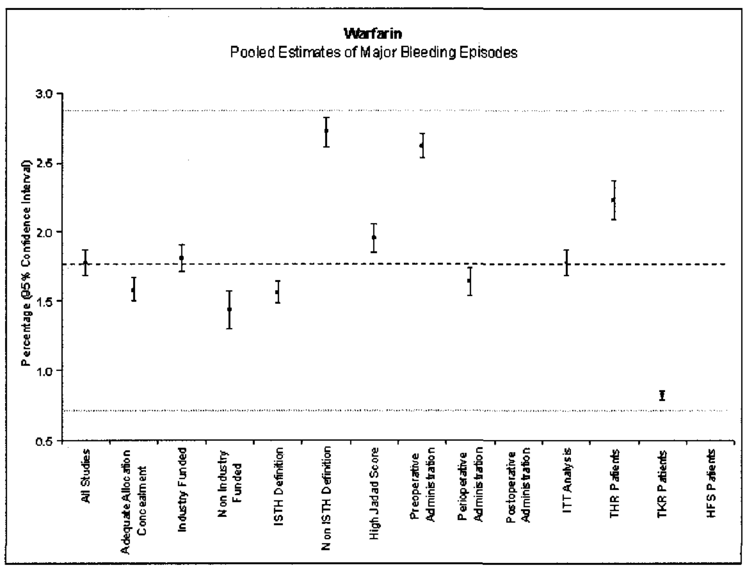

Figure S22. Subgroup and sensitivity analyses. Major bleeding events in patients receiving warfarin. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

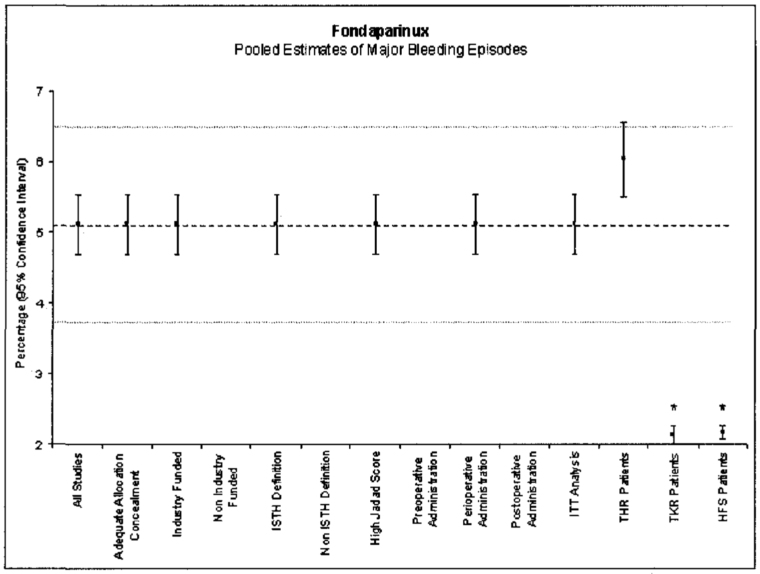

Figure S23. Subgroup and sensitivity analyses. Major bleeding events in patients receiving fondaparinux. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. Asterisks indicate significant differences. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

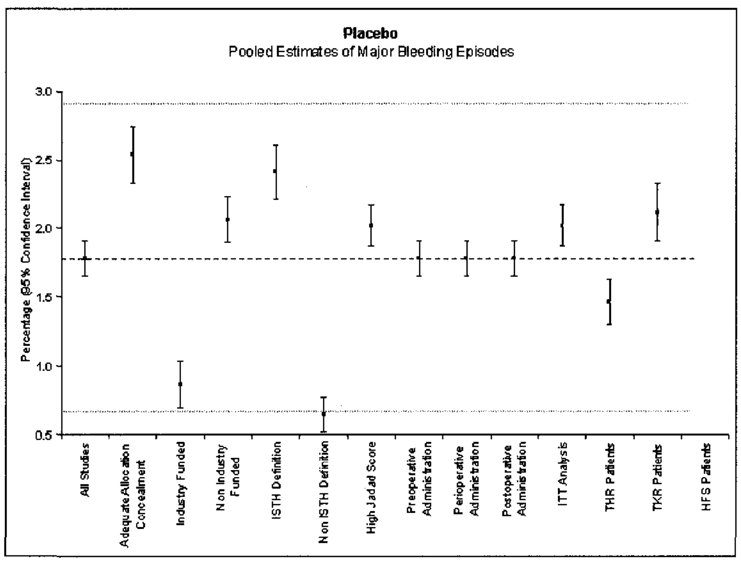

Figure S24. Subgroup and sensitivity analyses. Major bleeding events in patients receiving placebo. The bars represent the 95% confidence intervals. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. ISTH International Society on Thrombosis and Haemostasis; ITT Intention to treat; THR Total hip replacement; TKR Total knee replacement; HFS Hip fracture surgery.

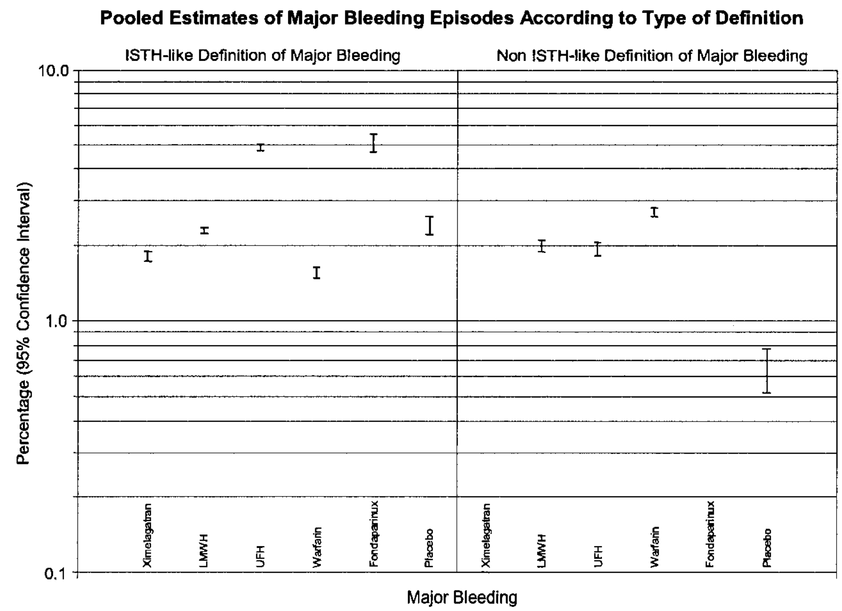

Figure S25. Pooled estimates of major bleeding events according to the type of definition of major bleeding event. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. Black bars indicate estimates of studies using an ISTH-like definition. Red bars indicate estimates of studies using a NonISTH-Like definition. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

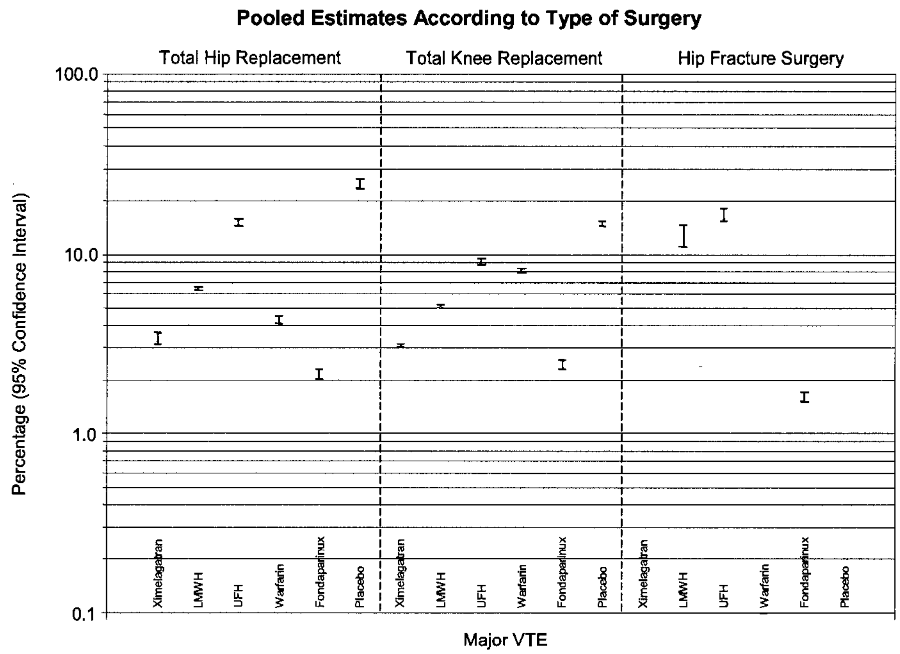

Figure S26. Pooled estimates of major venous thromboembolism according to type of surgery. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. Black bars indicate estimates in total hip replacement. Red bars indicate estimates in total knee replacement. Green bars indicate estimates in hip fracture surgery. LMWH Low molecular weight heparin; UFH Unfractionated heparin; VTE venous thromboembolism.

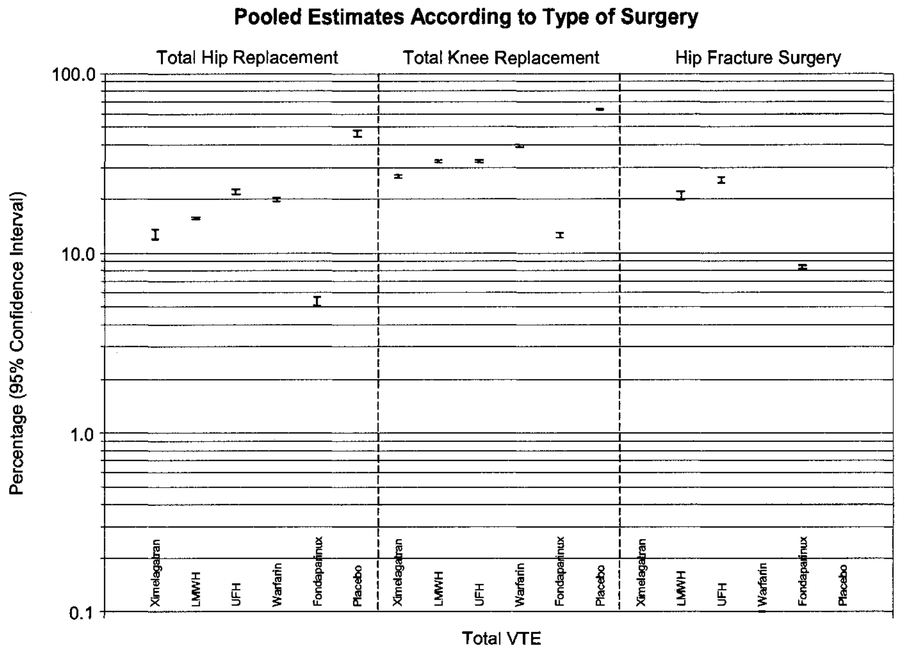

Figure S27. Pooled estimates of total venous thromboembolism according to type of surgery. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. Black bars indicate estimates in total hip replacement. Red bars indicate estimates in total knee replacement. Green bars indicate estimates in hip fracture surgery. LMWH Low molecular weight heparin; UFH Unfractionated heparin; VTE venous thromboembolism.

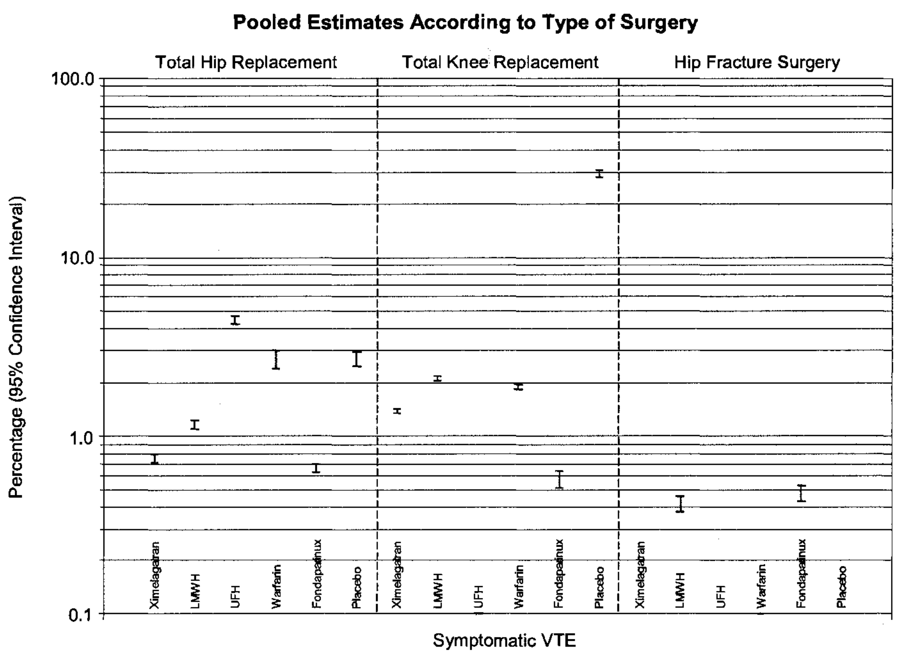

Figure S28. Pooled estimates of symptomatic venous thromboembolism according to type of surgery. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. Black bars indicate estimates in total hip replacement. Red bars indicate estimates in total knee replacement. Green bars indicate estimates in hip fracture surgery. LMWH Low molecular weight heparin; UFH Unfractionated heparin; VTE venous thromboembolism.

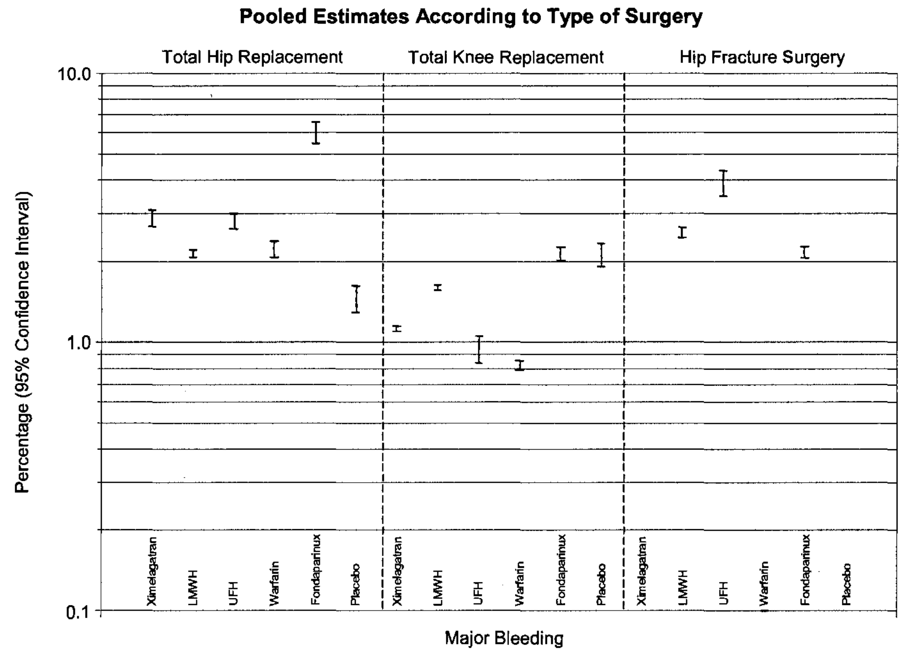

Figure S29. Pooled estimates of major bleeding according to type of surgery. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. Black bars indicate estimates in total hip replacement. Red bars indicate estimates in total knee replacement. Green bars indicate estimates in hip fracture surgery. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

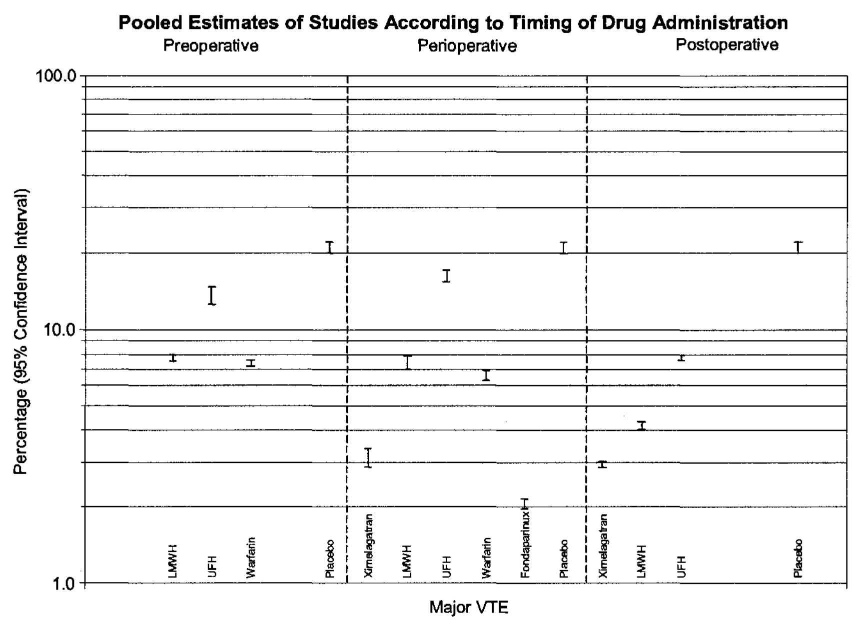

Figure S30. Pooled estimates of major venous thromboembolism according to timing of initiation. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. Black bars indicate estimates in the preoperative group. Red bars indicate estimates in the perioperative group. Green bars indicate estimates in the postoperative group. LMWH Low molecular weight heparin; UFH Unfractionated heparin; VTE venous thromboembolism.

