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PlasmaFlow allows a multimodal approach for venous thromboembolism (VTE) for high-risk orthopedic surgery patients. Current board guidelines indicate that aspirin is not appropriate as the only option for the prevention of DVT.

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To Whom It May Concern:

Thank you for taking the time to evaluate the PlasmaFlow portable sequential device. Per your request, we have attached our value analysis packet, presentation, and clinical studies.

Attached are the clinical studies.
1. Journal of Arthroplasty - The DVT rate for the post discharge Aspirin and Portable Mechanical Compression therapy group was 0% and 23.1% for the inpatient only SCDs and 325 mg of aspirin.
2. JBJS Study - Sequential devices (PlasmaFlow) are clinically equivalent to decrease risk of Blood Clots instead of using a pharmacologic option which may increase your bleed risks.
3. AAOS - Mechanical Prophylaxis dissertation. 895 Page AAOS but specifically highlighted mechanical.
4. Center for Disease Control - Hospitals should adopt a risk
5. AAOS Clot formation - 2009 - The risk of development is two to five days after surgery; a second peak development period occurs about 10 days after surgery, after most patients have been discharged from the hospital.

Bundled Payment Example - Average Medicare Bundled Payment for TJR = $26,000. 34% of that payment is for the 90 days of post op care after surgery--$8,840

ManaMed is introducing a new solution for your hospital's SCD program. We would like for your hospital to evaluate PlasmaFlow, a portable sequential device for the Comprehensive Joint Replacement program and the changes in insurance reimbursement. The PlasmaFlow is intended to be an easy to use portable system, prescribed by a physician, for use in the home or clinical setting to help prevent blood clots. The goal is to eliminate readmissions (which are not reimbursable events), mitigate the risk of blood clots, and to improve HCAHPS scores.

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- Non-Ambulatory hospital patients
- OBGYN – C sections and high risk pregnancies
- GI Bleed patients with high risk of DVT
- Patients with a low platelet count

Please let me know what the next steps are to schedule a follow up meeting to start the value analysis.

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Primary Arthroplasty

Efficacy in Deep Vein Thrombosis Prevention With Extended Mechanical Compression Device Therapy and Prophylactic Aspirin Following Total Knee Arthroplasty: A Randomized Control Trial

Mark A. Snyder, MD [a], Alexandra N. Sympson, BA, CCRC [b, *], Christina M. Scheuerman, RN, BSN, CCRC [b], Justin L. Gregg, MA, BDSCP [b], Lala R. Hussain, MSc, MHA [b]

[a] Trihealth Orthopaedic and Sports Institute, Cincinnati, Ohio
[b] Trihealth Hatton Research Institute, Good Samaritan Hospital, Cincinnati, Ohio

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ABSTRACT

Background: Aspirin at 325 mg twice daily is now included as a nationally approved venous thromboembolism (VTE) prophylaxis protocol for low-risk total knee arthroplasty (TKA) patients. The purpose of this study is to examine whether there is a difference in deep vein thrombosis (DVT) occurrence after a limited tourniquet TKA using aspirin-based prophylaxis with or without extended use of mechanical compression device (MCD) therapy.

Methods: One hundred limited tourniquet TKA patients, whose DVT risk was managed with aspirin 325 mg twice daily for 3 weeks, were randomized to either using an MCD during hospitalization only or extended use at home up to 6 weeks postoperatively. Lower extremity duplex venous ultrasonography (LEDVU) was completed on the second postoperative day, 14 days postoperatively, and at 3 months postoperatively to confirm the absence of DVT after treatment.

Results: The DVT rate for the postdischarge MCD therapy group was 0% and 23.1% for the inpatient MCD group ($P < .001$). All DVTs resolved by 3 months postoperatively. Patient satisfaction was 9.56 (±0.82) for postdischarge MCD patients vs 8.50 (±1.46) for inpatient MCD patients ($P < .001$).

Conclusion: Limited tourniquet TKA patients who were mobilized early, managed with aspirin for 3 weeks postoperatively, and on MCD therapy for up to 6 weeks postoperatively experienced superior DVT prophylaxis than patients receiving MCD therapy only as an inpatient ($P < .05$). The 0% incidence of nonsymptomatic DVTs prevented by aspirin and extended-use MCD further validates this type of prophylaxis in low DVT risk TKA patients.

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Among total joint surgery complications, the risk of venous thromboembolism (VTE) is of the utmost concern warranting VTE prophylaxis in even low-risk patients. Patients undergoing total knee arthroplasty (TKA) are particularly at risk of VTE with an incidence rate of 17%-53% depending on the method of prevention [1], therein warranting routine prevention in even low-risk patients [2-7]. Standard of care guidelines implemented by the American Academy of Orthopedic Surgeons (AAOS) have mandated a regimen of thromboprophylaxis for all total hip or knee arthroplasty patients and have outlined those regimens with updated research evidence, taking into account the patient's history and risk of thrombosis [2]. The 2014 guidelines on VTE management are the result of the Surgical Care Improvement Project, a national partnership of organizations including the Joint Commission and the Centers for Medicare and Medicaid Services, with the goal of reducing surgical complications and publishing a uniform set of national hospital quality measures. This goal is currently limited by the lack of conclusive evidence that would allow the endorsement of one regimen over another, and so the prevention method of choice remains controversial [2]. The conflicting evidence is well

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* Reprint requests: Alexandra N. Sympson, BA, CCRC, Trihealth Hatton Research Institute, Good Samaritan Hospital, 375 Dixmyth Avenue, Cincinnati, OH 45220.

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documented in the AAOS Guidelines citing such reasons as lack of standardized drug doses, unstandardized routes of administration, unstandardized durations of therapy, a dearth of placebo-controlled studies, as well as nonrepresentative research populations, or underpowered studies [2].

The AAOS guidelines have been revised to include aspirin in the list of acceptable thromboprophylactic regimens [2]. In a large level II evidence registry study, 3060 total joint arthroplasty patients receiving at least 10 days of MCD with or without aspirin were found to have similar incidence of VTE to patients receiving standard chemoprophylactics [3]. The AAOS recognizes that a surgeon may prefer to administer the safe and convenient aspirin over other common chemoprophylactic agents [7]. When using aspirin, the AAOS advises the addition of a mechanical compression device (MCD) to increase the efficacy of aspirin in VTE prevention [2].

MCDs have an assortment of modalities, such as pneumatic compression or sequential compression; although there is inconclusive evidence as to effectiveness between processes, MCDs are thought to influence Virchow's triad by reducing venous stasis, thereby reducing the incidence of DVT or PE [7,8]. When used in combination with the AAOS-indicated antiplatelet agent, aspirin, adequate thromboprophylaxis may be obtained, reducing the risk of debilitating side effects or severe bleeding associated with warfarin and other chemoprophylactics.

Differences among MCD products, or what modality of compression they employ, do not appear to have an impact on efficacy of thromboprophylaxis. The most marked indication of thromboprophylaxis is patient compliance, and the location of the compression [8]. Thus, ease of operation, reliability, and the ability to gauge compliance may be the most relevant features of an effective MCD.

The Cothera VPULSE Compression and Cold Therapy System (Cothera, LLC, Plano, TX) was FDA approved in 2013 and is designed for home use allowing extended postoperative therapy. The VPULSE device has the ability to provide intermittent sequential pneumatic compression for the prevention of venous thrombosis related to hospitalization [9], therein fulfilling the AAOS requirements following TKA [2]. The device is designed to be user-friendly and records usage data which will be instrumental for monitoring patient compliance for the purposes of this study [9].

As a multifactorial disease, VTE onset may occur during the knee surgery through periods of high flexion and tourniquet use; thus, VTE prophylaxis safety and efficacy may be maximized by the implementation of a multimodal thromboprophylactic regimen [7,10,11]. Multimodal enhancements strengthen protocols for VTE prevention in TKA patients. The use of a tourniquet during the TKA procedure results in venous stasis, trauma to the endothelium of deep veins in the leg, hypoxia of the leg, and increased clotting factors upon release of the tourniquet [7,11]. When compared with standard tourniquet utilization during TKA, a minimized tourniquet technique is associated with a lower rate of VTE [12]. Recent evidence suggests that postoperative recovery and early range of motion of the knee may be superior in a minimized tourniquet procedure [13]. Lack of mobilization may facilitate venous stasis and as such is a contributing factor for DVT, which makes early mobilization of the patient crucial in a multimodal regimen [14]. This study attempts to provide a randomized control trial providing clarification on a multimodal VTE approach that includes rapid postoperative mobilization of the patient, limiting the use of a tourniquet to no more than 5 minutes during cementation, prophylactic aspirin, and MCD therapy.