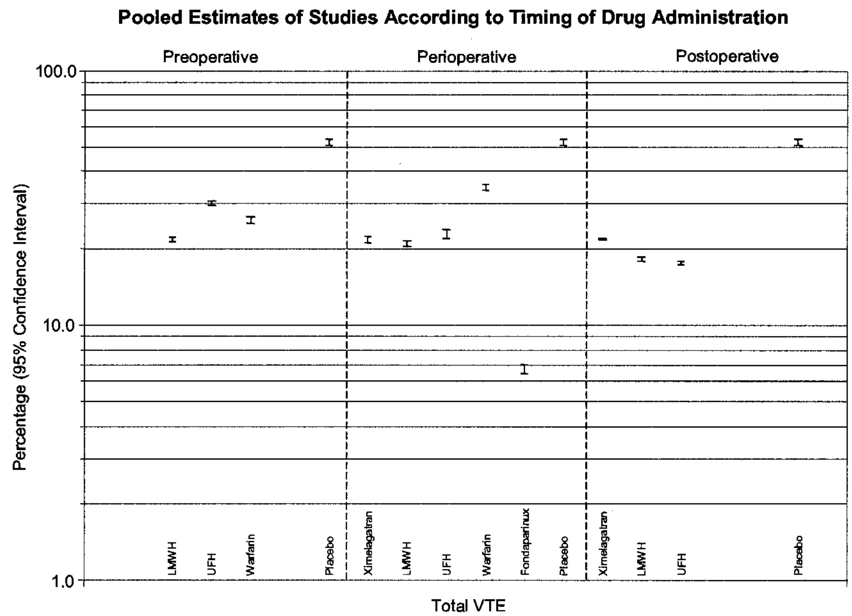

Figure S31. Pooled estimates of total venous thromboembolism according to timing of initiation. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. Black bars indicate estimates in the preoperative group. Red bars indicate estimates in the perioperative group. Green bars indicate estimates in the postoperative group. LMWH Low molecular weight heparin; UFH Unfractionated heparin; VTE venous thromboembolism.

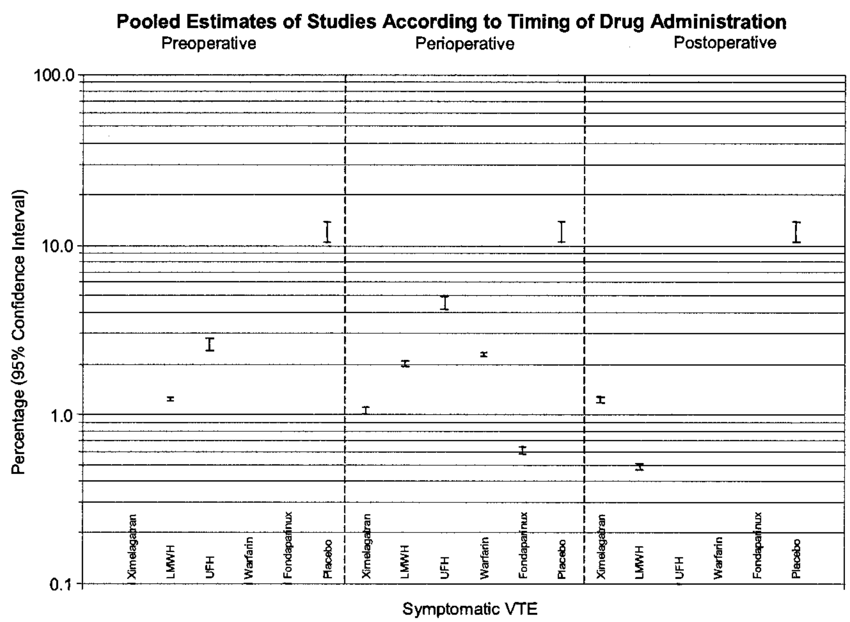

Figure S32. Pooled estimates of symptomatic venous thromboembolism according to timing of initiation. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. Black bars indicate estimates in the preoperative group. Red bars indicate estimates in the perioperative group. Green bars indicate estimates in the postoperative group. LMWH Low molecular weight heparin; UFH Unfractionated heparin; VTE venous thromboembolism.

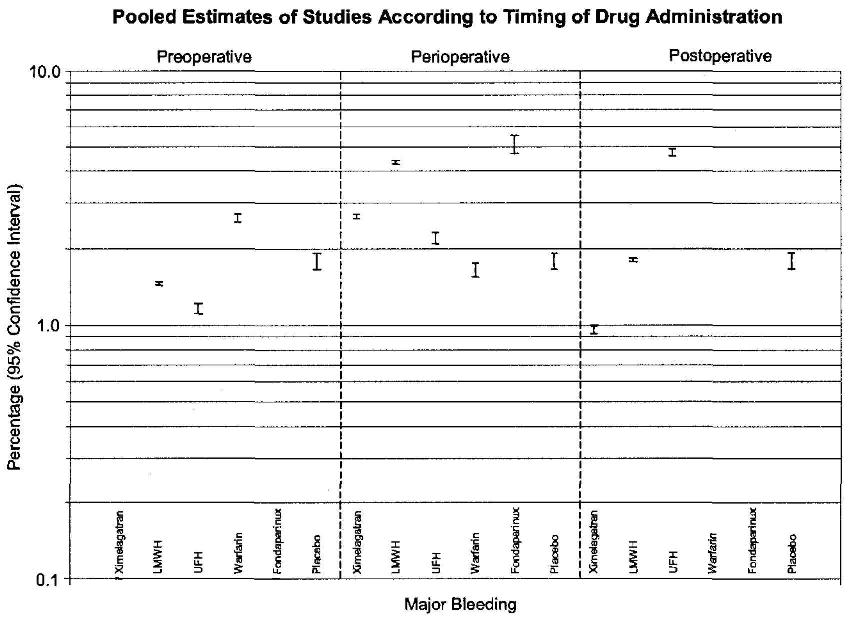

Figure S33. Pooled estimates of major bleeding according to timing of initiation. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. Black bars indicate estimates in the preoperative group. Red bars indicate estimates in the perioperative group. Green bars indicate estimates in the postoperative group. LMWH Low molecular weight heparin; UFH Unfractionated heparin; VTE venous thromboembolism.

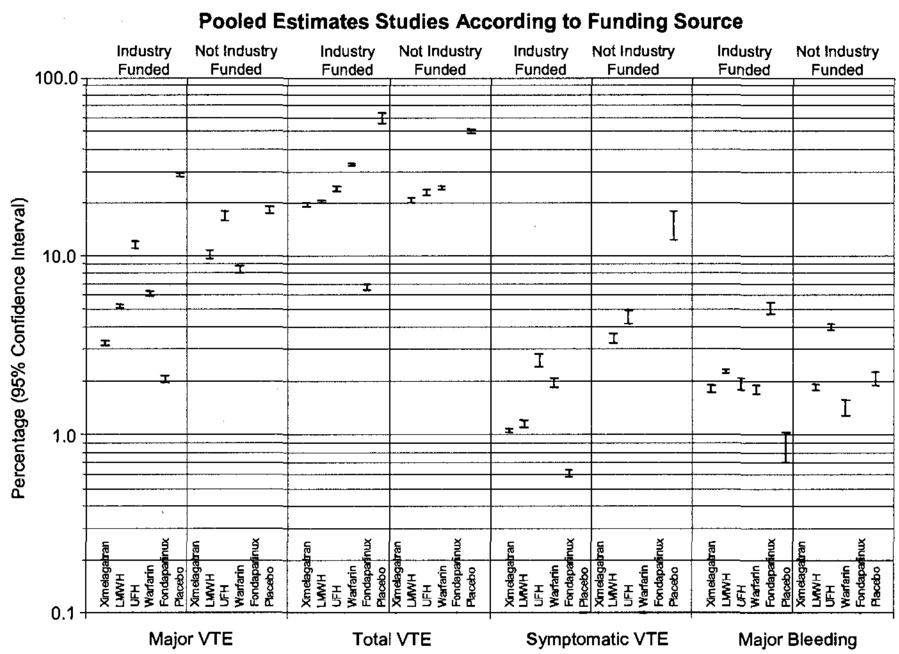

Figure S34. Pooled estimates of outcomes according to funding source. The bars represent the 95% confidence intervals around the point estimate. Percentage is plotted in a logarithmic scale. Black bars indicate estimates in industry funded studies. Red bars indicate estimates in not industry funded studies. LMWH Low molecular weight heparin; UFH Unfractionated heparin; VTE venous thromboembolism.

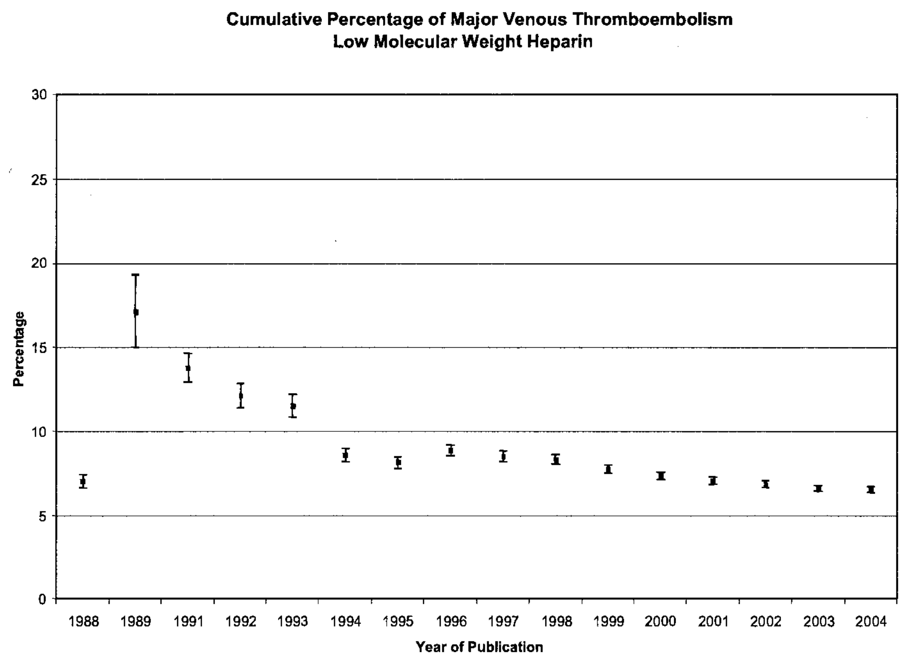

Figure S35. Cumulative meta-analysis of major venous thromboembolism in patients receiving low molecular weight heparin in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

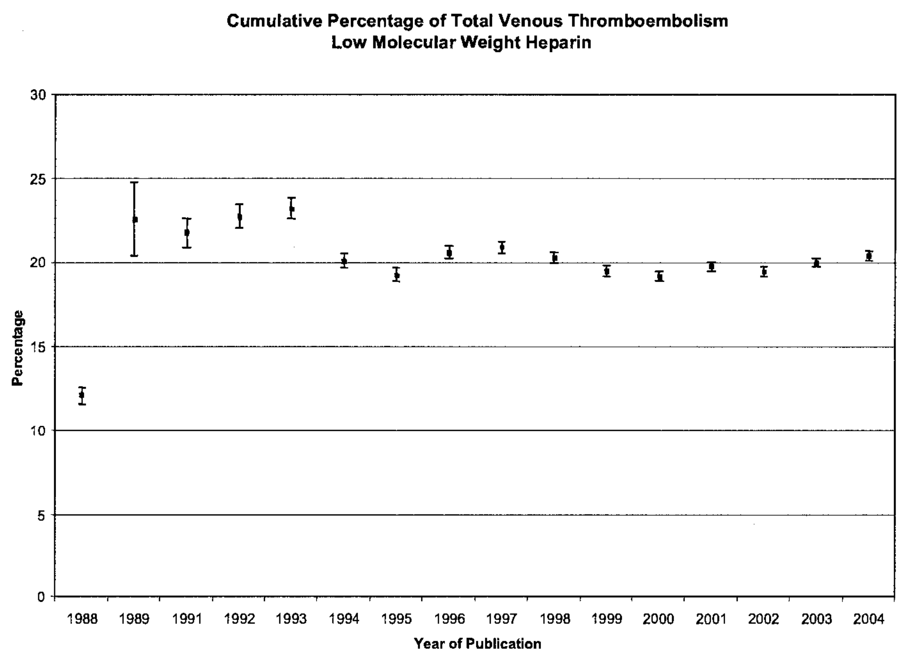

Figure S36. Cumulative meta-analysis of total venous thromboembolism in patients receiving low molecular weight heparin in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

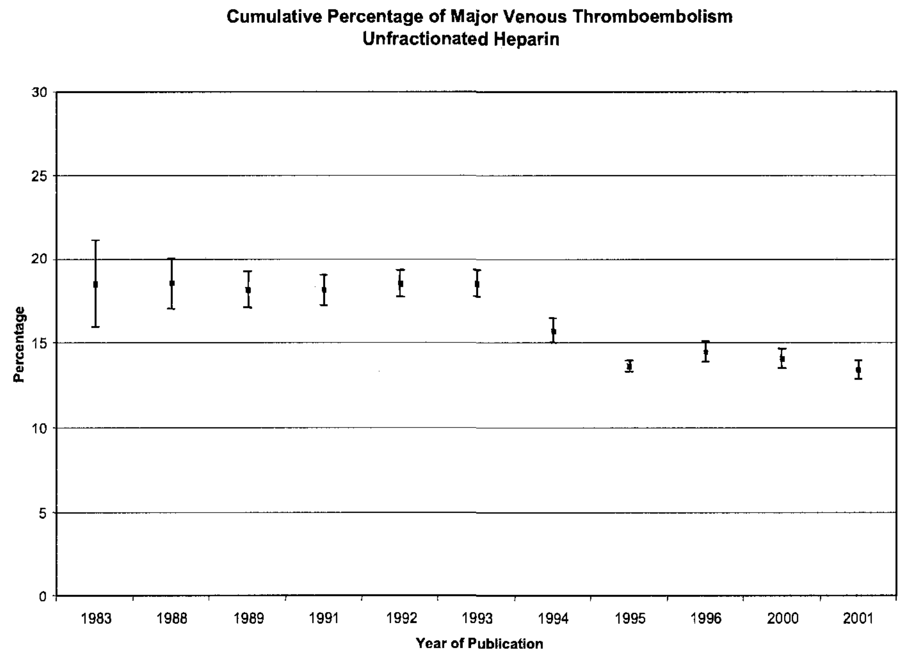

Figure S37. Cumulative meta-analysis of major venous thromboembolism in patients receiving unfractionated heparin in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

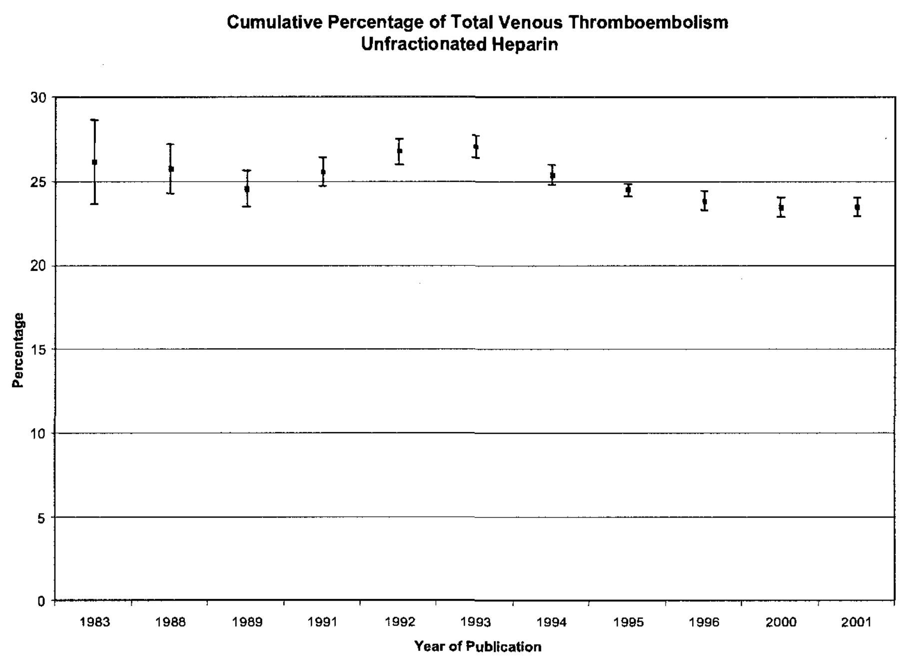

Figure S38. Cumulative meta-analysis of total venous thromboembolism in patients receiving unfractionated heparin in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

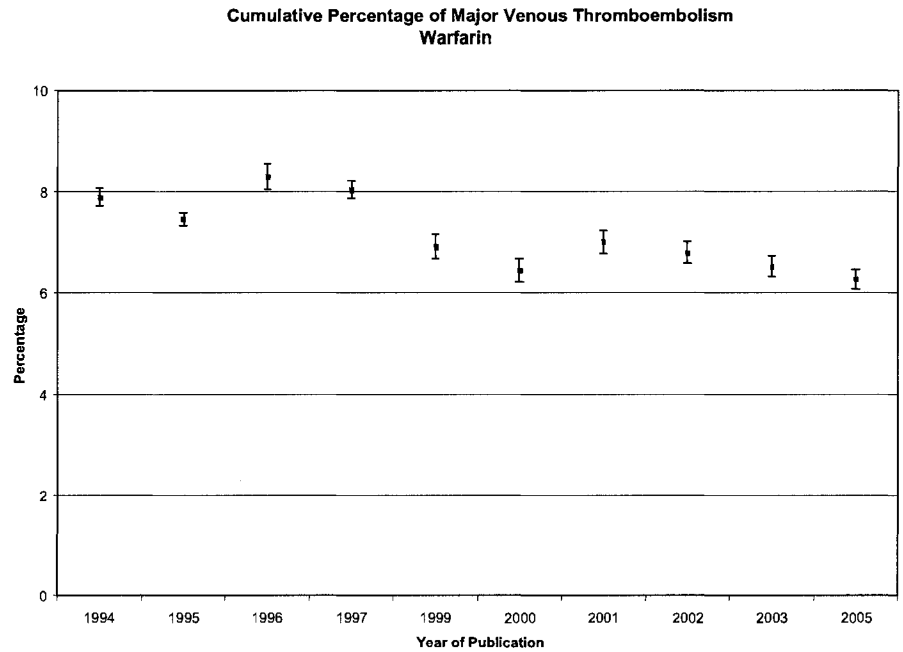

Figure S39. Cumulative meta-analysis of major venous thromboembolism in patients receiving warfarin in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

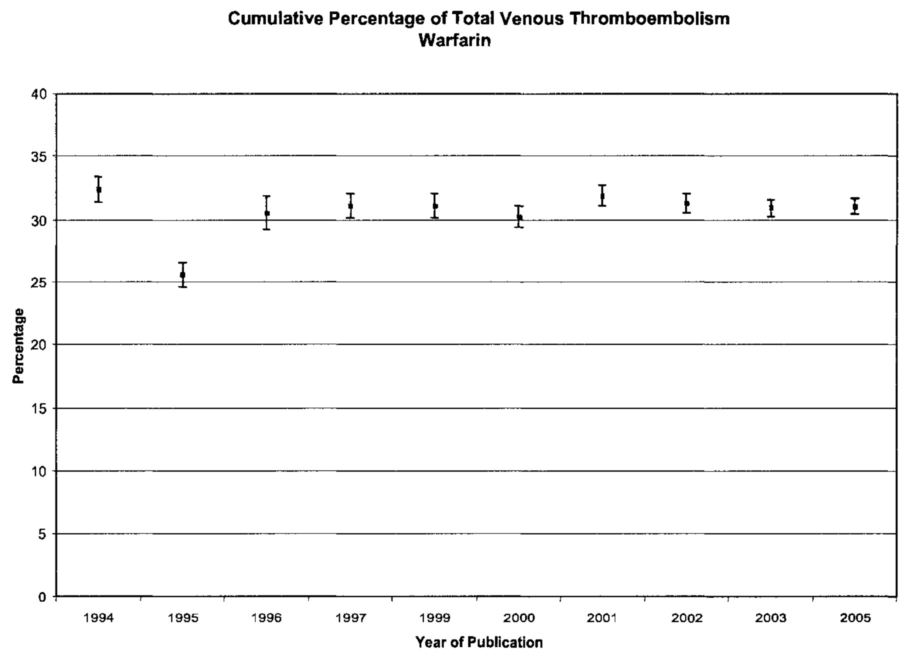

Figure S40. Cumulative meta-analysis of total venous thromboembolism in patients receiving warfarin in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

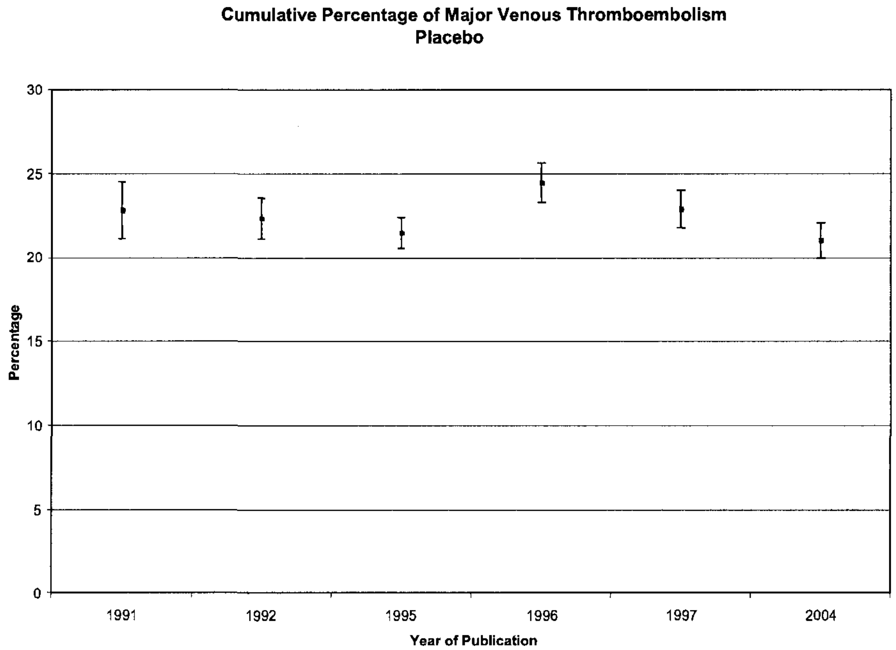

Figure S41. Cumulative meta-analysis of major venous thromboembolism in patients receiving placebo in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

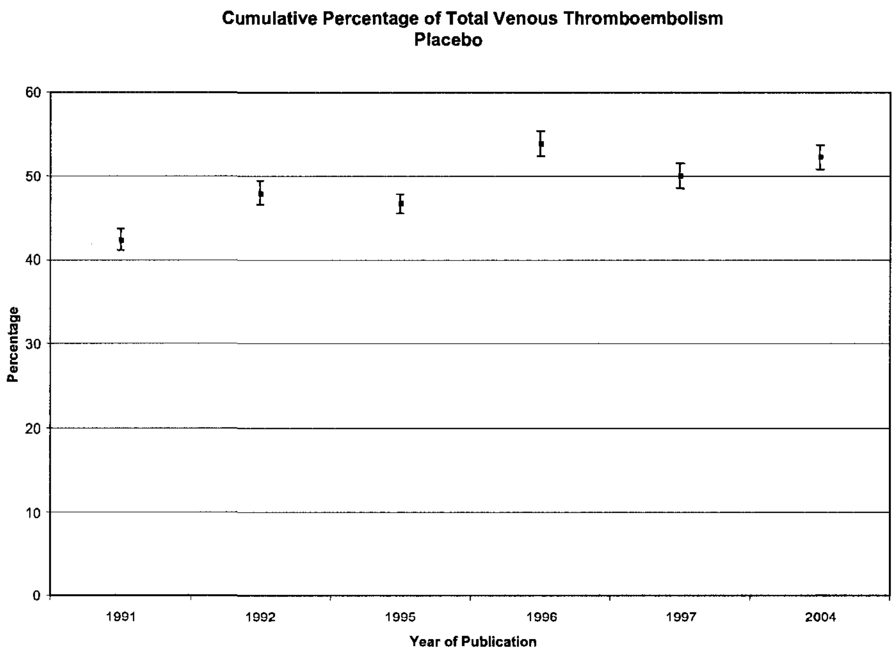

Figure S42. Cumulative meta-analysis of total venous thromboembolism in patients receiving placebo in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

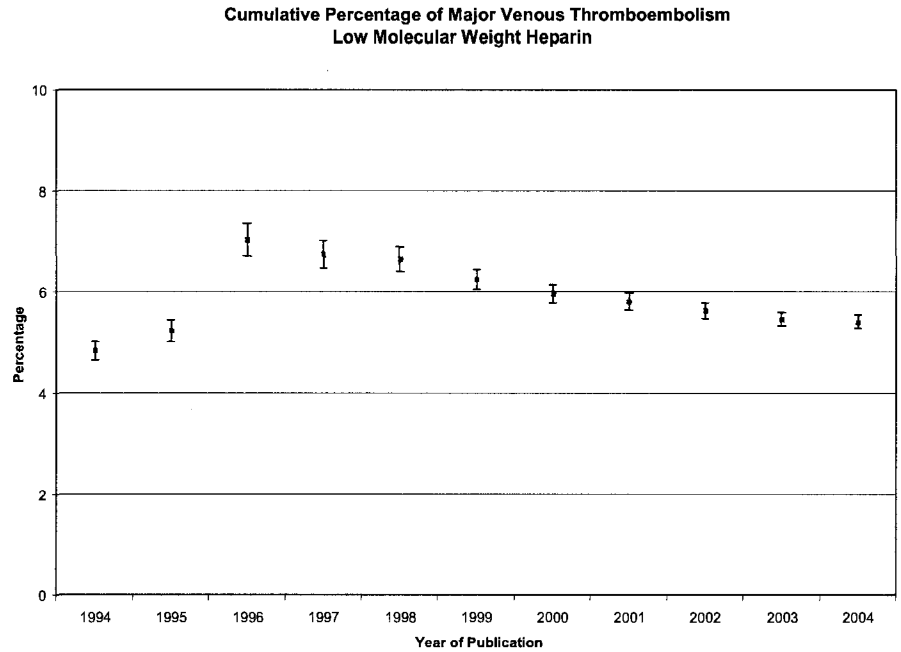

Figure S43. Cumulative meta-analysis of major venous thromboembolism in patients receiving low molecular weight heparin in studies published between 1994 and 2004. The bars represent the 95% confidence intervals around the point estimate.

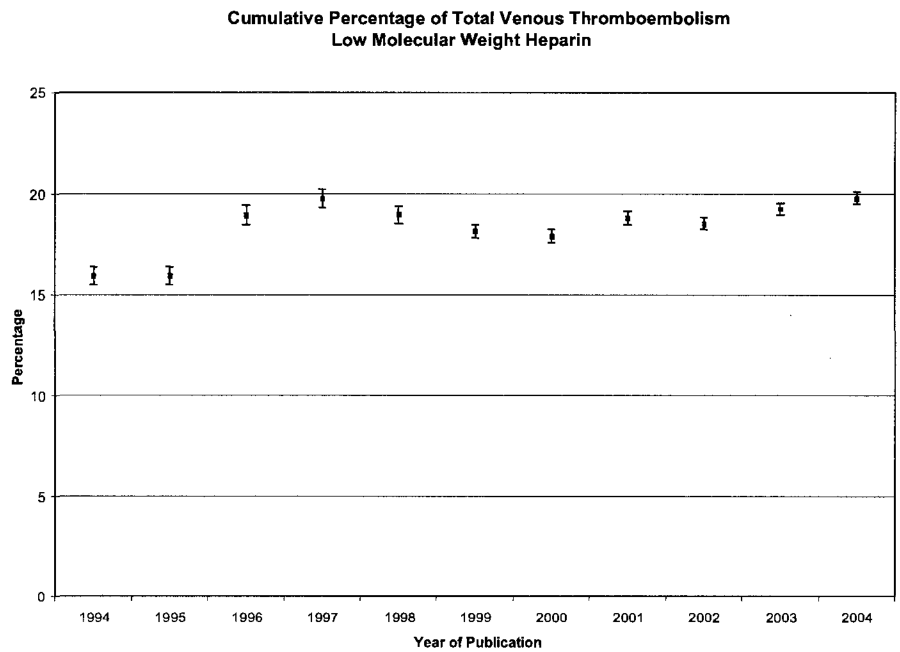

Figure S44. Cumulative meta-analysis of total venous thromboembolism in patients receiving low molecular weight heparin in studies published between 1994 and 2004. The bars represent the 95% confidence intervals around the point estimate.

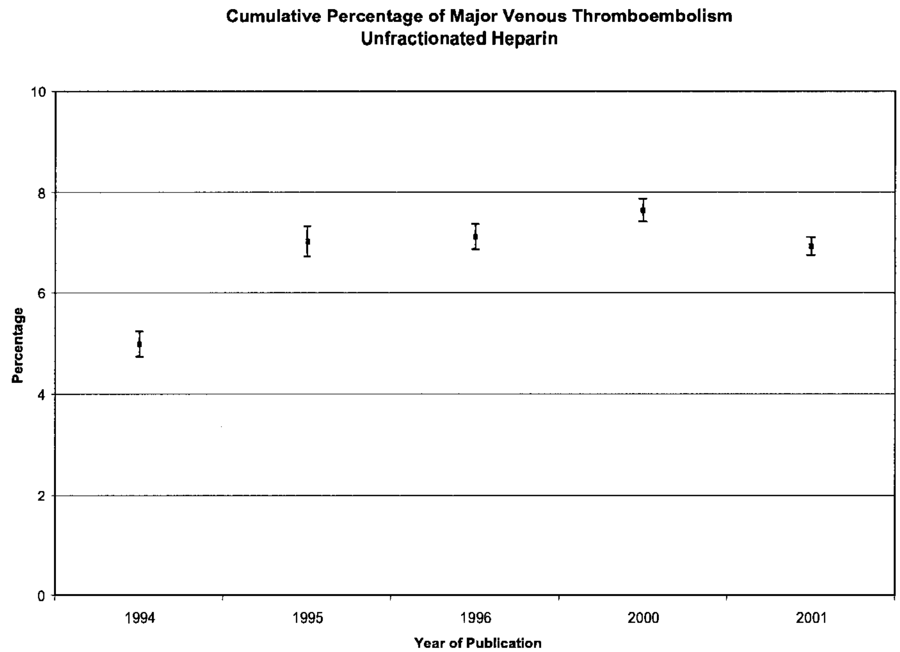

Figure S45. Cumulative meta-analysis of major venous thromboembolism in patients receiving unfractionated heparin in studies published between 1994 and 2004. The bars represent the 95% confidence intervals around the point estimate.