Materials and Methods

This study was an institutional review board–approved, prospective, randomized, control trial conducted in Cincinnati Ohio. Primary total knee arthroplasty patients 18 years or older were included if they were determined to be at low risk of VTE. Patients were excluded if they had a high-risk body mass index of greater than 40 kg/m^2, had an American Society of Anesthesiologist score greater than III, and experience nonsteroidal anti-inflammatory drug intolerance, or any orthopedic or medical comorbidity that would prevent postoperative rapid mobilization and compliance with MCD use. All subjects consented into the study were randomized by the research coordinator in a 1:1 ratio to either group A or group B by a permuted mixed block size randomization table. Group A served as the control group, only receiving MCD therapy while an inpatient following total knee arthroplasty. Group B, the experimental group, continued the MCD therapy for up to 6 weeks following discharge from the hospital. All patients underwent a multimodal VTE prophylactic regimen consisting of administration of 1 g of preoperative tranexamic acid, and limiting tourniquet application to a maximum of 5 minutes only during exsanguination to improve cementation and to minimize blood loss. Early rapid mobilization was facilitated, and all subjects received prophylactic aspirin at 325 mg twice daily for 3 weeks immediately postoperatively. To standardize the therapy among groups, the MCD used was the Cothera VPULSE for all study patients. Use of the MCD was initiated immediately postoperatively and continued for at least 3 weeks, and up to 6 weeks depending on when the patients had their second postoperative visit scheduled.

Postoperatively, bilateral lower extremity duplex venous ultrasonography (LEDVU) was conducted on all patients 2 days postoperatively and at 2 weeks (14-19 days) postoperatively to detect the incidence of DVT. Patients were seen 10 days (±7 days) postoperatively in the surgeon's office for routine follow-up knee examination. Patients were also seen at 3-6 weeks postoperatively for routine follow-up and to complete an overall satisfaction assessment. The VPULSE data chip was collected for recording the total number of hours of MCD usage. Length of hospital stay (LOS) and 30-day adverse events were recorded, and overall patient satisfaction was evaluated with a 10-point Likert scale [15].

The 10-point Likert scale was determined to be the best way to keep track of patient satisfaction because of its consistency and reliability in conveying patient responses. Ten points were chosen to try and maximize reliability, validity, and discriminating power without comprising consistency or test-retest reliability [16]. On the last study visit of each patient, the study coordinator asked each participant, “Overall on a scale of 1 to 10, where 1 is very dissatisfied, 5 is neutral, and 10 is very satisfied, where would you rate your satisfaction with the total knee arthroplasty you have received from the start of the study to today?”. Although the study coordinator was not able to be blinded to the randomization groups, the question was asked in exactly the same way with each patient. There was no leading of the patient, and no further inquiry into the patient's satisfaction to avoid leading the study subject into a higher satisfaction score. These patient-reported satisfaction scores were collected to ascertain whether the patient associated the MCD usage as a burden for his or her overall patient experience.

The sample size was determined to be 100 patients based on a meta-analysis comparing DVT incidence among 4 commonly ascribed treatment regimens [1], understanding that no prior studies had combined the same regimen of 325 mg aspirin twice daily for 3 weeks postoperatively in conjunction with MCD therapy. The assumption was made that this sample size would suffice for a medium effect size at 80% power and alpha <.05. DVT incidence rate was determined to be the primary outcome, as analyzed by a univariate chi-square analysis.

All statistical analyses were performed using IBM SPSS Statistics for Windows version 21 (IBM Corporation, Armonk, NY). Demographic variables included patient age, gender, race, anesthesia

Table 1
Subject Demographics.

Demographics and Clinical Data	Total (N = 100), Mean (SD); n (%)	Postdischarge VPULSE (n = 48), Mean (SD); n (%)	Inpatient VPULSE (n = 52), Mean (SD); n (%)	*P* Value
Age (y)	62.76 (9.24)	59.85 (8.20)	65.44 (9.40)	.002
Gender				.369
Male	40 (40.0)	17 (35.4)	23 (44.2)	
Female	60 (60.0)	31 (64.6)	29 (55.8)	
Race		51 (100)	48 (100)	.367
Caucasian	98 (98.0)	47 (97.9)	51 (98.1)	
African American	1 (1.0)	1 (2.1)	0 (0.00)	
Other	1 (1.0)	0 (0.00)	1 (1.9)	
BMI	30.09 (4.22)	30.85 (4.17)	29.38 (4.18)	.081
Comorbidity				
Hypertension (yes)	39 (39.0)	17 (35.4)	22 (42.3)	.480
CAD (yes)	4 (4.0)	3 (6.3)	1 (1.9)	.279
Diabetes (yes)	8 (8.0)	2 (4.2)	6 (11.5)	.162
Anesthesia type				.645
General	11 (11.0)	6 (12.5)	5 (9.6)	
Spinal	89 (89.0)	42 (87.5)	47 (90.4)	
Other	1 (1.0)	0 (0.00)	1 (1.9)	
ASA score				.711
1	7 (7.0)	4 (8.3)	3 (5.8)	
2	62 (62.0)	29 (60.4)	33 (63.5)	
3	30 (30.0)	14 (29.2)	16 (30.8)	
4	1 (1.0)	1 (2.1)	0 (0.00)	
Surgery				.961
Left TKA	56 (56.0)	27 (56.3)	29 (55.8)	
Right TKA	44 (44.0)	21 (43.8)	23 (44.2)	

SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; ASA, American Society of Anesthesiologist; TKA, total knee arthroplasty.

type, American Society of Anesthesiologist score, body mass index, surgery side, and associated comorbidities (Table 1). Secondary clinical outcome variables included LOS, tourniquet time, estimated blood loss, hemoglobin, hematocrit, days per week of physical therapy, hours of continuous passive motion, MCD usage type and hours, adverse events, and overall satisfaction (Table 2). A univariate chi-square analysis or Fisher exact test was employed to compare the postdischarge VPULSE group with the inpatient VPULSE group on DVT occurrence at postoperative day 2 and at 2 weeks postoperatively. An independent-samples *t*-test was performed on all normally distributed data and a nonparametric Mann-Whitney *U* test was used for non-normally distributed data. All *P* values were 1-tailed, and *P* value <.05 was considered statistically significant.

Results

A total of 163 patients were screened and after meeting the study eligibility, 100 patients enrolled in the study and were randomized either to the inpatient VPULSE group (n = 52) or to the postdischarge VPULSE group (n = 48). Recruitment and follow-up started in April 2014 until January 2015, and follow-up continued until all patients had completed the study in February 2015. All patients' mean age was 62.76 ± 9.24 years with the postdischarge VPULSE group's mean age 59.85 ± 8.20 years, and the inpatient VPULSE group's mean age 65.44 ± 9.40 years ($P = .002$, statistically significant). The study population was 40% male and 60% female with 35.4% (n = 17) male in the postdischarge VPULSE group and 44.2% (n = 23) male in the inpatient VPULSE group, and 64.6%

Table 2
Patient Outcomes and Clinical Data.

Patient Outcomes	Total (N = 100), n (%)	Postdischarge VPULSE (n = 48), n (%)	Inpatient VPULSE (n = 52), n (%)	Overall *P* Value
Total DVTs[a]	12 (12.0)	0 (0.0)	12 (23.1)	<.001
DVT postop day 2[a]	6 (6.0)	0 (0.0)	6 (11.5)	.017
DVT postop day 14[a]	6 (6.0)	0 (0.0)	6 (11.5)	.017
Length of stay (d)	2.12 (0.33)	2.06 (0.25)	2.17 (0.38)	.086
Tourniquet time (min)	5.18 (0.95)	5.27 (0.95)	5.08 (0.94)	.329
Estimated blood loss (mL)	89.00 (27.60)	89.06 (32.58)	88.94 (22.37)	.684
Hemoglobin (g/dL)	11.33 (1.35)	11.25 (1.05)	11.41 (1.58)	.543
Hematocrit (%)	32.76 (3.22)	32.85 (3.07)	32.67 (3.38)	.78
Physical therapy (days per week)	2.62 (0.49)	2.63 (0.49)	2.62 (0.49)	.922
CPM[b] (hours per day)	5.07 (0.99)	5.19 (1.09)	4.96 (0.90)	.269
MCD usage				
VPulse SC (h)[b]	91.40 (72.58)	147.71 (68.87)	39.43 (10.77)	<.001
VPulse cooling (h)[b]	91.90 (74.69)	149.79 (71.16)	38.47 (9.85)	<.001
VPulse DC (h)[b]	76.90 (63.57)	120.32 (67.87)	36.04 (8.89)	<.001
Adverse events[c]	2 (2.0)	1 (1)	1 (1.0)	.536
Overall patient satisfaction[d] (NRS)	9.01 (1.31)	9.56 (0.82)	8.50 (1.46)	<.001

DVT, deep vein thrombosis; CPM, continuous passive motion; MCD, mechanical compression device; SC, sequential compression; DC, dynamic compression; NRS, numeric rating scale.

[a] Chi-square analysis.
[b] Mann-Whitney *U* test.
[c] DVTs were not included as adverse events because the incidence of DVT was analyzed separately.
[d] Independent-samples *t*-test.