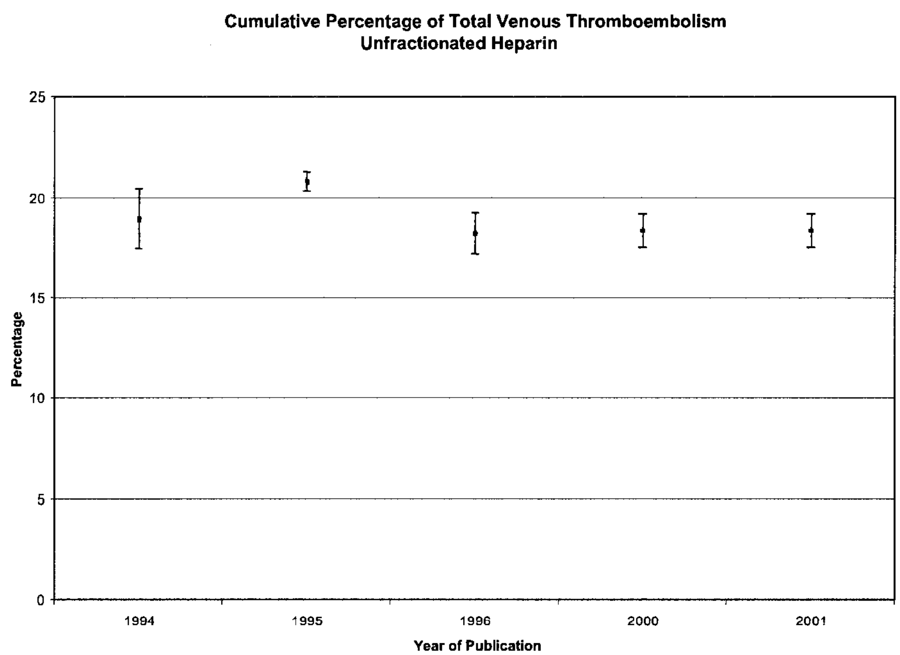

Figure S46. Cumulative meta-analysis of total venous thromboembolism in patients receiving unfractionated heparin in studies published between 1994 and 2004. The bars represent the 95% confidence intervals around the point estimate.

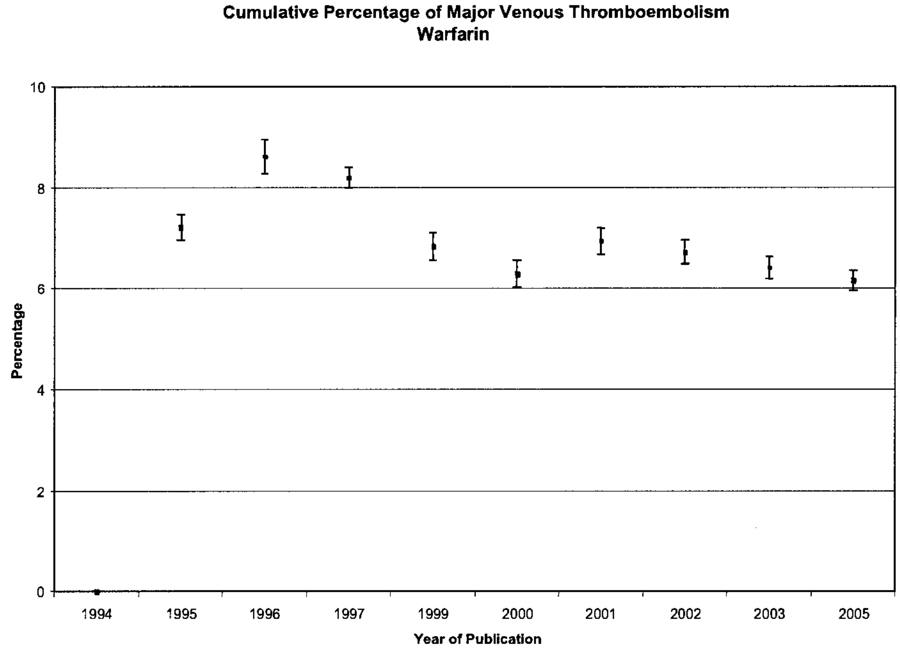

Figure S47. Cumulative meta-analysis of major venous thromboembolism in patients receiving warfarin in studies published between 1994 and 2004. The bars represent the 95% confidence intervals around the point estimate.

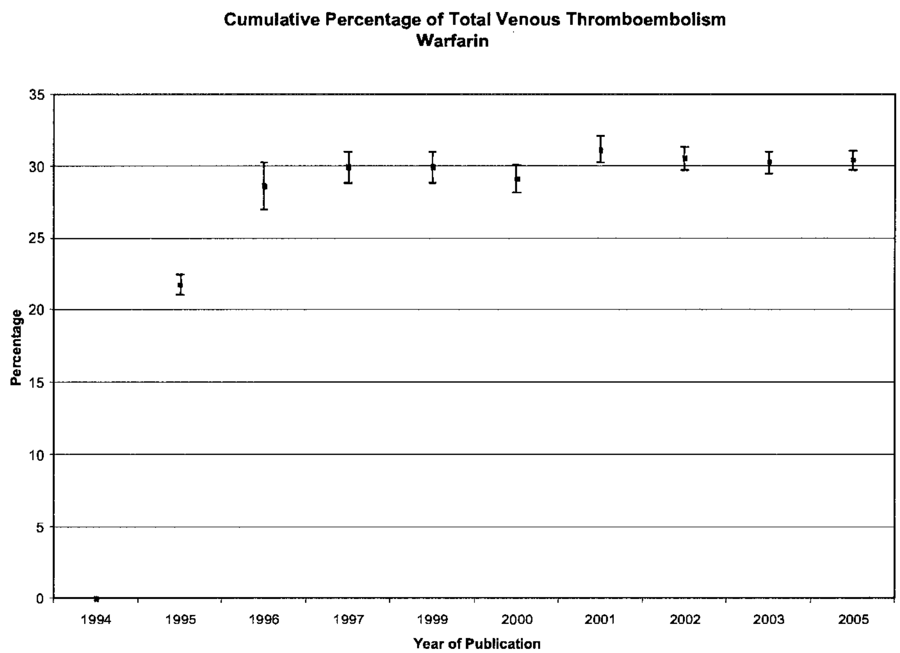

Figure S48. Cumulative meta-analysis of total venous thromboembolism in patients receiving warfarin in studies published between 1994 and 2004. The bars represent the 95% confidence intervals around the point estimate.

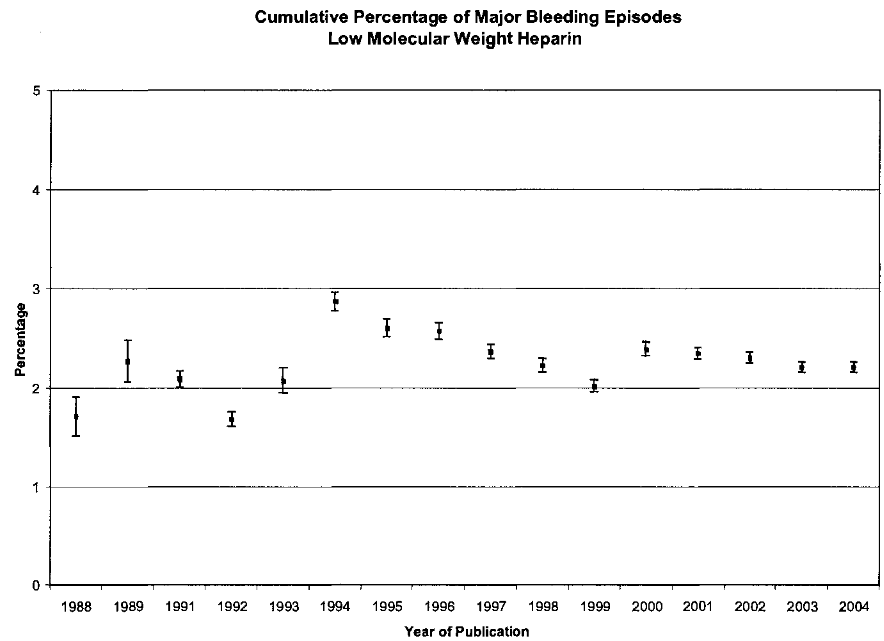

Figure S49. Cumulative meta-analysis of major bleeding episodes in patients receiving low molecular weight heparin in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

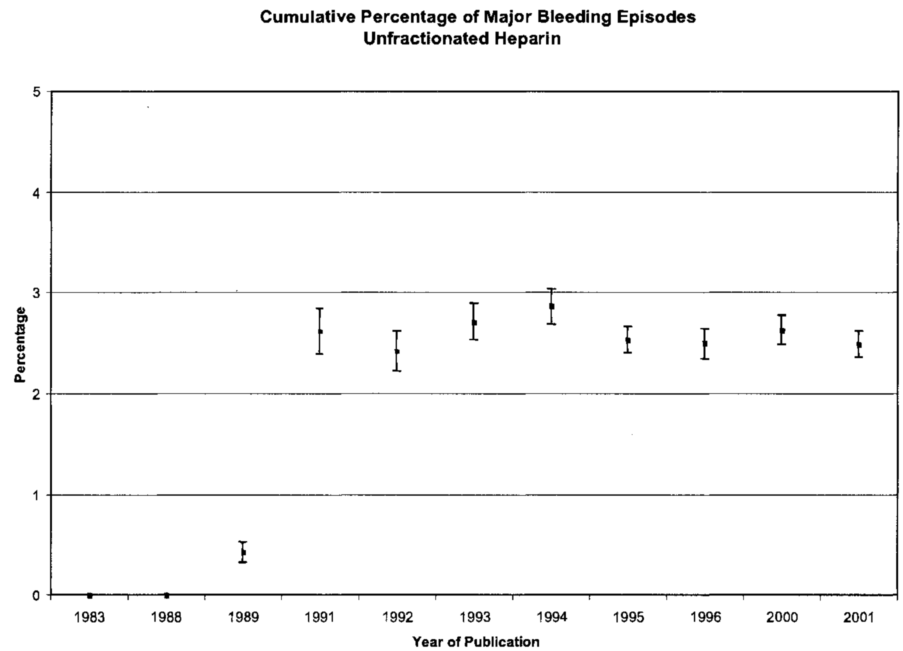

Figure S50. Cumulative meta-analysis of major bleeding episodes in patients receiving unfractionated heparin in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

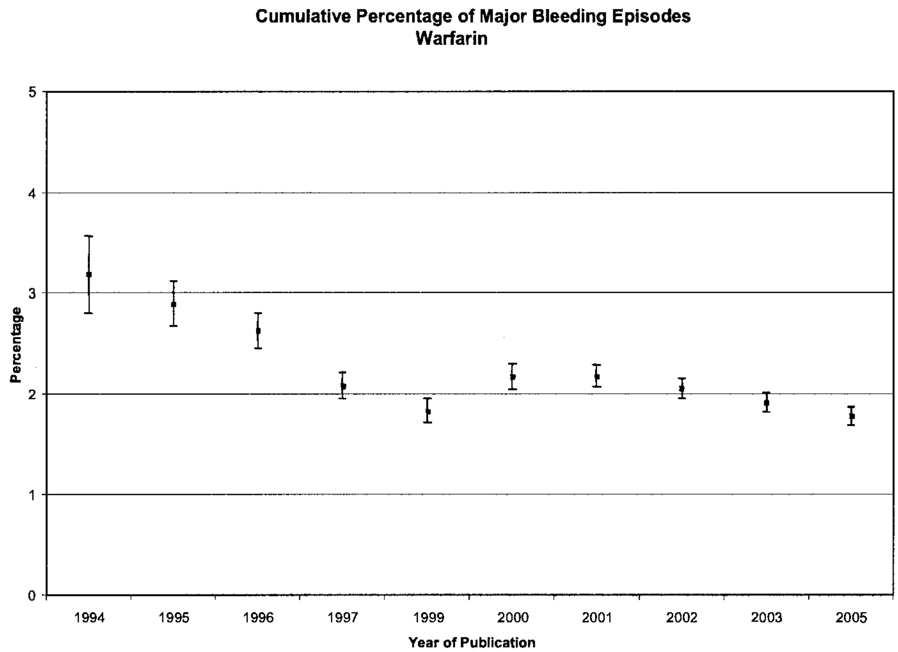

Figure S51. Cumulative meta-analysis of major bleeding episodes in patients receiving warfarin in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

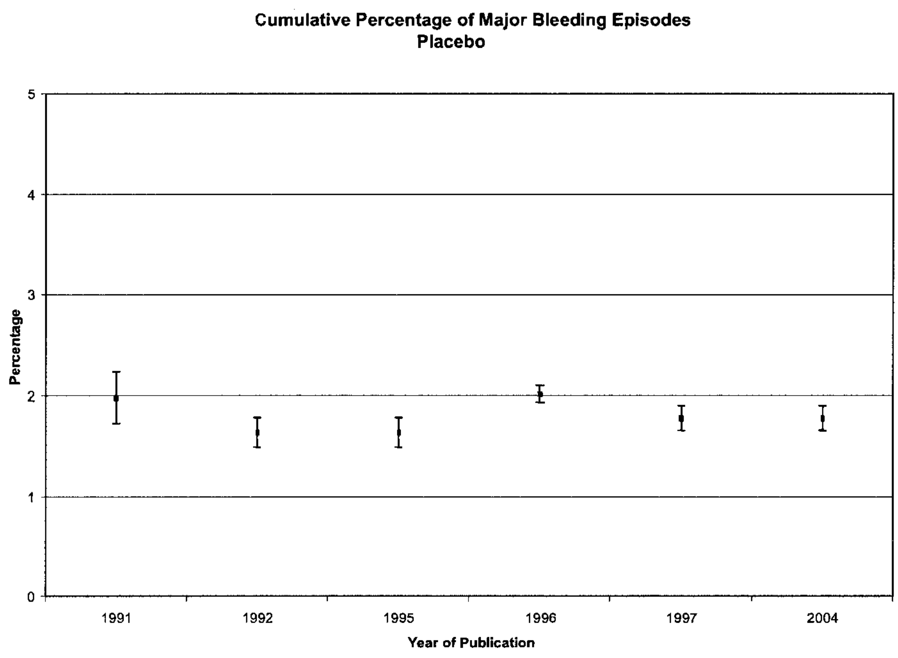

Figure S52. Cumulative meta-analysis of major bleeding episodes in patients receiving placebo in studies published between 1980 and 2004. The bars represent the 95% confidence intervals around the point estimate.

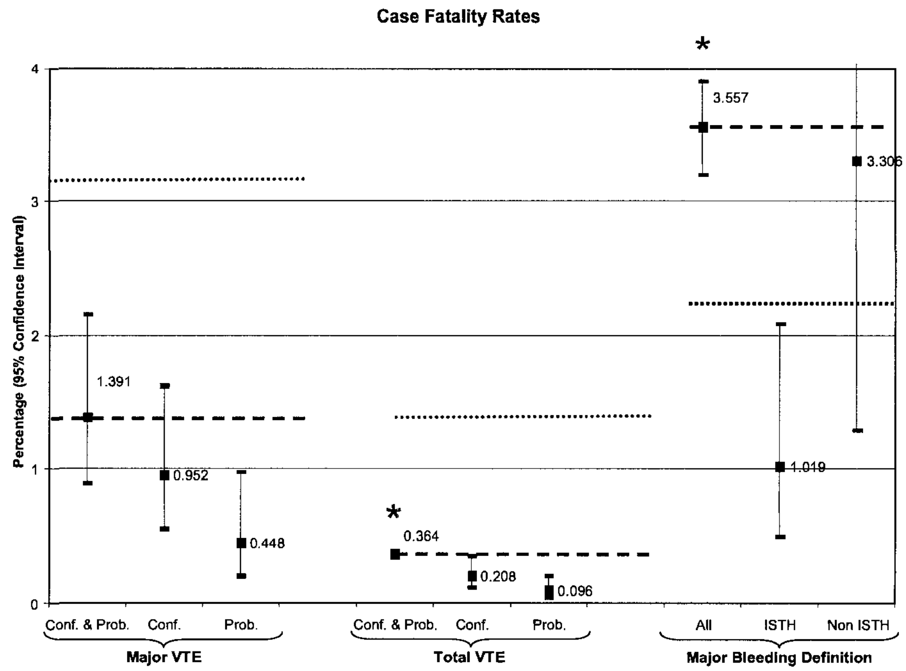

Figure S53. Case fatality rates for thromboembolic and bleeding events. The squares represent the point estimates. The bars represent the 95% confidence intervals around the estimate. The dashed line represents the pooled point estimate for all studies. The dotted lines limit the band of clinical relevance. The asterisks indicate statistically heterogeneous estimates. Conf Confirmed; Prob Probable; VTE Venous thromboembolism; ISTH International Society on Thrombosis and Haemostasis.