(n = 31) female in the postdischarge VPULSE group and 55.8% (n = 29) female in the inpatient VPULSE group. A significantly decreased risk of DVT was observed at both postoperative day 2 and week 2 in the postdischarge VPULSE group compared to the inpatient VPULSE group (0% vs 11.5%, n = 6, $P = .017$). The total incidence of DVT was 23.1% in the inpatient VPULSE group (n = 12) and 0% in the postdischarge VPULSE group ($P < .001$). VPULSE usage time was tested using nonparametric analysis, specifically the independent-samples Mann-Whitney *U* test, and a statistically significant difference was found in the postdischarge VPULSE group vs the inpatient VPULSE group, that is, patients used the machine significantly longer in the postdischarge VPULSE group. Finally, an independent-samples *t*-test demonstrated a significant increase in patient satisfaction in the postdischarge VPULSE group (9.56 ± 0.82) vs the inpatient VPULSE group (8.50 ± 1.46). This difference was significant at the $P < .001$ level (Table 2).

The absolute risk reduction (ARR), also termed the risk difference, was calculated by subtracting the proportion of patients with DVT in the postdischarge VPULSE group from that in the inpatient VPULSE group. Because 11.5% (n = 6) of the patients developed DVT in the inpatient VPULSE group, with no patients developing DVT in the postdischarge VPULSE group after day 2 and week 2 of observation, the ARR was 11.5% at each time point. Additionally, the relative risk reduction, calculated as the proportion of the ARR and the event rate in the control group, was 100%, with the overall ARR at 23.1%.

Discussion

The results of this study demonstrate the utility of implementing an extended-use MCD in the prevention of DVT incidence and provide further evidence that a prophylactic regimen of aspirin and MCD therapy might be at least as effective as other comparable methods of thromboprophylaxis. The multimodal approach of limiting the use of a tourniquet to no more than 5 minutes, rapid postoperative patient mobilization, and 325 mg aspirin twice daily for 3 weeks postoperatively in combination with MCD therapy demonstrated a low nonsymptomatic incidence rate (12%), and an even lower symptomatic DVT incidence rate (1%), while minimizing bleeding complications (1%). Aspirin is a generally safe, inexpensive, and readily available thrombolytic agent and when used in combination with at least 3 weeks of MCD therapy demonstrates superiority to the standard treatment of MCD therapy only during the inpatient stay following TKA (0% DVT incidence compared to 12.0% DVT incidence). Low-risk VTE patients may benefit from the findings in this study, as the side effects of concurrent aspirin and extended MCD use minimized bleeding complications (0% in the postdischarge VPULSE patients). This awareness of a safe alternative to disproportionate use of high-risk chemoprophylactics contributes to the future development of effective VTE prevention in total joint arthroplasty guidelines.

Reitman et al examined the effects of a multimodal approach using intraoperative heparin before tourniquet inflation, hypotensive epidural anesthesia, inpatient use of pneumatic compression boots, and 6 weeks of aspirin (325 mg twice daily) and reported an overall DVT rate of 4.0% (n = 954 TKA patients). However, ultrasonography was only performed in this study population at the time of discharge, and they reported a longer average LOS (4.47 days vs 2.12 ± 0.33), which makes the DVT incidence rate difficult to compare. It also suggests evidence that the longer hospital stay and consequently the longer use of the MCD therapy might have decreased the DVT incidence rate in this study [7]. Furthermore, only performing ultrasonography at the time of discharge would have missed the 6% incidence of DVT in the inpatient VPULSE patients that developed DVT 2 weeks postoperatively, thus making the discordant DVT incidence rates less significant (4% vs 6% inpatient VPULSE group, and 0% postdischarge VPULSE group).

Although preoperative baseline scans were not performed, the postoperative day 2 scan served as a baseline, because all patients were receiving equivalent treatments until this point. Following discharge, the postdischarge VPULSE group experienced no DVTs (n = 0), whereas the inpatient VPULSE group experienced the 6% incidence of DVT (n = 6). That DVT occurred before the experimental treatment in half of the patients found to develop a DVT may be attributed to an inherent increased risk of developing DVT in these patients. Although every effort was made to include only patients at low risk of developing DVT by identifying contributing factors preoperatively, these patients may have had an unknown slightly increased risk of DVT. Patients may not have known or reported certain risk factors such as an unknown family history of DVT, or an unknown vein condition.

Overall, only 1 patient (1%) was symptomatic for DVT developing mild pain in the calf of the operative leg at his postoperative day 2 scan, and this DVT persisted to his 2-week postoperative LEDVU scan (inpatient VPULSE group). The efficacy of this multimodal thromboprophylactic regimen becomes evident when compared to a 0.92% incidence rate of 3060 TKA and THA patients symptomatic for VTE (and confirmed by imaging) [3], as well as the superiority of the postdischarge VPULSE group's outcome. The low overall incidence of VTE (23.1% in the inpatient VPULSE group; and 0% in the postdischarge VPULSE group) in this study is significantly lower than the estimated nonsymptomatic DVT incidence rate of 17%-53% in TKA patients without optimal prophylaxis [1].

The mean LOS was 2 days, and the complication rate was 2% (n = 2). One such complication was a gastrointestinal bleed occurring after the patient had been placed on enoxaparin to alleviate a DVT found 2 weeks postoperatively (inpatient VPULSE group), and the other adverse event was an emergency room visit due to an acute case of gastritis (postdischarge VPULSE group), which was not definitively related to the procedure or aspirin administration, because all patients were treated with 10 mg of famotidine for up to 6 weeks.

The laterality of the DVTs that were found was primarily located in the operative limb, although 2 patients had DVTs in the nonoperative limb, and not in the operative limb. One patient had a right knee TKA and developed a right soleal vein DVT, whereas the other patient had a right knee TKA and was found to have a left soleal vein DVT. These 2 patients were in the inpatient VPULSE group and the DVTs were only identified during the 2-week postoperative LED scan. Of those DVTs that were located in the operative limb, 3 were found in the popliteal vein, 7 in the soleal vein, 2 in an unspecified location of the lower extremity, and 1 patient had a total occluding saphenous vein DVT. All DVTs, except for those found in 1 patient, found at the postoperative day 2 scan persisted to the postoperative week 2 scan. Once identified, all DVTs were treated with either warfarin or rivaroxaban until resolved. No transfusions were performed, no patients were readmitted, and all DVTs were resolved by the 3-month follow-up knee examination, as verified by LEDVU.

The multimodal regimen used in this study was chosen for its low risk and seemingly high efficacy; however, Parvizi et al presented the efficacy of a similar study using only 81 mg of aspirin twice daily concurrently with inpatient MCD therapy. This prospective study found no difference in VTE incidence between the high-dose and low-dose aspirin group (0% vs 0.2%), and a decrease in gastrointestinal bleeding among the low-dose aspirin patients [17]. Because low-dose aspirin is found to have sufficient antiplatelet properties, this would encourage a follow-up study with low-dose aspirin, MCD use, and LEDVU imaging to establish an equivalent or superior nonsymptomatic DVT rate.

Overall satisfaction was statistically higher ($P < .001$) among the postdischarge VPULSE group (9.56 ± 0.82) than the inpatient VPULSE group (8.50 ± 1.46). Although patient satisfaction was hypothesized to be statistically insignificant between the groups, the higher satisfaction may be an indication of improved satisfaction due to patient activation. Evidence suggests higher satisfaction scores when patients are involved in their own health improvement [18], such as compliant MCD usage. If the study were able to be blinded, then this hypothesis may be able to be supported or refuted, which cannot be done at this time. This study was only able to provide evidence that overall satisfaction scores with the patient experience were not compromised by instructing the patient to use the MCD consistently and reliably throughout the 3-week postoperative period.

The younger patient population in the postdischarge VPULSE group may also be attributed, at least in part, to the superior overall satisfaction in this group; however, this finding has not been supported by the literature. Although not well understood, younger patients are considered a high-risk patient population for reporting lower satisfaction scores following total knee arthroplasty [19,20], which was not reflected in this study. The mechanism behind the improved patient satisfaction requires further investigation, perhaps through the use of a blinded postoperative assessor rather than the study coordinator to prevent bias, or even through a more comprehensive satisfaction questionnaire.

Some weaknesses of this study include the data usage chip of the MCD. The postdischarge VPULSE group did use the sequential compression setting of the MCD more hours total than the inpatient VPULSE group (147.71 ± 68.87 vs 91.40 ± 72.58, $P < .001$); however, the data chip of the MCD did not allow the researchers to examine how this usage was spread over the 3 weeks. This means that patient compliance in the postdischarge VPULSE group may have dropped off significantly following the first several days postdischarge.

Although this study could be improved by further describing patient compliance, this observation may be offset by the role of rapid mobilization that all patients underwent. In this way, the MCD therapy may act as a bridge between the inpatient hospital stay and the length of time before resumption of a patient's activities of daily living where venous stasis is mitigated, and the elements of Virchow's triad are interrupted [21]. The multimodal approach used in this study complemented the design of the clinical trial to minimize any conflicting factors, such as the varying hours of MCD therapy completed each day.

Although the implementation of postdischarge VPULSE MCD therapy was able to entirely reduce the risk of DVT for the patients in the postdischarge VPULSE group (relative risk reduction = 100%) eliminating the incidence in DVT among the 48 patients randomized to extended use of the device, this study did not establish the best VTE prevention protocol. However, additional examinations of the use of aspirin in conjunction with MCD therapy may reinforce the findings of this study and lead to the creation and subsequent implementation of optimized regimens that offer low incidence of VTE, and fewer bleeding and surgical wound complications in postoperative TKA patients.

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A Mobile Compression Device for Thrombosis Prevention in Hip and Knee Arthroplasty

Clifford W. Colwell Jr., MD, Mark I. Froimson, MD, Scott D. Anseth, MD, Nicholas J. Giori, MD, PhD, William G. Hamilton, MD, Robert L. Barrack, MD, Knute C. Buehler, MD, Michael A. Mont, MD, Douglas E. Padgett, MD, Pamela A. Pulido, BSN, and C. Lowery Barnes, MD

Investigation performed at the Scripps Clinic, La Jolla, California; Cleveland Clinic, Cleveland, Ohio; Twin Cities Orthopaedics, Edina, Minnesota; VA Palo Alto Health Care System, Palo Alto, California; Anderson Orthopaedic Clinic, Alexandria, Virginia; Washington University School of Medicine, St. Louis, Missouri; The Center, Orthopedic & Neurosurgical Care & Research, Bend, Oregon; Rubin Institute for Advanced Orthopedics, Baltimore, Maryland; Hospital for Special Surgery, New York, NY; and Arkansas Specialty Orthopaedics, Little Rock, Arkansas

Background: Venous thromboembolic events, either deep venous thrombosis or pulmonary embolism, are important complications in patients undergoing knee or hip arthroplasty. The purpose of this study was to evaluate the effectiveness of a mobile compression device (ActiveCare+S.F.T.) with or without aspirin compared with current pharmacological protocols for prophylaxis against venous thromboembolism in patients undergoing elective primary unilateral arthroplasty of a lower-extremity joint.

Methods: A multicenter registry was established to capture the rate of symptomatic venous thromboembolic events following primary knee arthroplasty (1551 patients) or hip arthroplasty (1509 patients) from ten sites. All patients were eighteen years of age or older with no known history of venous thromboembolism, coagulation disorder, or solid tumor. Use of the compression device began perioperatively and continued for a minimum of ten days. Patients with symptoms of deep venous thrombosis or pulmonary embolism underwent duplex ultrasonography and/or spiral computed tomography. All patients were evaluated at three months postoperatively to document any evidence of deep venous thrombosis or pulmonary embolism.

Results: Of 3060 patients, twenty-eight (0.92%) had venous thromboembolism (twenty distal deep venous thrombi, three proximal deep venous thrombi, and five pulmonary emboli). One death occurred, with no autopsy performed. Symptomatic venous thromboembolic rates observed in patients who had an arthroplasty of a lower-extremity joint using the mobile compression device were noninferior (not worse than), at a margin of 1.0%, to the rates reported for pharmacological prophylaxis, including warfarin, enoxaparin, rivaroxaban, and dabigatran, except in the knee arthroplasty group, in which the mobile compression device fell short of the rate reported for rivaroxaban by 0.06%.

Conclusions: Use of the mobile compression device with or without aspirin for patients undergoing arthroplasty of a lower-extremity joint provides a noninferior risk for the development of venous thromboembolism compared with current pharmacological protocols.

Level of Evidence: Therapeutic Level II. See Instructions for Authors for a complete description of levels of evidence.

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A commentary by Piers Yates, MBBS(Hons), BSc(Hons), MRCS(Eng), FRCS(Tr&Orth), FRACS(Ortho), FAOrthA, is linked to the online version of this article at jbjs.org.

Deep venous thrombosis and pulmonary embolism continue to be important complications after orthopaedic surgical procedures on the lower extremity. Several different modalities have been implicated as responsible for the decreased prevalence of thromboembolic events after surgery, including decreased surgical time and early mobilization. Two broad groups of prophylactic modalities are routinely used: pharmacological agents (anticoagulant and antiplatelet) and mechanical compression devices. Both are effective for the prevention of venous thromboembolism[1-5]; however, each carries its own advantages and disadvantages. The pharmacological agents have the risk of bleeding complications[1,3], which are especially high during the most vulnerable period for venous thromboembolism formation. The mechanical methods have the potential risk of being less efficacious, possibly related to variability in patient compliance, and often are not used following discharge to home. Many studies utilizing compression devices have been published[2,4,5], but all have relied on the use of compression devices while the patient is hospitalized or in a rehabilitation facility. The present study evaluated the efficacy of a mobile compression device (ActiveCare+S.F.T; Medical Compression Systems, Or Akiva, Israel) that is small and portable enough to send the patient home with the device. The use of this compression device for prophylaxis against venous thromboembolism could be recommended if adequate efficacy could be established and if it afforded a reduction in the risk of bleeding complications associated with pharmacological agents.

Previously, a randomized prospective study was powered to evaluate major bleeding events after hip arthroplasties with the pharmacological agent most utilized worldwide (Lovenox; enoxaparin) compared with the mobile compression device[6]. The device was found to be associated with significantly less major bleeding ($p = 0.0004$). Although the venous thromboembolism rate was equal in each arm of this randomized study, the study was not powered sufficiently to determine efficacy[6]. We are aware of no large-scale studies or registries that have evaluated the use of any mobile compression device with or without aspirin to prevent venous thromboembolism after lower-extremity joint arthroplasty.

In order to evaluate the efficacy of this mobile compression device, a registry was established at ten high-volume joint arthroplasty sites across the United States. The trial was designed as a noninferiority trial, which aimed to demonstrate that the mobile compression device was not worse than the comparator pharmacological agents by more than a small, prespecified amount (1.0%). The purpose of the registry was to evaluate the effectiveness of the mobile compression device with or without aspirin in lowering the potential risk of venous thromboembolism during and after hip or knee arthroplasty with the clinical end point of symptomatic deep venous thrombosis and/or pulmonary embolism within three months postoperatively. We compared these rates with the most commonly used pharmacological agents and protocols for noninferiority in preventing venous thromboembolism after arthroplasty of a lower-extremity joint.

Materials and Methods

Orthopaedic surgeons at ten sites in the United States participated in a registry to collect data on postoperative venous thromboembolism in patients who had an arthroplasty of a lower-extremity joint using the mobile compression device. Data were collected from April 1, 2011, to September 30, 2011, on consecutive patients. Data collection was at one designated site that maintained and analyzed the entire registry. Deidentified data from each of the other nine sites were sent to the data collection site. Institutional review board approval was obtained at each site. The trial was registered at ClinicalTrials.gov (NCT01984190). One patient returned for a follow-up evaluation at four weeks postoperatively and had no signs or symptoms of venous thromboembolism, but did not return at the three-month time point and was considered lost to follow-up. Another patient died in the hospital on postoperative day 3. The patient's family declined an autopsy, and therefore venous thromboembolic status could not be determined.

Inclusion and exclusion criteria were the same as those used in a prior study on safety[6] and in other randomized controlled studies of prophylaxis against venous thromboembolism[7-13]. Patients included in the registry were eighteen years of age or older and underwent primary unilateral hip arthroplasty (including hip resurfacing) or primary unilateral knee arthroplasty (including unicondylar knee arthroplasty) using only the mobile compression device with or without aspirin for the prevention of venous thromboembolism. Patients were excluded if they were scheduled for a revision surgery or had a history of venous thromboembolism, a coagulation disorder, a solid malignant tumor, or a major surgical procedure in the three months prior to the arthroplasty. The mobile compression device was applied to all patients perioperatively. The devices were applied to the contralateral leg during the surgical procedures for both knee and hip arthroplasties, and the device was applied to the operatively treated leg at the completion of the procedure before transferring the patient to the postanesthesia care unit. The device was used for a minimum of ten days with or without aspirin. The decision to use aspirin and the aspirin dosage were at the discretion of each surgeon participating in the registry.

This registry collected data on the occurrence of postoperative venous thromboembolism in patients who had an arthroplasty of a lower-extremity joint using this device for prophylaxis against venous thromboembolism. In addition to portability, this device has a liquid crystal display to allow the patient and medical personnel to monitor compliance. Another potential benefit of this mobile compression device is the synchronized flow technology. This technology synchronizes external compressions of the device to the patient's venous phasic flow such that compression occurs in synchronization with the natural venous phasic flow, allowing for a 66% increase in the peak venous velocity as measured at the common femoral vein[14].

If patients presented with symptoms consistent with a deep venous thrombosis or pulmonary embolism at any time before three months postoperatively, they were appropriately studied. At three months, patients completed a questionnaire or were asked routine questions describing any diagnosed deep venous thrombosis or pulmonary embolism event and were examined by the site clinician for swelling, redness, tenderness, and excessive warmth of the extremities. Symptomatic patients were studied by duplex ultrasound for deep venous thrombosis and spiral computed tomography (CT)-angiography for pulmonary embolism at the time of their symptoms within the three-month interval. Deep venous thrombosis was defined as proximal if the thrombus occurred in the popliteal vein or more proximally in the leg. Additional data collected included type of surgery (hip or knee arthroplasty), patient demographics (age, sex, height, and weight), and aspirin use (yes or no). Aspirin usage was assessed dichotomously because the sites that used aspirin had varying protocols for dose and duration of use. The frequency of anesthesia type (percent regional, general, or combined) was collected from each of the sites. Patient characteristics are presented in the Appendix.