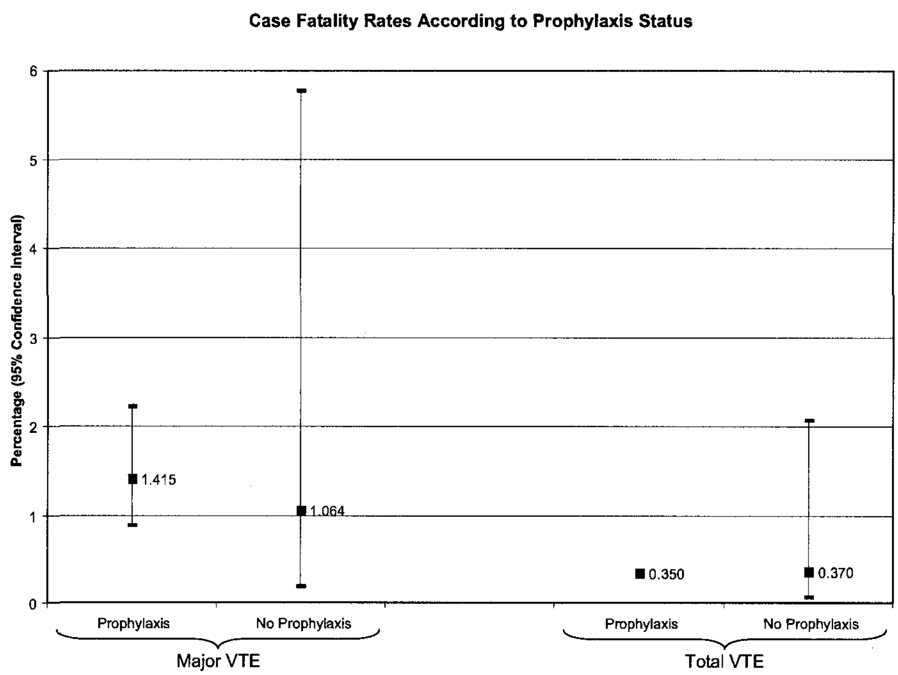

Figure S54. Case fatality rates for thromboembolic events according to prophylaxis use. The squares represent the point estimates. The bars represent the 95% confidence intervals around the estimate. VTE Venous thromboembolism.

Risk-benefit planes. Ximelagatran

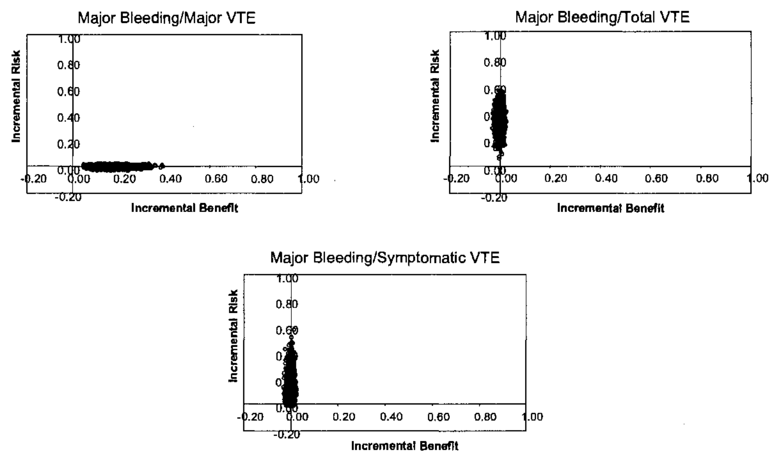

Figure S55. Risk benefit planes showing paired observations of incremental benefit and incremental risk of ximelagatran compared to placebo. VTE Venous thromboembolism.

Risk-benefit planes. Low molecular weight heparin.

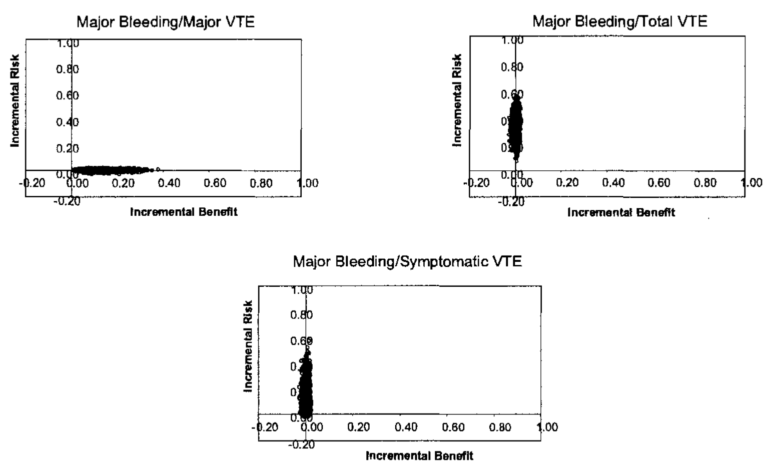

Figure S56. Risk benefit planes showing paired observations of incremental benefit and incremental risk of low molecular weight heparin compared to placebo. VTE Venous thromboembolism.

Risk-benefit planes. Unfractionated heparin.

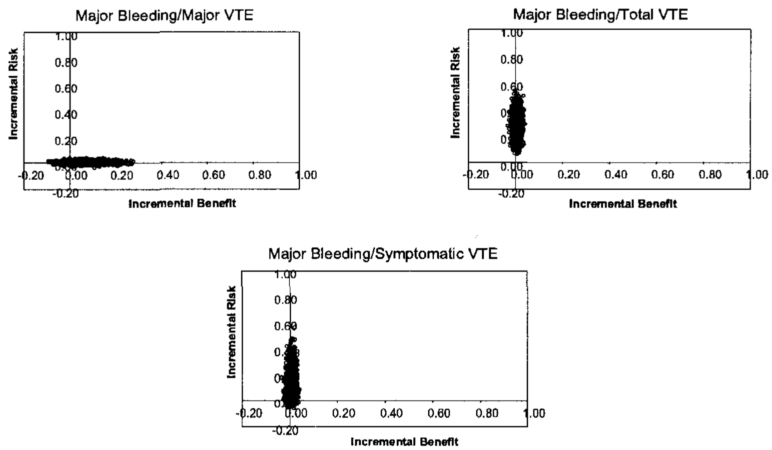

Figure S57. Risk benefit planes showing paired observations of incremental benefit and incremental risk of unfractionated heparin compared to placebo. VTE Venous thromboembolism.

Risk-benefit planes. Warfarin.

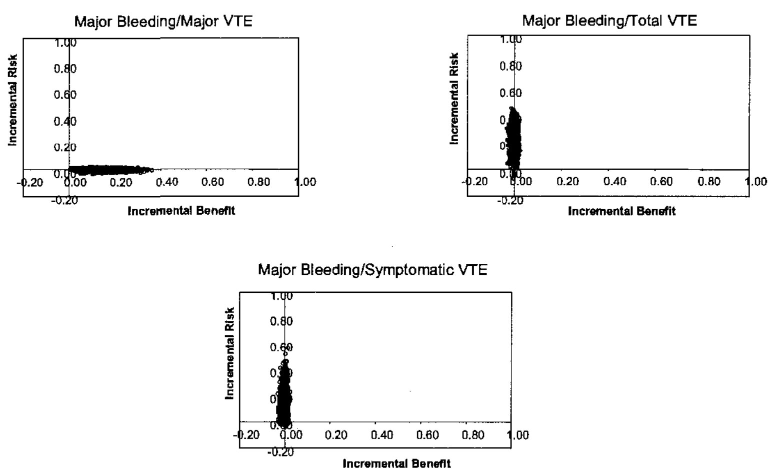

Figure S58. Risk benefit planes showing paired observations of incremental benefit and incremental risk of warfarin compared to placebo. VTE Venous thromboembolism.

Risk-benefit planes. Fondaparinux.

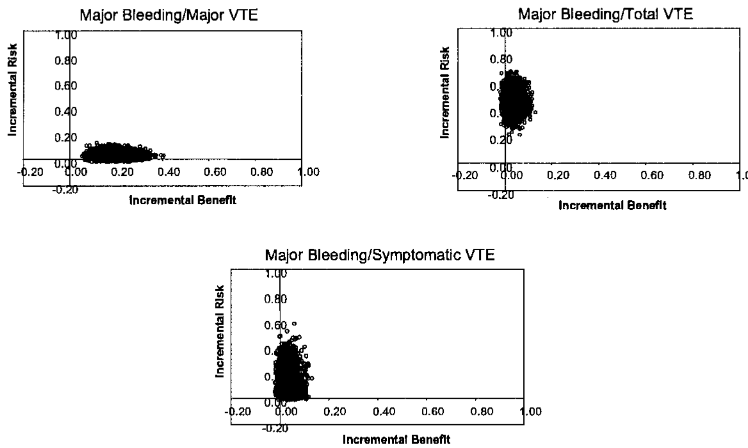

Figure S59. Risk benefit planes showing paired observations of incremental benefit and incremental risk of fondaparinux compared to placebo. VTE Venous thromboembolism.

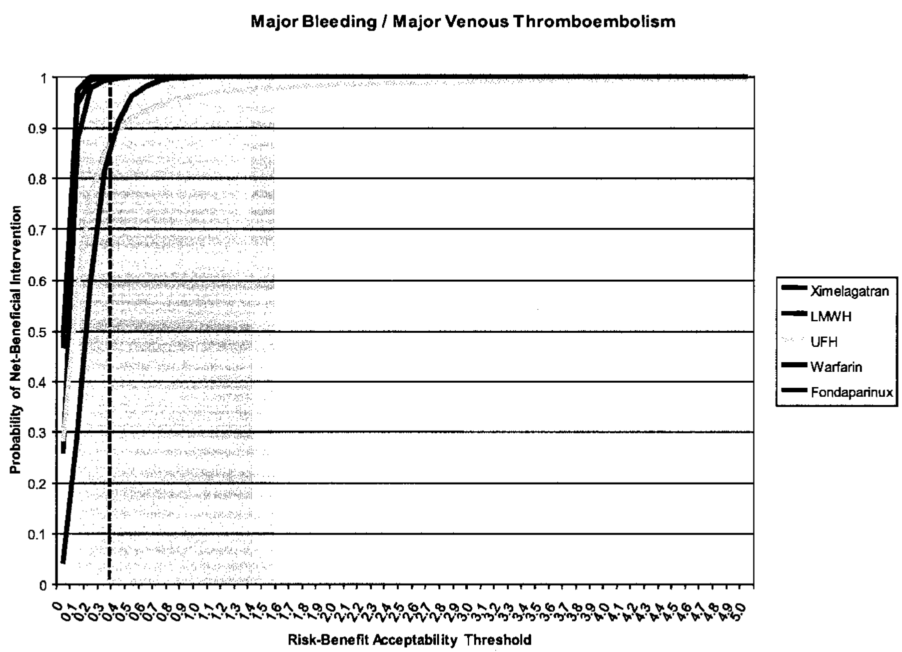

Figure S60. Risk-benefit acceptability curves for major bleeding and major venous thromboembolism in all patients. Each curve represents the probability that the drug is net-beneficial relative to placebo at a given value of the risk-benefit acceptability threshold using major bleeding as cost and major venous thromboembolism as benefit. The dashed line represents the case fatality rate ratio of major venous thromboembolism to major bleeding and the shadowed area represents its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

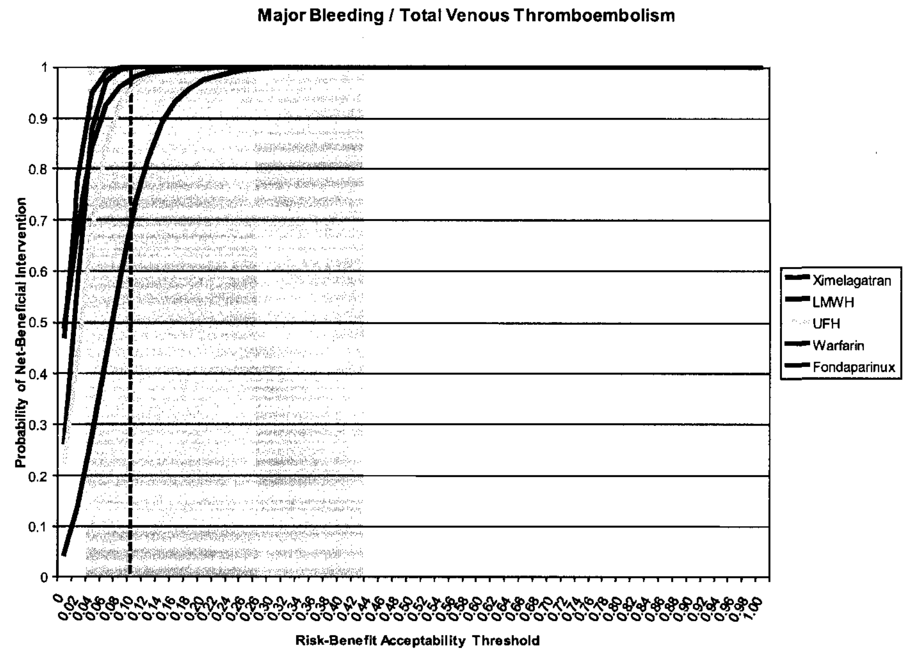

Figure S61. Risk-benefit acceptability curves for major bleeding and total venous thromboembolism in all patients. Each curve represents the probability that the drug is net-beneficial relative to placebo at a given value of the risk-benefit acceptability threshold using major bleeding as cost and total venous thromboembolism as benefit. The dashed line represents the case fatality rate ratio of total venous thromboembolism to major bleeding and the shadowed area represents its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

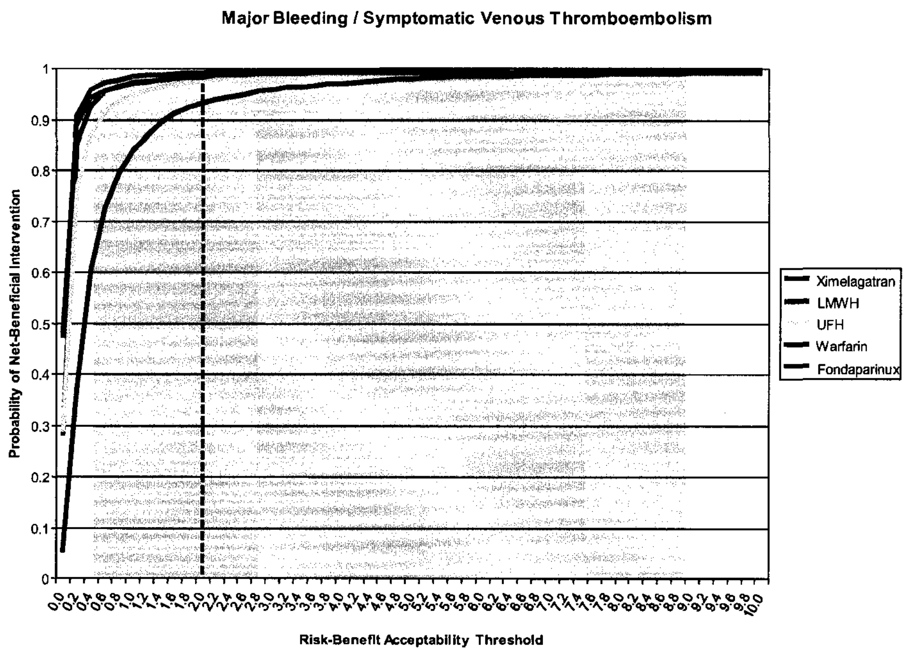

Figure S62. Risk-benefit acceptability curves for major bleeding and symptomatic venous thromboembolism in all patients. Each curve represents the probability that the drug is net-beneficial relative to placebo at a given value of the risk-benefit acceptability threshold using major bleeding as cost and symptomatic venous thromboembolism as benefit. The dashed line represents the case fatality rate ratio of symptomatic venous thromboembolism to major bleeding and the shadowed area represents its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

Appendix III. Clinical cost-effectiveness analysis after excluding ximelagatran

During the conduct of the study ximelagatran was withdrawn from the market by the manufacturer, therefore a second analysis after its exclusion was done. The results showed that the agent of choice varied according to the outcome of interest and the level of risk acceptance as can be seen if the reference risk acceptance threshold was set using different bleeding definitions. It should also be noted that although the probabilities varied, in general there was no concordance between major and total or symptomatic VTE regarding which should be the agent of choice.