Statistical Analysis

The prevalence of venous thromboembolism with so-called standard pharmacological prophylaxis is quite low; hence, establishing that the compression device would be superior to these other regimens would be difficult. Taking

TABLE I Rate of Symptomatic Venous Thromboembolic Events in Patients Using a Mobile Compression Device with or without Aspirin

Event	Total Joint Arthroplasty (N = 3060)	Total Hip Arthroplasty (N = 1509)	Total Knee Arthroplasty (N = 1551)
Venous thromboembolism *(no. [%])*	28 (0.92)	8 (0.53)	20 (1.29)
Deep venous thrombosis *(no. [%])*	23 (0.75)	5 (0.33)	18 (1.16)
Proximal deep venous thrombosis *(no. [%])*	3 (0.10)	1 (0.07)	2 (0.13)
Pulmonary embolism *(no. [%])*	5 (0.16)	3 (0.20)	2 (0.13)

this into consideration, we hypothesized that the mobile compression device would have approximately the same efficacy as pharmacological prophylaxis without the risk of major bleeding. We thus designed a noninferiority study of the mobile compression device versus the standard pharmacological prophylaxis, including warfarin, enoxaparin, rivaroxaban, and dabigatran, with symptomatic end points and similar patient demographics.

Formally, a noninferiority study aims to demonstrate that a treatment is not worse than the comparator (the control) by more than a prespecified, small amount, commonly known as the noninferiority margin. The choice of the noninferiority margin is somewhat subjective; we adopted a 1.0% margin in the present study, with the belief that a 1.0% difference in venous thromboembolism rates between the mobile compression device registry cohort and the pharmacological comparators would not constitute a clinically meaningful difference (e.g., a difference of such magnitude that a physician might choose one or the other regimen). Our margin of 1.0% is more rigorous than the 1.5% margin used in most drug studies. The U.S. Food and Drug Administration published guidelines for the design and conduct of noninferiority trials[15], and these trials have been widely adopted by the pharmaceutical industry.

The noninferiority margin was based on absolute event rate differences. We accepted that the mobile compression device was noninferior if the upper bound of the one-sided 97.5% confidence interval (97.5% CI) around the estimated difference in event rates was below the noninferiority margin. The sample size calculation was based on symptomatic venous thromboembolism rates in patients using warfarin[16-19], enoxaparin[8,11-13], rivaroxaban[8,11-13], and dabigatran[9,10,20] from previously published clinical trial data. We calculated a number of power comparisons prior to initiating the study. We found that sample sizes of 1500 in the device group and any drug group would be sufficient to achieve power in excess of 90% to detect a noninferiority margin difference between the venous thromboembolism proportions in the two groups of 1.0%. In these calculations, we considered venous thromboembolism rates in the drug groups to be between 0.5% and 1.0% and the venous thromboembolism rate in the device group was taken to be the drug group rate + 1.0% under the null hypothesis of inferiority. Power was calculated for the case when the actual venous thromboembolism rate for the device was identical to that for the drug comparator. The test statistic used was the one-sided score test, with the significance level set at 0.025.

SPSS software (version 13.0; SPSS, Chicago, Illinois) and NCSS software (version 7.1.21; NCSS, Kaysville, Utah) were used for sample size calculations and analysis of the registry data. Means were calculated to describe continuous variables (age, height, and weight), and frequencies were calculated to describe categorical variables (surgery type, aspirin use, and the occurrence of symptomatic venous thromboembolism). Upper bound 97.5% CIs were calculated around the observed difference in the rate of venous thromboembolism between the mobile compression device and each drug comparator.

Source of Funding

The funding for this registry was provided by Medical Compression Systems (Or Akiva, Israel). Beyond funding the registry, Medical Compression Systems did not participate in, nor did any of the authors receive compensation for, the registry conduct, analysis, or manuscript preparation.

Results

Overall, symptomatic venous thromboembolism occurred in 0.92% (twenty-eight) of 3060 patients who had an arthroplasty of a lower-extremity joint. Twenty-three patients who had a joint arthroplasty (0.75%) experienced deep venous thrombosis (three proximal and twenty distal thrombi), and five patients (0.2%) had a pulmonary embolism (Table I). The

TABLE II Rates of Symptomatic Venous Thromboembolism and Pulmonary Embolism in the Present Registry Study and in Previous Studies with Similar Demographics

Prophylaxis	Total Joint Arthroplasty*		Hip Arthroplasty*		Knee Arthroplasty*	
	Venous Thromboembolism	Pulmonary Embolism	Venous Thromboembolism	Pulmonary Embolism	Venous Thromboembolism	Pulmonary Embolism
Mobile compression device in the present study	28/3060 (0.92)	5/3060 (0.16)	8/1509 (0.53)	3/1509 (0.20)	20/1551 (1.29)	2/1551 (0.13)
Warfarin[7-10]	45/2012 (2.24)	9/1816 (0.50)	15/534 (2.81)	0/338 (0.0)	30/1478 (2.03)	9/1478 (0.60)
Enoxaparin[11-14]	68/6138 (1.11)	14/3932 (0.35)	26/3413 (0.76)	2/1207 (0.17)	42/2725 (1.54)	12/2725 (0.44)
Rivaroxaban[11-14]	39/6132 (0.64)	1/6132 (0.02)	12/3405 (0.35)	1/3405 (0.03)	27/2727 (0.99)	0/2707 (0.0)
Dabigatran[15-17]	69/5918 (1.17)	10/5918 (0.17)	28/3294 (0.85)	7/3294 (0.21%)	41/2624 (1.56)	3/2624 (0.11)

*The values are given as the number of patients affected divided by the total number in the study, with the percentage in parentheses. Symptomatic deep venous thrombosis location (proximal versus distal) was not specified in published results for the pharmacological agents. The 97.5% confidence intervals are presented in Figures 1-A, 1-B, and 1-C.

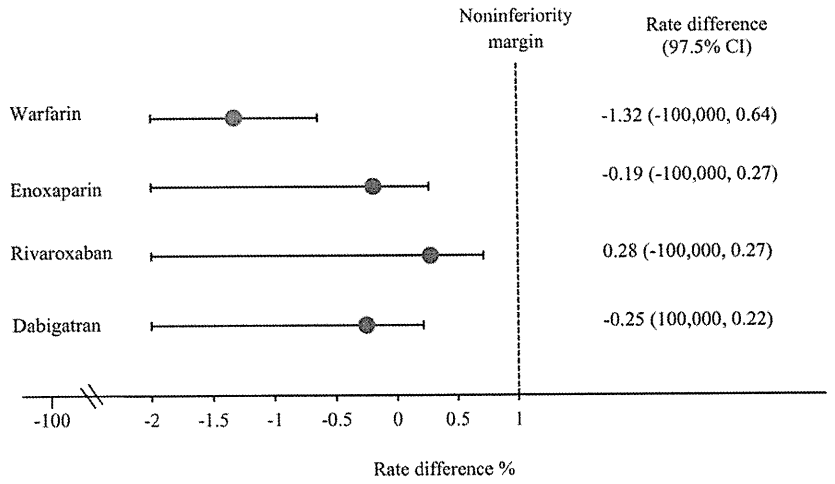

Fig. 1-A

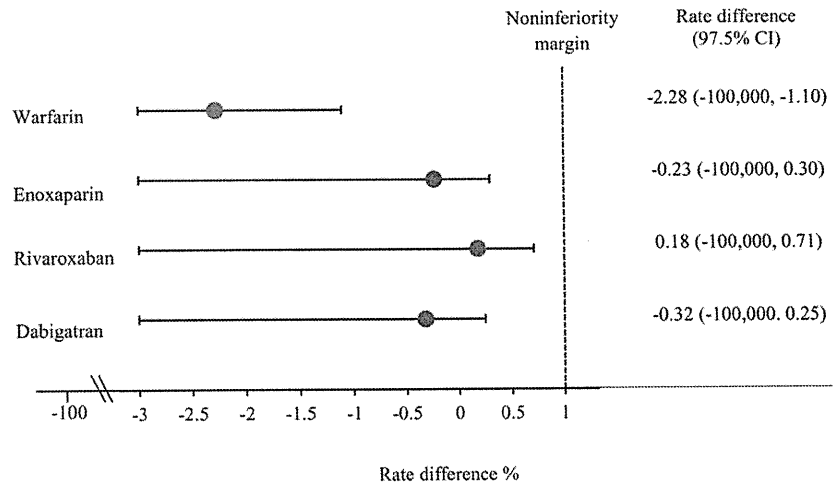

Fig. 1-B

Fig. 1-A Observed rate differences for venous thromboembolism (venous thromboembolism rate with the mobile compression device minus the venous thromboembolism rate with the pharmacological comparator, which is represented by the circular markers) and the 97.5% confidence intervals between the mobile compression device and the current pharmacological comparators in patients who had an arthroplasty of a lower-extremity joint. **Fig. 1-B** Observed rate differences for venous thromboembolism (venous thromboembolism rate with the mobile compression device minus venous thromboembolism rate with the pharmacological comparator, which is represented by the circular markers) and the 97.5% confidence intervals between the mobile compression device and the current pharmacological comparators in patients who had a hip arthroplasty.

1509 patients managed with a hip arthroplasty had eight venous thromboembolic events (a rate of 0.5%), with five deep venous thrombi (one proximal and four distal thrombi) and three pulmonary emboli. The rate of venous thromboembolism in the 1551 patients who had a knee arthroplasty was 1.3% (twenty patients), with eighteen deep venous thrombi (two proximal and sixteen distal thrombi) and two pulmonary emboli (Table I). No fatal pulmonary emboli were reported. One death of a patient with a long-standing history of cardiac disease and previous cardiac stent placement was reported. "Coronary failure" was listed as the cause of death, and the family was unwilling to allow an autopsy, so pulmonary embolism could not be ruled out. The association between aspirin use and the occurrence of venous thromboembolism could not be assessed; among the twenty-eight patients who experienced venous thromboembolism, thirteen (46.4%) were using aspirin and fifteen (53.6%) were not.

The rate of symptomatic venous thromboembolism was reported as 2.2% for warfarin[16-19], as 1.1% for enoxaparin[8,11-13], as 0.64% for rivaroxaban[8,11-13], and as 1.2% for dabigatran[9,10,20] after arthroplasty of a lower-extremity joint (Table II). The rates of symptomatic venous thromboembolism observed in patients who had an arthroplasty of a lower-extremity joint using the mobile compression device were noninferior at a margin of 1.0% to the rates reported for pharmacological prophylaxis, including warfarin, enoxaparin, rivaroxaban, and dabigatran (Figs. 1-A, 1-B, and 1-C). In the knee arthroplasty group, the mobile compression device fell short of the noninferior 1.0% margin to rivaroxaban by 0.06%, but it was noninferior at the 1.0% margin for all other knee and hip arthroplasty groups.

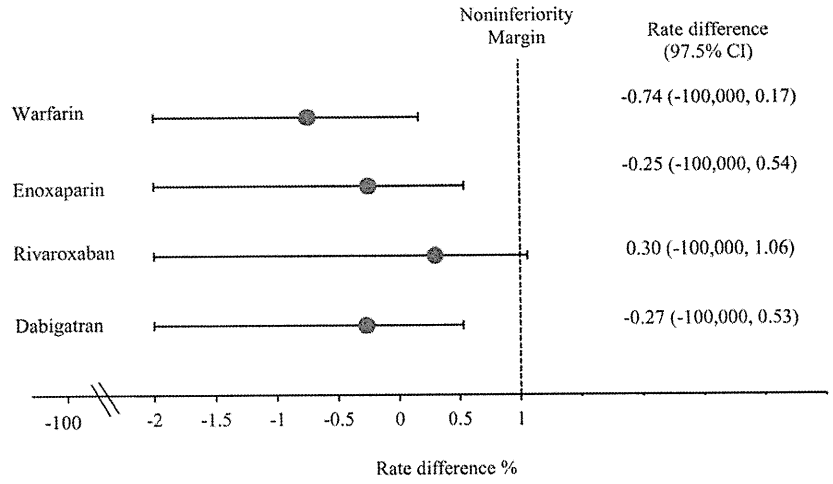

Fig. 1-C

Observed rate differences for venous thromboembolism (venous thromboembolism rate with the mobile compression device minus venous thromboembolism rate with the pharmacological comparator represented by the circular markers) and the 97.5% confidence intervals between the mobile compression device and the current pharmacological comparators in patients who had a knee arthroplasty.

Discussion

We evaluated whether the rates of symptomatic venous thromboembolism associated with the mobile compression device with or without aspirin were noninferior compared with those for warfarin[16-19], enoxaparin[8,11-13], rivaroxaban[8,11-13], and dabigatran[9,10,20] in patients who had hip arthroplasty, patients who had knee arthroplasty, and combined groups of patients who had a hip or knee arthroplasty. These reports compared favorably with the finding in our study of a rate of 0.92% for symptomatic venous thromboembolism after arthroplasty of a lower-extremity joint. Anticoagulants, however, carry an increased risk of major and minor bleeding events. This has been well-documented for enoxaparin[21,22], as well as in a previous study comparing this specific device with enoxaparin[6]. The bleeding risk profiles of warfarin and dabigatran are generally similar to enoxaparin, which is most commonly utilized as the control group in the clinical trials for these newer anticoagulants[23,24]. Rivaroxaban, on the other hand, has a higher risk of bleeding compared with enoxaparin, but is more efficacious at preventing symptomatic venous thromboembolism[23]. This is important information for the orthopaedic surgeon providing an alternative to pharmacological methodology without the risk of major bleeding and with similar efficacy. A cost analysis for the prevention of major bleeding events has been previously published[25]. Because of variations in cost by region and by facility, no comparison with other compression devices could reasonably be conducted. Although we know of no studies on the prevention of venous thromboembolism with the use of inpatient compression systems as monotherapy with symptomatic end points during hospitalization and follow-up after discharge, Froimson et al. compared this mobile compression device with the standard nonmobile compression device commonly used in acute care settings following lower-extremity arthroplasty[26]. The mobile compression device showed a 70% reduction in venous thromboembolic events compared with the nonmobile compression device (when both arms were used as adjunctive therapy to enoxaparin).

A series of guidelines have been developed and published by the American College of Chest Physicians (ACCP)[27] and by the American Academy of Orthopaedic Surgeons (AAOS)[28]. These guidelines utilized a systematic review of the current literature to determine an ideal or best methodology and duration for prophylaxis against venous thromboembolism. Both guidelines use symptomatic end points with duplex ultrasound documentation for deep venous thrombosis and imaging studies for confirmation of pulmonary embolism.

The limitations of our study are those of any registry that lacks a randomized control group. Selection bias is a concern with patient registries. We designed the mobile compression device registry to utilize the same inclusion and exclusion criteria that were used in randomized clinical trials assessing the efficacy of pharmacological agents for prophylaxis against venous thromboembolism. The patients enrolled consecutively in this registry had similar demographics to those reported in the clinical trials of the pharmacological agents. A surgeon at one or more sites could have possibly deviated from the inclusion and exclusion criteria when deciding which of his or her patients should receive the device, potentially resulting in a higher or lower-risk cohort of patients enrolled at that site. The rate of venous thromboembolism at each of the ten sites was similar, leading to the conclusion that the registry protocol was followed cohesively. A selection bias could have also resulted if not all patients who received the device were included in the registry. However, we had only one patient lost to follow-up, who had no signs or symptoms of venous thromboembolism at one month postoperatively.

The registry had a limited data set, and neither bleeding rates nor compliance were documented. These limitations were offset by a previous study of the device[6], which showed a 0% rate of major bleeding events. There is no reason that the bleeding rate would have been greater than in the previous study[6] or with

any other compression device study[29,30]. Compliance, which increases the effectiveness of compression devices[31], was not documented in the registry. If the participants in this study used the device less than the ten days and twenty hours per day reported in the previous study[6], the venous thromboembolism rates would only improve with greater use. The study was not powered to establish any conclusions with respect to the use or nonuse of aspirin in addition to the mobile compression device. Of the twenty-eight patients who had a venous thromboembolic event, 46% were on the aspirin protocol. Similarly, the study was not powered to assess the relationship between anesthesia type and the occurrence of venous thromboembolism. The anesthesia protocols for hip and knee arthroplasty differed from site to site, and we were able to present frequencies only (see Appendix). Another potential study weakness is that each institution reported its duplex ultrasound data and spiral CT data with no adjudication committee to evaluate these studies. However, if any of the positive diagnostic studies had been disallowed by an adjudication committee, a lower rate of deep venous thrombi and pulmonary emboli would have been observed.

To our knowledge, this is the first large multicenter study utilizing an external mobile compression device in an inpatient or outpatient setting for ten days or greater. The results demonstrated noninferior efficacy in the prevention of venous thromboembolism compared with the most commonly used pharmacological protocols, except for rivaroxaban in knee arthroplasty, which lacked noninferiority by 0.06% at the 1.0% margin. On the basis of this study, we recommend that surgeons consider the use of this mobile compression device with or without aspirin for prophylaxis as an alternative to pharmacological prophylaxis in patients treated with arthroplasty of a lower-extremity joint.