Analysis in all patients is shown in figures S63-S65 and in table S2. In the analysis of major VTE in all patients the preferred agent would be warfarin at the reference RBAT; however, when analyzing total and symptomatic VTE, the preferred agent would be low molecular weight heparin. If higher RBAT are considered (such as the one calculated from ISTH-like bleeding definitions) then the choice between warfarin or low molecular weight heparin and fondaparinux might be indifferent.

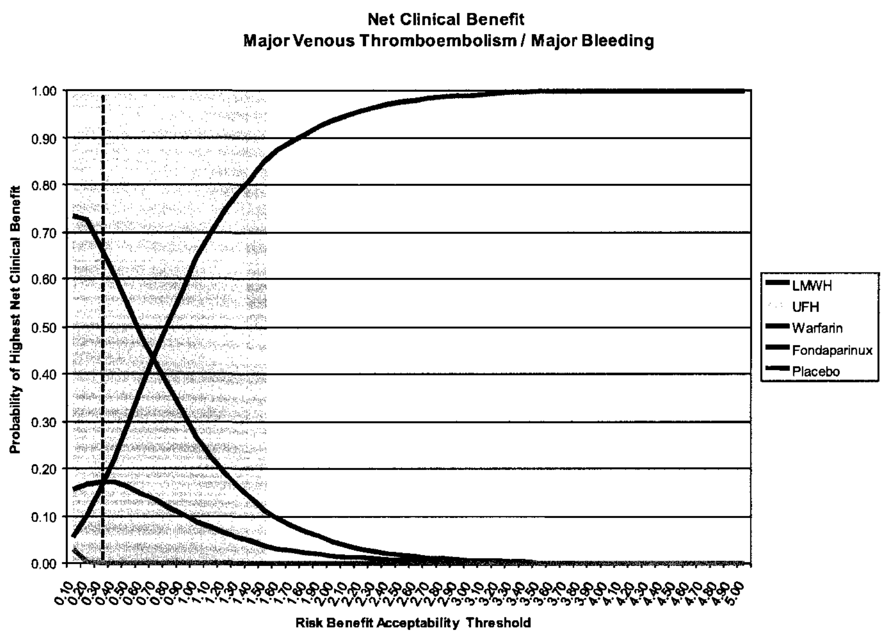

Figure S63. Net clinical benefit probability curves for major venous thromboembolism and major bleeding in all patients after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

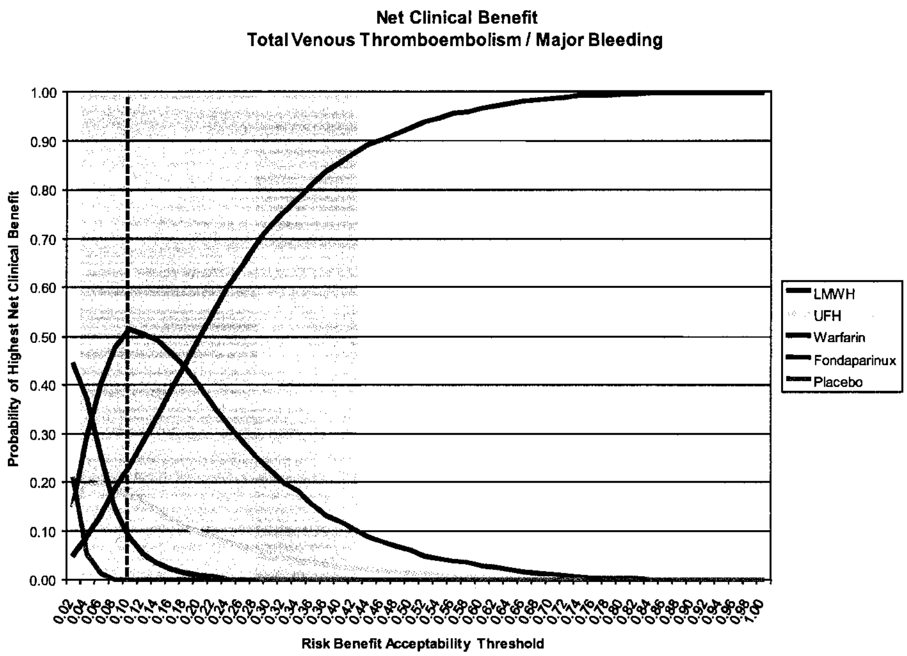

Figure S64. Net clinical benefit probability curves for total venous thromboembolism and major bleeding in all patients after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

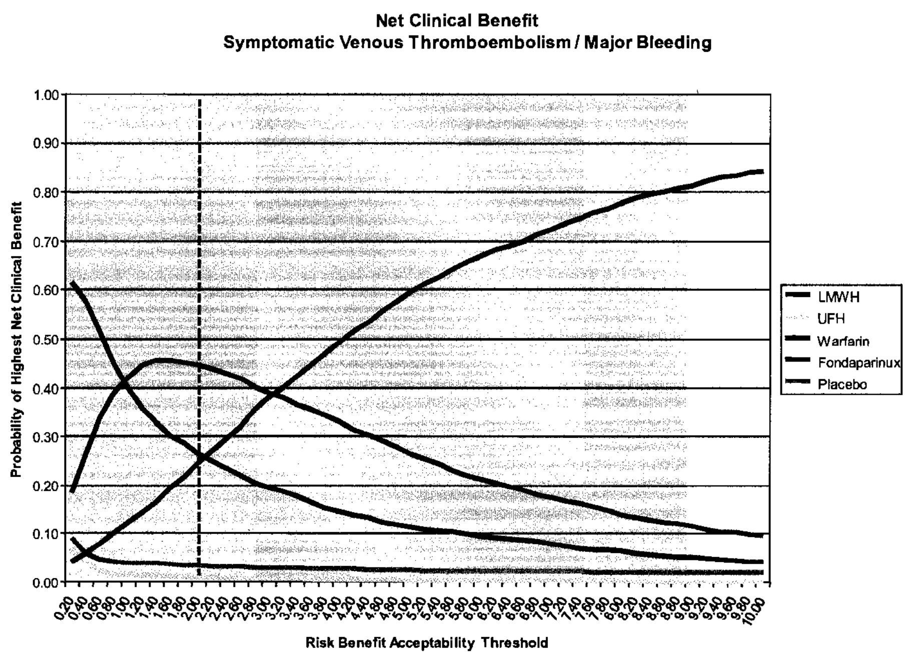

Figure S65. Net clinical benefit probability curves for symptomatic venous thromboembolism and major bleeding in all patients after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

Table S2. Probability (%) of obtaining the highest net clinical benefit for each agent used for venous thromboembolism prophylaxis in patients undergoing major orthopedic surgery according to different risk-benefit acceptability thresholds estimated from case fatality rate-ratios. Sub-analysis after excluding ximelagatran [a]

Outcome / Anticoagulant	*Case Fatality Rate – Ratio of* Major Venous Thromboembolism to Major Bleeding		Total Venous Thromboembolism to Major Bleeding		Symptomatic Venous Thromboembolism to Major Bleeding	
	All bleeding definitions	*ISTH-like bleeding definition*	*All bleeding definitions*	*ISTH-like bleeding definition*	*All bleeding definitions*	*ISTH-like bleeding definition*
Major Venous Thromboembolism						
Placebo	**0.1**	**0.0**	3.0	0.1	0.0	0.0
LMWH	**16.9**	**4.9**	15.9	17.0	1.5	0.0
UFH	**0.0**	**0.0**	2.1	0.0	0.0	0.0
Warfarin	**61.5**	**14.8**	73.3	63.5	4.0	0.0
Fondaparinux	**21.5**	**80.3**	5.7	19.4	94.5	100.0
Total Venous Thromboembolism						
Placebo	0.0	0.0	**0.0**	**0.0**	0.0	0.0
LMWH	12.4	0.0	**51.4**	**15.8**	0.0	0.0
UFH	3.0	0.0	**17.0**	**3.6**	0.0	0.0
Warfarin	0.0	0.0	**8.2**	**0.0**	0.0	0.0
Fondaparinux	84.6	100.0	**23.4**	**80.6**	100.0	100.0
Symptomatic Venous Thromboembolism						
Placebo	6.0	3.8	14.5	6.3	**3.3**	**2.1**
LMWH	26.1	45.6	13.2	25.2	**44.2**	**16.6**
UFH	4.1	1.4	9.2	4.3	**0.9**	**0.1**
Warfarin	57.9	33.1	59.9	58.7	**25.8**	**7.3**
Fondaparinux	5.8	16.1	3.2	5.4	**25.7**	**73.9**

ISTH International Society on Thrombosis and Haemostasis; LMWH Low molecular weight heparin; UFH Unfractionated heparin
[a] Bold numbers indicate the results of the ideal combination of outcome and risk-benefit acceptability threshold

III.1 Sub-analysis according to type of surgery

Total hip replacement. When analyzing only patients undergoing total hip replacement it was found that for major VTE the agent of choice was warfarin (Fig. S66) but for total VTE it was low molecular weight heparin (Fig. S67). There was no correlation between major, total or symptomatic VTE (Fig. S66-S68, table S3), however it has to be said that the number of informative studies for symptomatic VTE was rather low, and therefore the results regarding this outcome should be interpreted cautiously.

It was again observed that at high values of the RBAT fondaparinux was the dominant intervention when analyzing major and total VTE. A consistent finding was that unfractionated heparin was never the agent of choice.

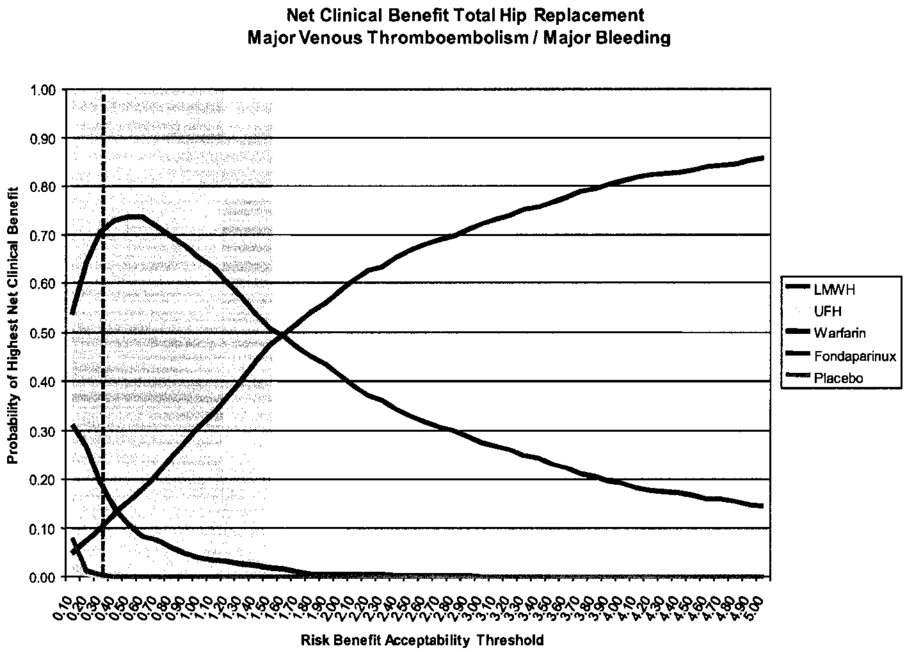

Figure S66. Net clinical benefit probability curves for major venous thromboembolism and major bleeding in patients undergoing total hip replacement after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

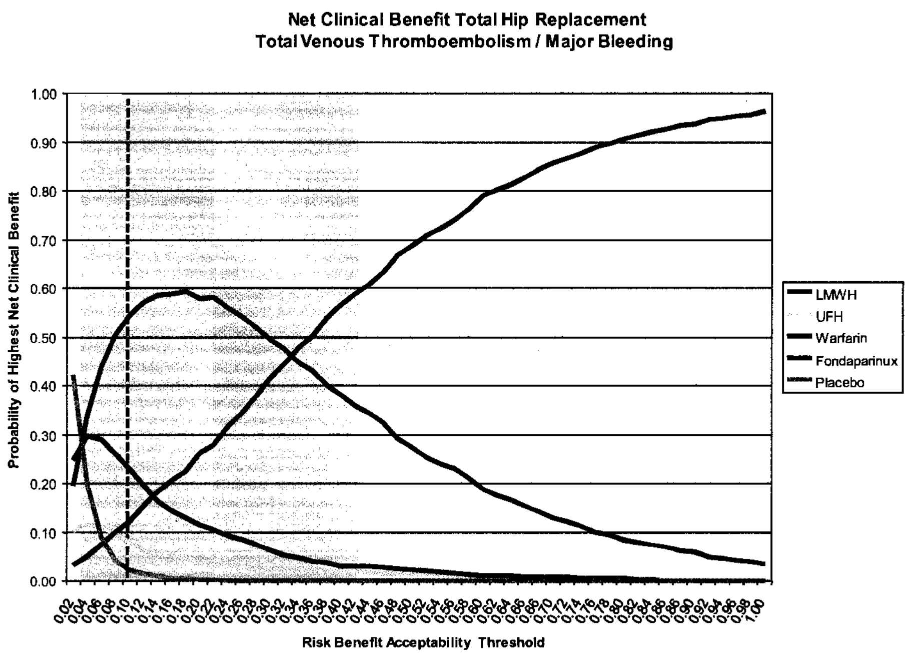

Figure S67. Net clinical benefit probability curves for total venous thromboembolism and major bleeding in patients undergoing total hip replacement after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

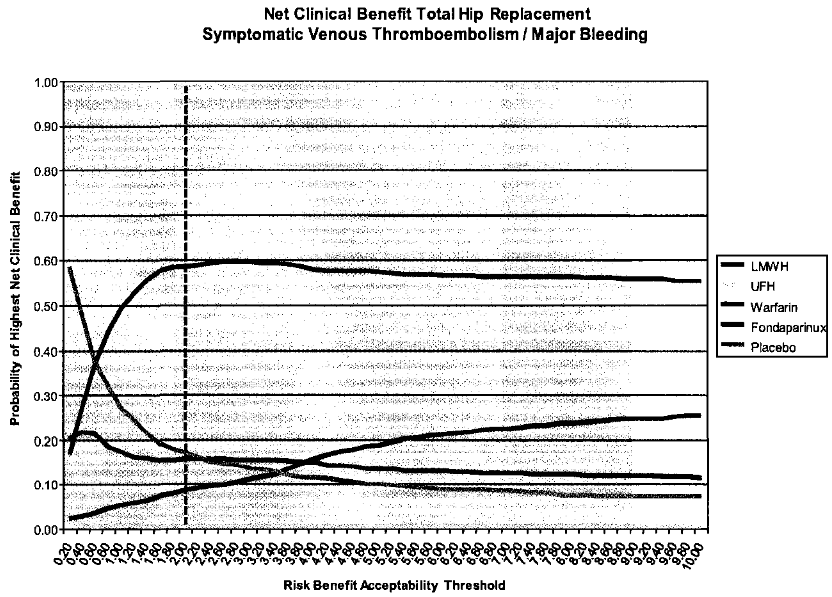

Figure S68. Net clinical benefit probability curves for symptomatic venous thromboembolism and major bleeding in patients undergoing total hip replacement after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

Table S3. Probability (%) of obtaining the highest net clinical benefit for each agent according to different risk-benefit acceptability thresholds estimated from case fatality rate-ratios. Sub-analysis in patients undergoing total hip replacement after excluding ximelagatran [a]

Outcome / Anticoagulant	*Case Fatality Rate – Ratio of* Major Venous Thromboembolism to Major Bleeding: All bleeding definitions	Major Venous Thromboembolism to Major Bleeding: ISTH-like bleeding definition	Total Venous Thromboembolism to Major Bleeding: All bleeding definitions	Total Venous Thromboembolism to Major Bleeding: ISTH-like bleeding definition	Symptomatic Venous Thromboembolism to Major Bleeding: All bleeding definitions	Symptomatic Venous Thromboembolism to Major Bleeding: ISTH-like bleeding definition
Major Venous Thromboembolism						
Placebo	**0.2**	**0.0**	7.7	0.2	0.0	0.0
LMWH	**14.7**	**2.3**	31.2	16.2	0.5	0.0
UFH	**0.0**	**0.0**	2.3	0.0	0.0	0.0
Warfarin	**72.9**	**55.0**	54.0	72.1	39.2	10.4
Fondaparinux	**12.2**	**42.7**	4.8	11.5	60.3	89.6
Total Venous Thromboembolism						
Placebo	0.1	0.0	**2.1**	**0.1**	0.0	0.0
LMWH	39.1	1.5	**55.2**	**43.6**	0.1	0.0
UFH	2.1	0.0	**7.8**	**2.5**	0.0	0.0
Warfarin	3.2	0.0	**22.3**	**4.2**	0.0	0.0
Fondaparinux	55.5	98.5	**12.6**	**49.6**	99.9	100.0
Symptomatic Venous Thromboembolism						
Placebo	48.0	22.5	63.7	50.3	**16.8**	**8.4**
LMWH	26.6	55.2	12.0	24.7	**58.5**	**56.2**
UFH	0.7	0.4	4.2	0.7	**0.4**	**0.4**
Warfarin	21.8	15.5	18.0	21.5	**15.5**	**12.1**
Fondaparinux	2.9	6.4	2.1	2.8	**8.8**	**22.9**

ISTH International Society on Thrombosis and Haemostasis; LMWH Low molecular weight heparin; UFH Unfractionated heparin
[a] Bold numbers indicate the results of the ideal combination of outcome and risk-benefit acceptability threshold. The box indicates the results of the primary analysis

***Total knee replacement*.** The analysis of patients undergoing total knee replacement is shown in figures S69-S71 and table S4. When analyzing patients undergoing total knee replacement it was observed that for major, total or symptomatic VTE, the agent most likely to derive the highest net clinical benefit was fondaparinux at almost all RBAT values. When analyzing major VTE at very low RBAT values (high risk aversion), the choice would probably be indifferent between fondaparinux and warfarin.

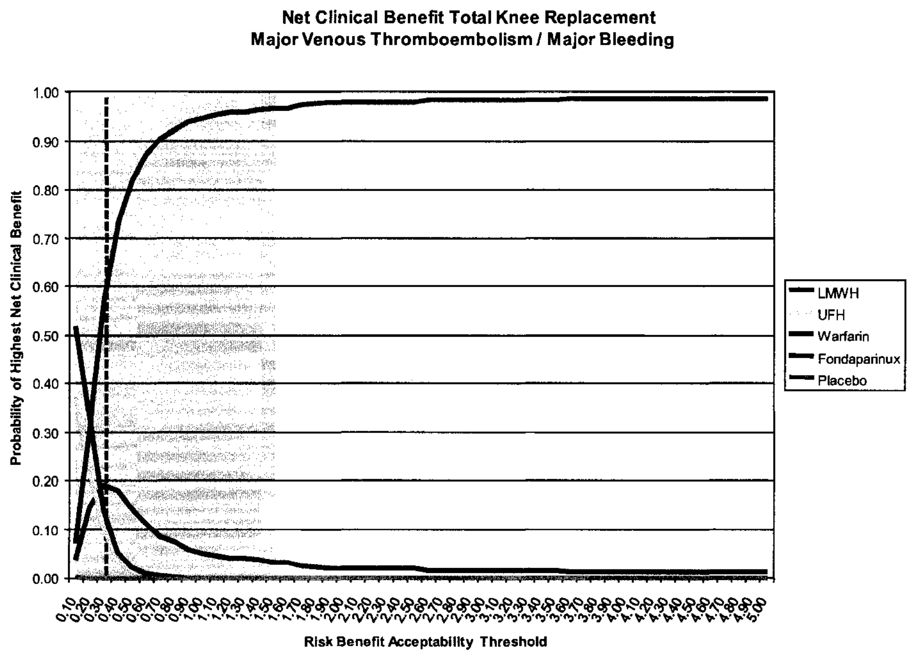

Figure S69. Net clinical benefit probability curves for major venous thromboembolism and major bleeding in patients undergoing total knee replacement after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

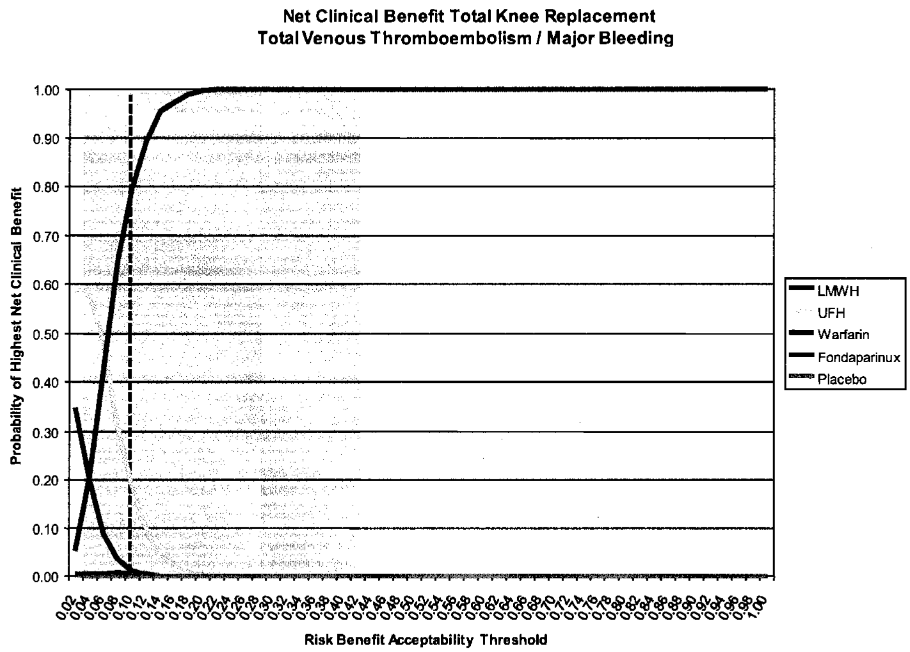

Figure S70. Net clinical benefit probability curves for total venous thromboembolism and major bleeding in patients undergoing total knee replacement after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

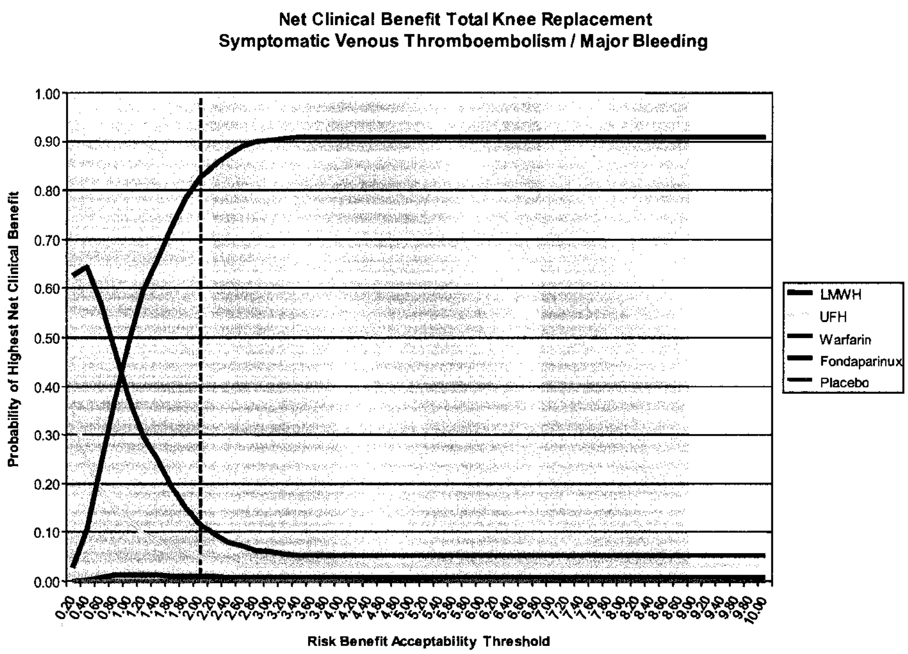

Figure S71. Net clinical benefit probability curves for symptomatic venous thromboembolism and major bleeding in patients undergoing total knee replacement after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

Table S4. Probability (%) of obtaining the highest net clinical benefit for each agent according to different risk-benefit acceptability thresholds estimated from case fatality rate-ratios. Sub-analysis in patients undergoing total knee replacement after excluding ximelagatran [a]

	Case Fatality Rate – Ratio of					
Outcome / Anticoagulant	*Major Venous Thromboembolism to Major Bleeding*		*Total Venous Thromboembolism to Major Bleeding*		*Symptomatic Venous Thromboembolism to Major Bleeding*	
	All bleeding definitions	*ISTH-like bleeding definition*	*All bleeding definitions*	*ISTH-like bleeding definition*	*All bleeding definitions*	*ISTH-like bleeding definition*
Major Venous Thromboembolism						
Placebo	**0.0**	**0.0**	0.4	0.0	0.0	0.0
LMWH	**18.5**	**3.7**	3.8	19.1	2.0	1.1
UFH	**4.6**	**0.1**	37.1	6.7	0.1	0.1
Warfarin	**5.3**	**0.0**	51.1	8.1	0.0	0.0
Fondaparinux	**71.6**	**96.2**	7.6	66.1	97.9	98.8
Total Venous Thromboembolism						
Placebo	0.0	0.0	**0.0**	**0.0**	0.0	0.0
LMWH	0.0	0.0	**0.6**	**0.0**	0.0	0.0
UFH	0.0	0.0	**17.8**	**0.0**	0.0	0.0
Warfarin	0.0	0.0	**1.2**	**0.0**	0.0	0.0
Fondaparinux	100.0	100.0	**80.4**	**100.0**	100.0	100.0
Symptomatic Venous Thromboembolism						
Placebo	0.0	0.0	0.0	0.0	**0.0**	**0.0**
LMWH	0.3	1.3	0.1	0.3	**0.9**	**0.8**
UFH	25.3	8.4	41.9	26.8	**4.8**	**3.1**
Warfarin	64.6	25.7	57.0	64.6	**11.0**	**5.2**
Fondaparinux	9.8	64.6	1.0	8.3	**83.3**	**90.9**

ISTH International Society on Thrombosis and Haemostasis; LMWH Low molecular weight heparin; UFH Unfractionated heparin
[a] Bold numbers indicate the results of the ideal combination of outcome and risk-benefit acceptability threshold. The box indicates the results of the primary analysis

III.2 Sub-analysis according to timing of administration

In the analysis according to the initial timing of administration of the prophylaxis (Fig. S72-S73 and table S5) it can be seen that at low levels of the RBAT, such as the reference value (calculated using all bleeding definitions), the agent of choice would be LMWH administered postoperatively, if analyzed by major VTE, or LMWH administered preoperatively, if analyzed by total VTE. Fondaparinux, which was always administered in close proximity to the time of the surgery, was only the agent of choice at higher levels of risk acceptance. Of note, when considering total VTE, fondaparinux became the agent of choice at values of the RBAT that were well within the 95% CI around the reference RBAT. This was not the case when analyzed by major VTE, showing again that the choice of the outcome influences the selection of the agent.

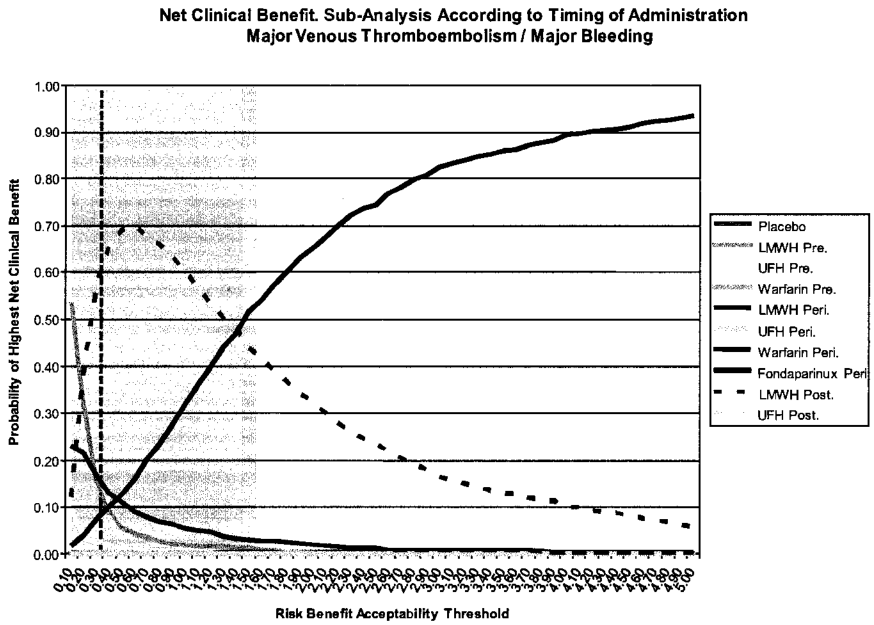

Figure S72. Net clinical benefit probability curves for major venous thromboembolism and major bleeding in all patients analyzed according to timing of administration after excluding ximelagatran from the analysis. Curves represent the probability of having the highest net clinical benefit. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin; Pre Preoperative (up 2 hours before surgery) ; Peri Perioperative (within 2 hours before and up to 12 hours after surgery); Pos Postoperative (12 hours or more after surgery).

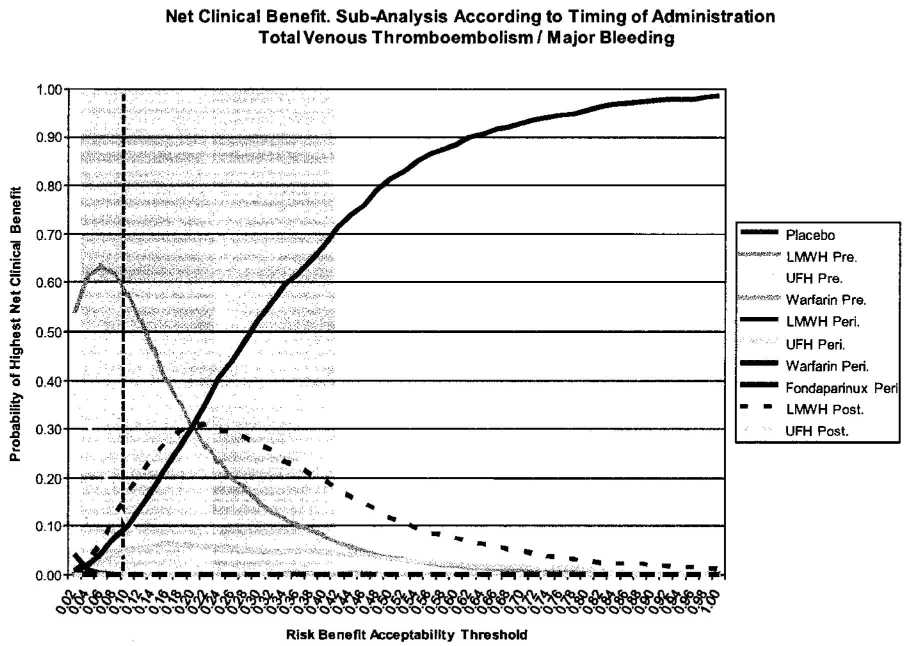

Figure S73. Net clinical benefit probability curves for total venous thromboembolism and major bleeding in all patients according to timing of administration after excluding ximelagatran from the analysis. Curves represent the probability of having the highest net clinical benefit. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin; Pre Preoperative (up 2 hours before surgery) ; Peri Perioperative (within 2 hours before and up to 12 hours after surgery); Pos Postoperative (12 hours or more after surgery).