Appendix

(eA) A table showing patient demographic data is available with the online version of this article as a data supplement at jbjs.org. ■

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Clifford W. Colwell Jr., MD
Pamela A. Pulido, BSN
Shiley Center for Orthopaedic Research and Education at Scripps Clinic,
11025 North Torrey Pines Road, Suite 200,
La Jolla, CA 92037.
E-mail address for C.W. Colwell Jr.: colwell@scripps.edu

Mark I. Froimson, MD
Euclid Cleveland Clinic,
Euclid Hospital – Administration,
18901 Lake Shore Boulevard,
Euclid, OH 44119

Scott D. Anseth, MD
Twin Cities Orthopaedics,
4010 West 65th Street,
Edina, MN 55435

Nicholas J. Giori, MD, PhD
VA Palo Alto Health Care System,
3801 Miranda Avenue (112),
Palo Alto, CA 94304

William G. Hamilton, MD
Anderson Orthopaedic Clinic,
2501 Parkers Lane,
Alexandria, VA 22306

Robert L. Barrack, MD
Department of Orthopaedic Surgery,
Washington University School of Medicine,
Campus Box 8233, 660 South Euclid Avenue,
St. Louis, MO 63110

Knute C. Buehler, MD
The Center, Orthopedic & Neurosurgical Care & Research,
2200 N.E. Neff Road, Suite 200,
Bend, OR 977041-4281

Michael A. Mont, MD
Rubin Institute for Advanced Orthopedics,
Sinai Hospital of Baltimore,
2401 West Belvedere Avenue,
Baltimore, MD 21215

Douglas E. Padgett, MD
Hospital for Special Surgery,
535 East 70th Street,
New York, NY 10021-4892

C. Lowery Barnes, MD
Arkansas Specialty Orthopaedics,
1701 Aldersgate Road, Suite 3,
Little Rock, AR 72205

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PREVENTING VENOUS THROMBOEMBOLIC DISEASE IN PATIENTS UNDERGOING ELECTIVE HIP AND KNEE ARTHROPLASTY

EVIDENCE-BASED GUIDELINE AND EVIDENCE REPORT

RECOMMENDATION 5

We suggest the use of pharmacologic agents and/or mechanical compressive devices for the prevention of venous thromboembolic disease in patients undergoing elective hip or knee arthroplasty, and who are not at elevated risk beyond that of the surgery itself for venous thromboembolism or bleeding.

Grade of Recommendation: Moderate

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. A **Moderate** recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the strength of the supporting evidence is not as strong.

Implications: Practitioners should generally follow a **Moderate** recommendation but remain alert to new information and be sensitive to patient preferences.

Current evidence is unclear about which prophylactic strategy (or strategies) is/are optimal or suboptimal. Therefore, we are unable to recommend for or against specific prophylactics in these patients.

Grade of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence resulting in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

In the absence of reliable evidence about how long to employ these prophylactic strategies, it is the opinion of this work group that patients and physicians discuss the duration of prophylaxis.

Grade of Recommendation: Consensus

Description: The supporting evidence is lacking and requires the work group to make a recommendation based on expert opinion by considering the known potential harm and benefits associated with the treatment. A **Consensus** recommendation means that expert opinion supports the guideline recommendation even though there is no available empirical evidence that meets the inclusion criteria of the guideline's systematic review.

Implications: Practitioners should be flexible in deciding whether to follow a recommendation classified as **Consensus,** although they may give it preference over alternatives. Patient preference should have a substantial influencing role.

RATIONALE

We recognize the diversity of opinion concerning the clinical importance of DVT as an isolated event or as a surrogate outcome for PE or post-thrombotic syndrome, (for further discussion, please see the Methods section), and understand that for clinical, and sometimes for even medico-legal reasons, DVT prevention may be the clinician's immediate concern. There is moderate evidence to suggest that pharmacological agents and/or mechanical compression devices reduce DVT rates in patients undergoing elective knee or hip arthroplasty. This is why we are suggesting prophylaxis. Readers of this guideline should recognize, however, that the available, published evidence does not establish whether these prophylactic strategies affect rates of all-cause mortality, fatal PE, symptomatic PE, or symptomatic DVT in patients undergoing elective hip or knee arthroplasty.

We also note that the present recommendation for prophylaxis is of a "Moderate" (rather than "Strong") grade partly because it is based on a surrogate outcome we do not consider "critical" (we considered major bleeding, pulmonary emboli, and all cause mortality as "critical," and symptomatic DVT, any DVT, and proximal DVT as not critical). The "critical" outcomes are all patient-oriented. The non-critical outcomes are not.

The inability to recommend a specific prophylactic strategy is a direct result of the network meta-analyses we performed. We performed numerous such analyses with sensitivity analyses that included separately analyzing data from patients who underwent hip and knee arthroplasty, analyzing these data combined, evaluating the impact of study quality on the results, and by comparing the results of each prophylactic strategy to placebo (or no treatment) and, when placebo/no treatment data were not available, comparing the results of each strategy to results obtained with enoxaparin (as discussed in the Methods section, this use of two comparators allows us to check the logical consistency of our models). The results of these analyses did not consistently suggest that any one strategy is preferable to another (please see Figure 38 - Figure 55 and Table 32 - Table 34; and, for the results of our sensitivity analyses, see Appendix XV).

We also analyzed data on other outcomes but, due to lack of data, network meta-analysis was not possible for them. In total, then, our analyses of the different prophylactic strategies is comprised of 112 high-or medium quality randomized controlled studies that enrolled patients undergoing elective hip and/or knee arthroplasty (see Appendix XIII, Table 53). As with the network meta-analyses, the data did not suggest that any specific prophylactic strategy was superior or inferior.

Part of the reason that current data do not permit a conclusion about specific prophylactic strageties is that, in our final network meta-analyses, no pharmacological agents showed a statistically significant effect in preventing all-cause mortality, symptomatic pulmonary emboli, symptomatic DVT, and major bleeding, when data from hip and knee studies were analyzed separately or when they were combined. This may be because these events are rare. In addition, infection rates and re-operations (for any reason) were not reported. Reoperations due to bleeding were reported, but were often part of the study authors' definition of major bleeding.

Many of the commonly used agents such as sodium warfarin and various low molecular weight heparinoids did not show efficacy for preventing VTED. This may be partially explained by the lack of comparison studies with placebo controls and by the rarity of the events of interest. In the final model with PE as the outcome, there were 181 events among 42,390 patients across 25 trials, and only 3 of these trials had a placebo or no prophylaxis arm.

There were a limited number of studies that evaluated mechanical compression devices. In one study on total hip arthroplasties,[48] there was a lower risk of major bleeding in the mechanical group. However, this study was only of moderate quality, partially because only 37% of the compression group had this device alone, with the remainder of the patients receiving low dose aspirin (81 mg/day) as well. There were also difficulties with the comparability of the control and intervention groups (that some of the studies we examined were not of high quality is another reason why the present recommendation is of "Moderate" strength).

In some analyses of mechanical compression device studies, less bleeding was found in comparison to no treatment. This may not appear intuitively logical, but might be occurring because of problems with randomization and the patient populations which may not be generalizable to the standard population of patients typically undergoing total hip and knee arthroplasties. The effect may also be occurring for some presently unknown physiological reasons. Other potentially confounding factors with these studies are enumerated below.

Conclusions about specific prophylactic strategies are also difficult because, in addition to the above-mentioned challenges posed by the rarity of the events of interest and the lack of reporting of critical outcomes, the available studies:

- Enrolled a select group of patients and did not necessarily include patients who had a high risk for VTED or bleeding and may not be representative of a typical patient population
- Used different drug doses (e.g. Enoxaparin at 30 mg bid vs. 40 mg per day).
- Used different timing of administration of agents (short-term vs. longer-term dosing)
- Used different routes of administration

Comparing different prophylactic strategies is difficult because there is a paucity of placebo-controlled trials because of early acceptance of prophylaxis being the standard of care.

Also, we are unable to recommend specific pharmacologic agents and/or mechanical devices because the results of our analyses with DVT as the outcome were not robust on sensitivity analyses. Due to the rarity of the critical outcomes of interest and the limited number of placebo-controlled trials, we had to rely on the analysis of DVT (i.e., any DVT), a surrogate measure, to evaluate the relative efficacy of the prophylactic strategies. However, the results of these analyses depend on the structure of the model

used, as agents shown to significantly reduce the occurrence of DVT in one model are often not statistically significant in an alternate model (see Table 97 in Appendix XV).

Some clinical practice guidelines make recommendations about the duration of pharmacologic prophylaxis. The available evidence is partially from manufacturer-funded trials, and is of only one agent. The latter is particularly problematic because the potential differences in the risks and benefits of various pharmacological agents may become more prominent as the duration of prophylaxis increases. We are, therefore, reluctant to make such a recommendation until more is known about the relative risk/benefit profiles of these different agents. Rather, the work group recommends that patients and physicians discuss the appropriate duration of prophylaxis for each individual situation. This physician-patient discussion is low cost and consistent with current practice.

As of April 1, 2011, several of the analyzed agents are not approved for marketing or the treatment of any medical condition in the United States. The United States Food and Drug Administration's (FDA) current policy regarding disclosure of marketing applications can be found in "Current Disclosure Policies for Marketing Applications" on the FDA website.

We excluded some studies we retrieved for this recommendation. The reasons for doing so are shown in Appendix XIV, Table 62).