Table S5. Probability (%) of obtaining the highest net clinical benefit for each agent according to different risk-benefit acceptability thresholds estimated from case fatality rate-ratios. Sub-analysis according to timing of administration after excluding ximelagatran [a]

Outcome / Anticoagulant / Timing		Case Fatality Rate – Ratio of: Major Venous Thromboembolism to Major Bleeding		Total Venous Thromboembolism to Major Bleeding		Symptomatic Venous Thromboembolism to Major Bleeding	
		All bleeding definitions	ISTH-like bleeding definition	All bleeding definitions	ISTH-like bleeding definition	All bleeding definitions	ISTH-like bleeding definition
Major Venous Thromboembolism							
	Placebo	**0**	**0**	0.2	0	0	0
Pre	LMWH	**9.3**	**1.3**	53.2	10.8	0.2	0
Pre	UFH	**2**	**0.3**	9.2	2.3	0.1	0
Pre	Warfarin	**0**	**0**	0	0	0	0
Peri	LMWH	**0**	**0.2**	0	0	0.2	0.2
Peri	UFH	**0**	**0**	0	0	0	0
Peri	Warfarin	**13.3**	**3.4**	23.1	14.3	1.8	0.1
Peri	Fondaparinux	**9.9**	**45.6**	1.8	9	67.3	96.7
Pos	LMWH	**65.5**	**49.2**	12.5	63.6	30.4	3
Pos	UFH	**0**	**0**	0	0	0	0
Total Venous Thromboembolism							
	Placebo	0	0	**0**	**0**	0	0
Pre	LMWH	8.6	0.1	**57.3**	**10.3**	0	0
Pre	UFH	0.5	0	**10.3**	**0.7**	0	0
Pre	Warfarin	0.1	0	**0**	**0.1**	0	0
Peri	LMWH	0	0	**0**	**0**	0	0
Peri	UFH	4.7	0	**5.1**	**4.9**	0	0
Peri	Warfarin	0	0	**0**	**0**	0	0
Peri	Fondaparinux	65.9	99.6	**10.4**	**61.6**	99.9	99.9
Pos	LMWH	20.2	0.3	**16.9**	**22.4**	0.1	0.1
Pos	UFH	0	0	**0**	**0**	0	0

ISTH International Society on Thrombosis and Haemostasis; LMWH Low molecular weight heparin; UFH Unfractionated heparin Pre Preoperative (up 2 hours before surgery) ; Peri Perioperative (within 2 hours before and up to 12 hours after surgery); Pos Postoperative (12 hours or more after surgery)

[a] Bold numbers indicate the results of the ideal combination of outcome and risk-benefit acceptability threshold. The box indicates the results of the primary analysis

Appendix IV. Sensitivity analysis according to type of major bleeding definition

The sensitivity analysis according to the type of major bleeding definition is shown for all agents (Figs. S74 and S75) and also after excluding ximelagatran (Figs. S76 and S77). These figures show the net clinical benefit probability curves obtained when only studies using an ISTH-like bleeding definition were included. It can be easily seen that the curves are very similar to the ones obtained using all studies. Figures S78 and S79 show the results that were obtained from studies using a non ISTH-like bleeding definition. These curves only include three agents, namely LMWH, UFH and warfarin, because no study evaluating ximelagatran or fondaparinux used a non ISTH- like bleeding definition. Therefore, this subgroup analysis must be interpreted with precaution, because its results are not comparable to the results of the main analysis due to the non inclusion of the aforementioned agents.

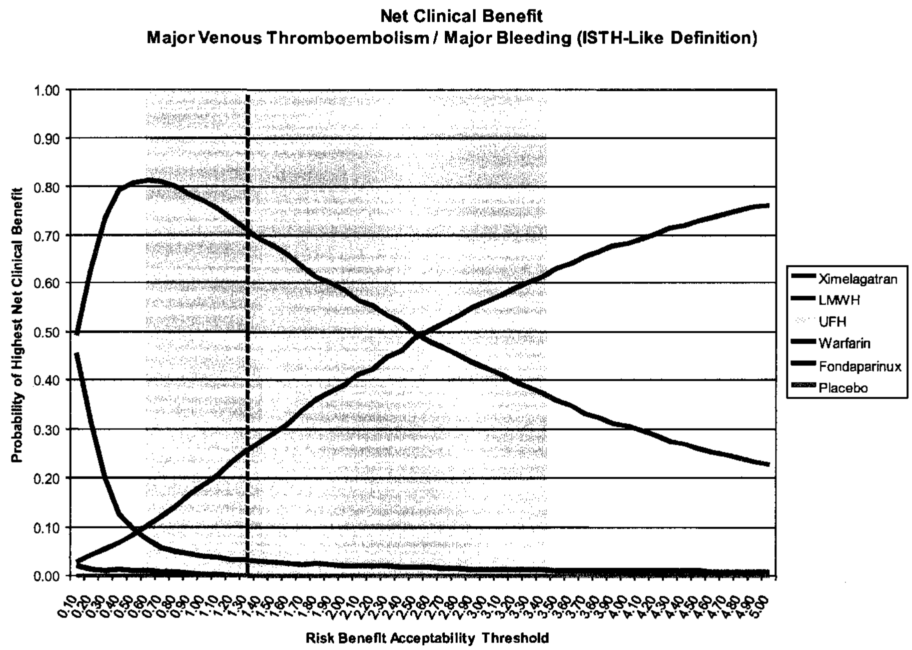

Figure S74. Net clinical benefit probability curves for major venous thromboembolism and major bleeding in all patients in studies using an ISTH-like definition of major bleeding. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

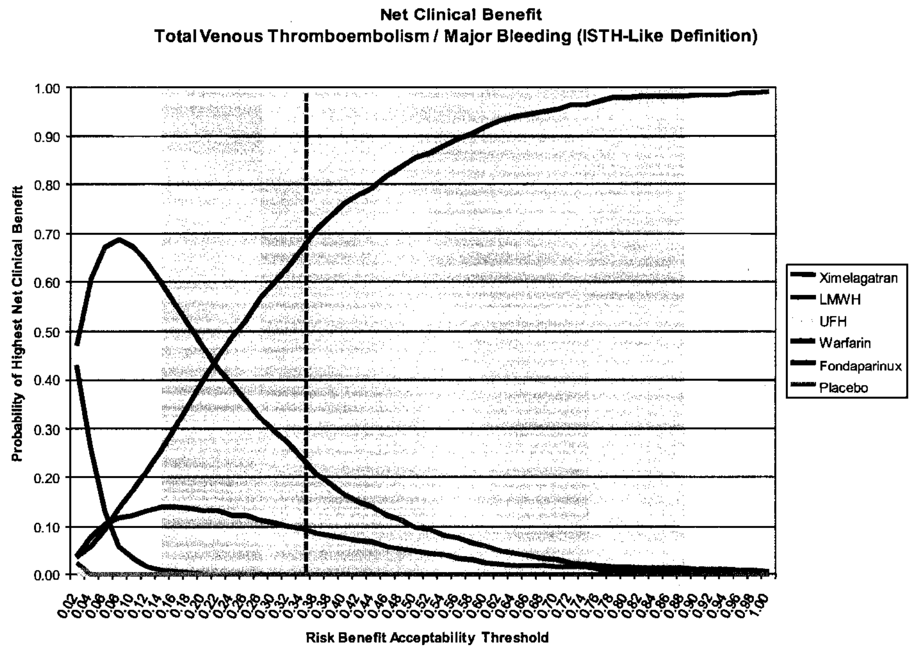

Figure S75. Net clinical benefit probability curves for total venous thromboembolism and major bleeding in all patients in studies using an ISTH-like definition of major bleeding. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

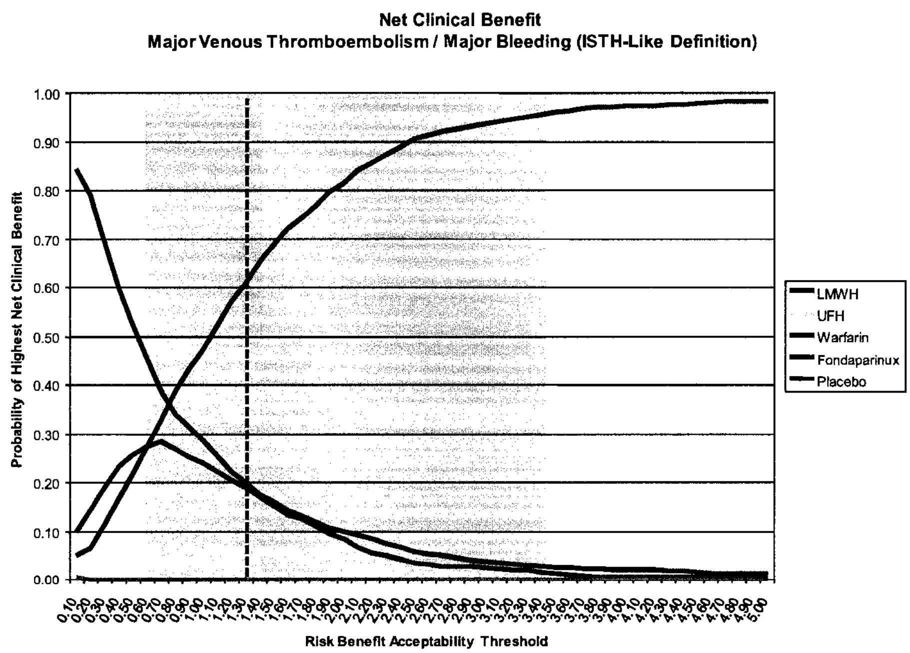

Figure S76. Net clinical benefit probability curves for major venous thromboembolism and major bleeding in all patients in studies using an ISTH-like definition of major bleeding, after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

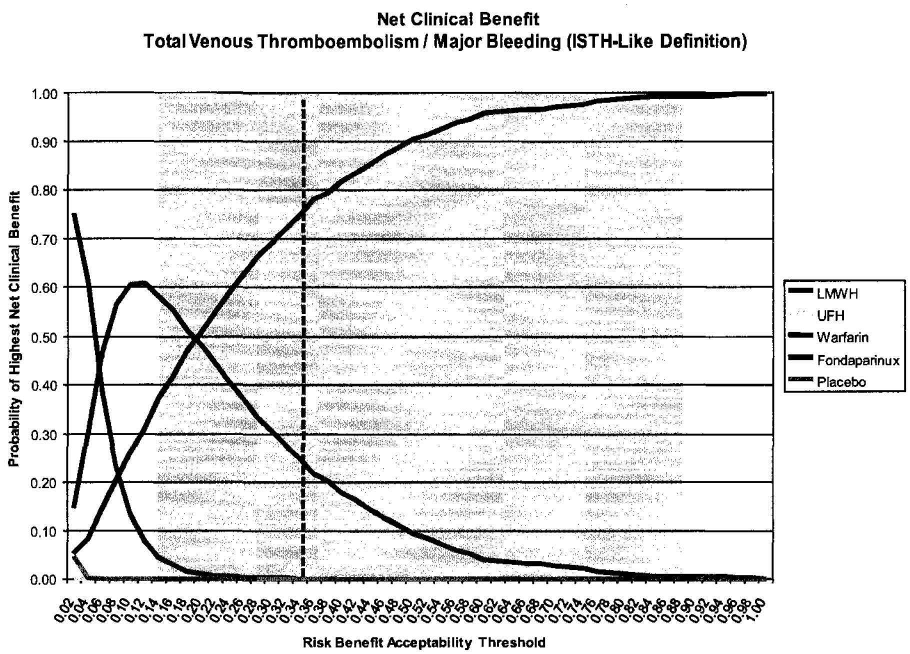

Figure S77. Net clinical benefit probability curves for total venous thromboembolism and major bleeding in all patients in studies using an ISTH-like definition of major bleeding, after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

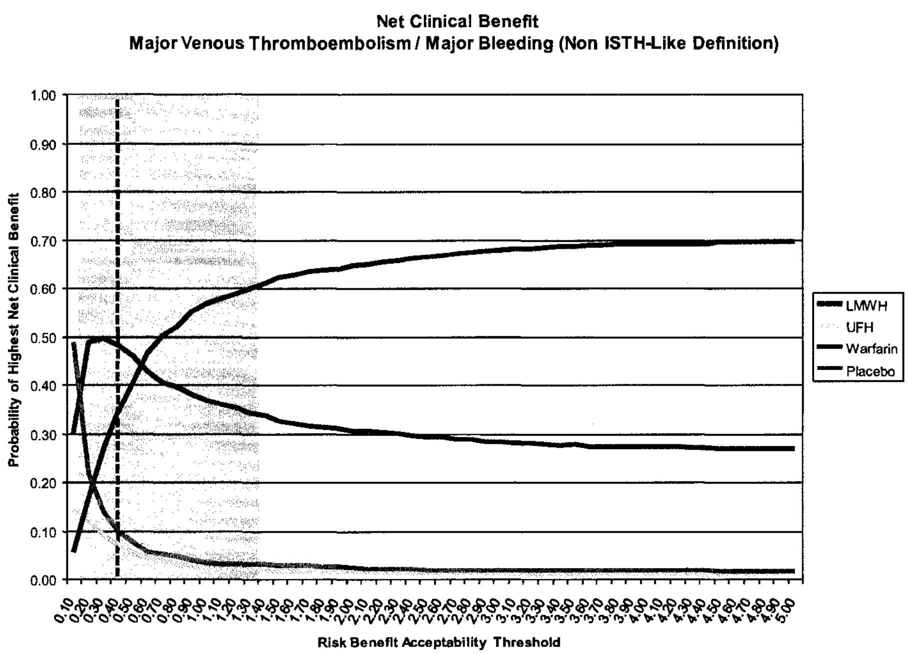

Figure S78. Net clinical benefit probability curves for major venous thromboembolism and major bleeding in all patients in studies not using an ISTH-like definition of major bleeding. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.

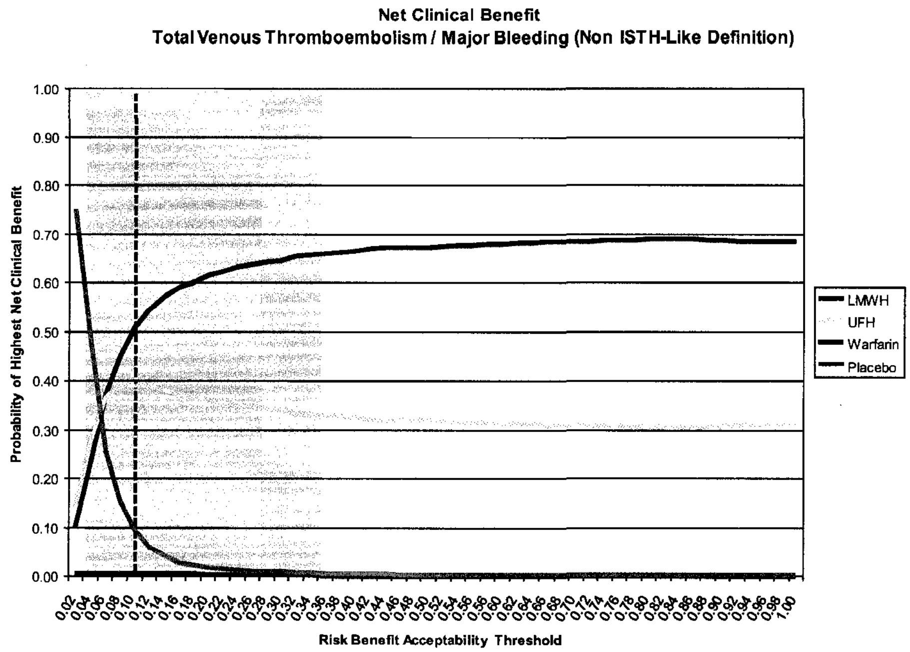

Figure S79. Net clinical benefit probability curves for total venous thromboembolism and major bleeding in all patients in studies not using an ISTH-like definition of major bleeding, after excluding ximelagatran from the analysis. Each curve represents the probability that the drug has of having the highest net clinical benefit across a range of risk-benefit acceptability thresholds. The reference threshold is indicated by the vertical line with the shadowed area indicating its 95% confidence interval. LMWH Low molecular weight heparin; UFH Unfractionated heparin.