FINDINGS

QUALITY AND APPLICABILITY

Of the 112 included studies for this recommendation, 87 were of high quality and 25 were of moderate quality. All but two studies were of moderate applicability; the other two were of low applicability. For details, see Table 53 in Appendix XIII.

RESULTS

SUMMARY OF DIRECT COMPARISONS

The figures below summarize the results of direct comparisons made for the six outcomes addressed by the network meta-analysis. If a single study addressed a given comparison of two treatments, that is the result presented. If multiple studies addressed a given comparison, results of the corresponding meta-analysis are presented. More information on these direct comparisons can be found in Appendix XV (Table 67 through Table 84). Studies with no events in any arm are not included in this analysis.

Note: For all figures and tables in this recommendation, the outcome Deep Vein Thrombosis (DVT) refers to any DVT: symptomatic or asymptomatic.

Figure 2. Pulmonary Embolism Direct Comparisons among Hip and Knee Patients

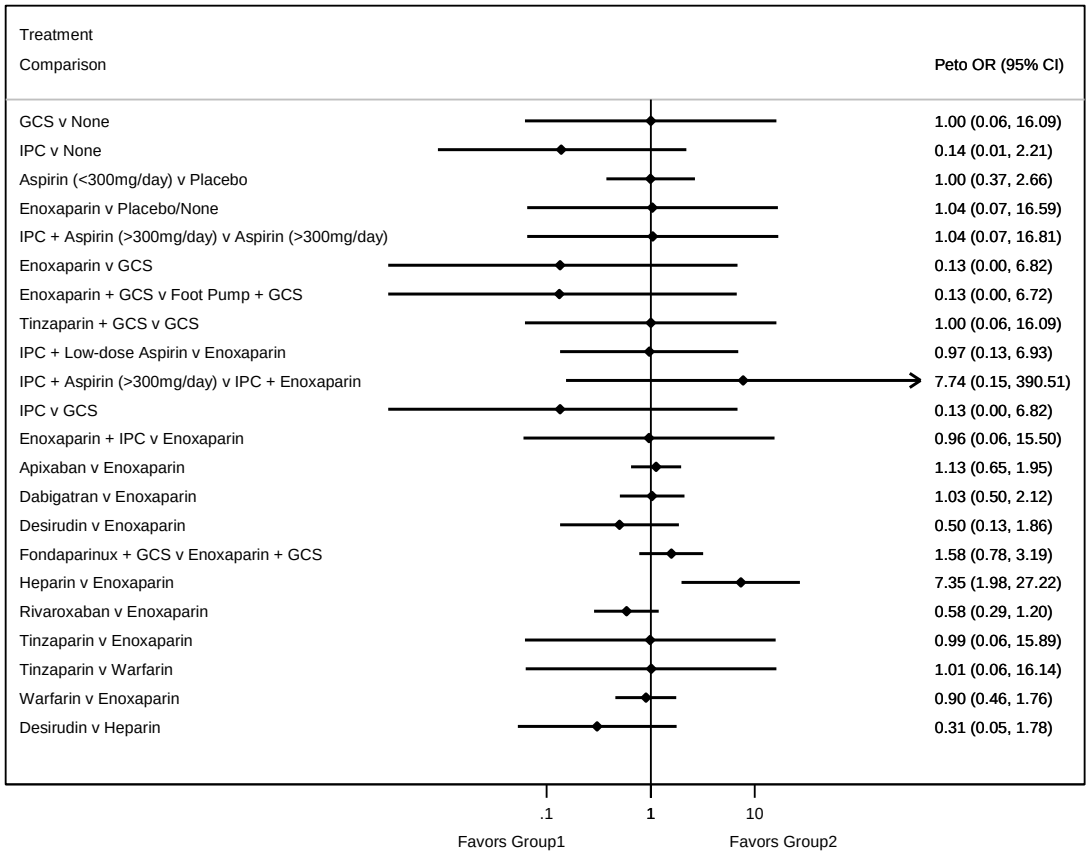


Figure 3. Pulmonary Embolism Direct Comparisons among Hip Patients

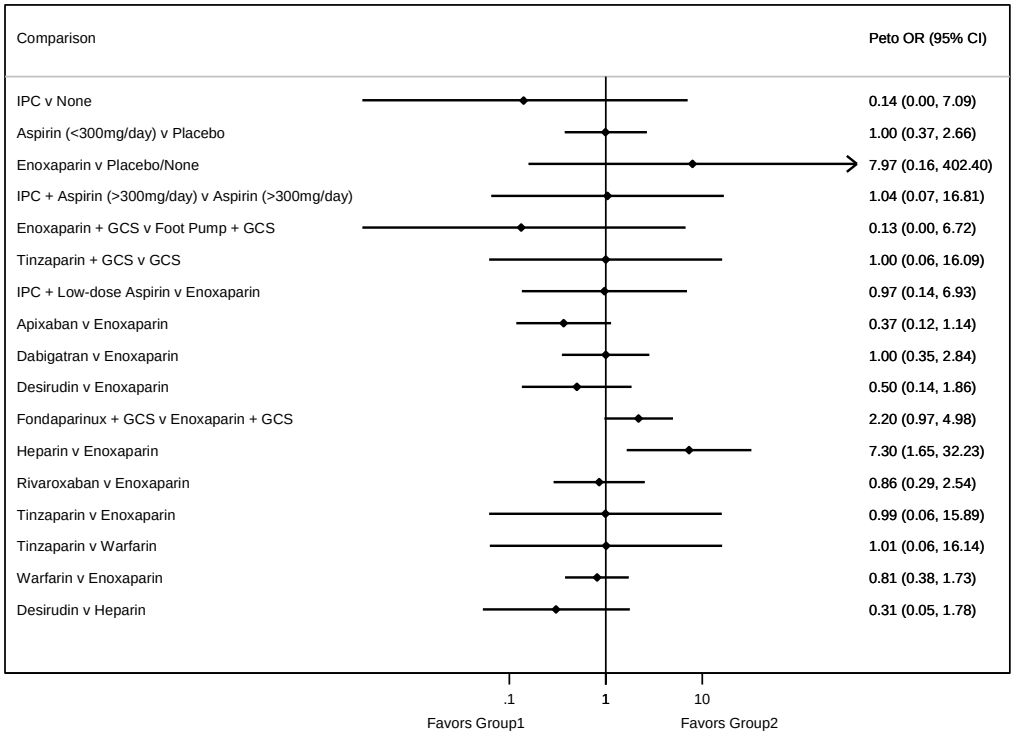


Figure 4. Pulmonary Embolism Direct Comparisons among Knee Patients

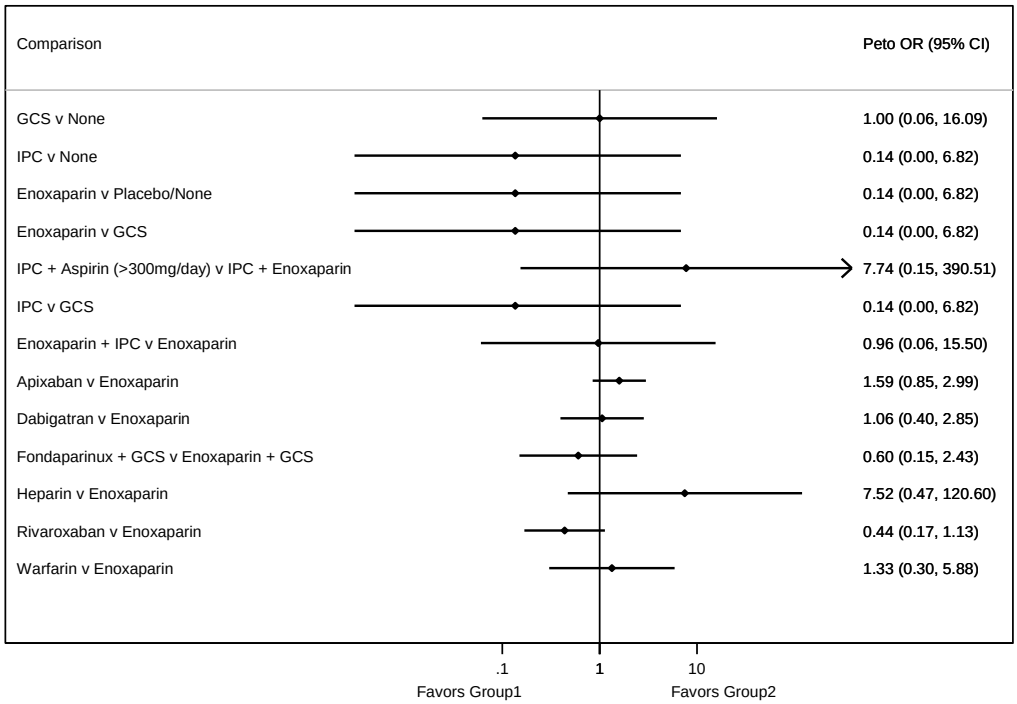


Figure 5. Major Bleeding Direct Comparisons among Hip and Knee Patients

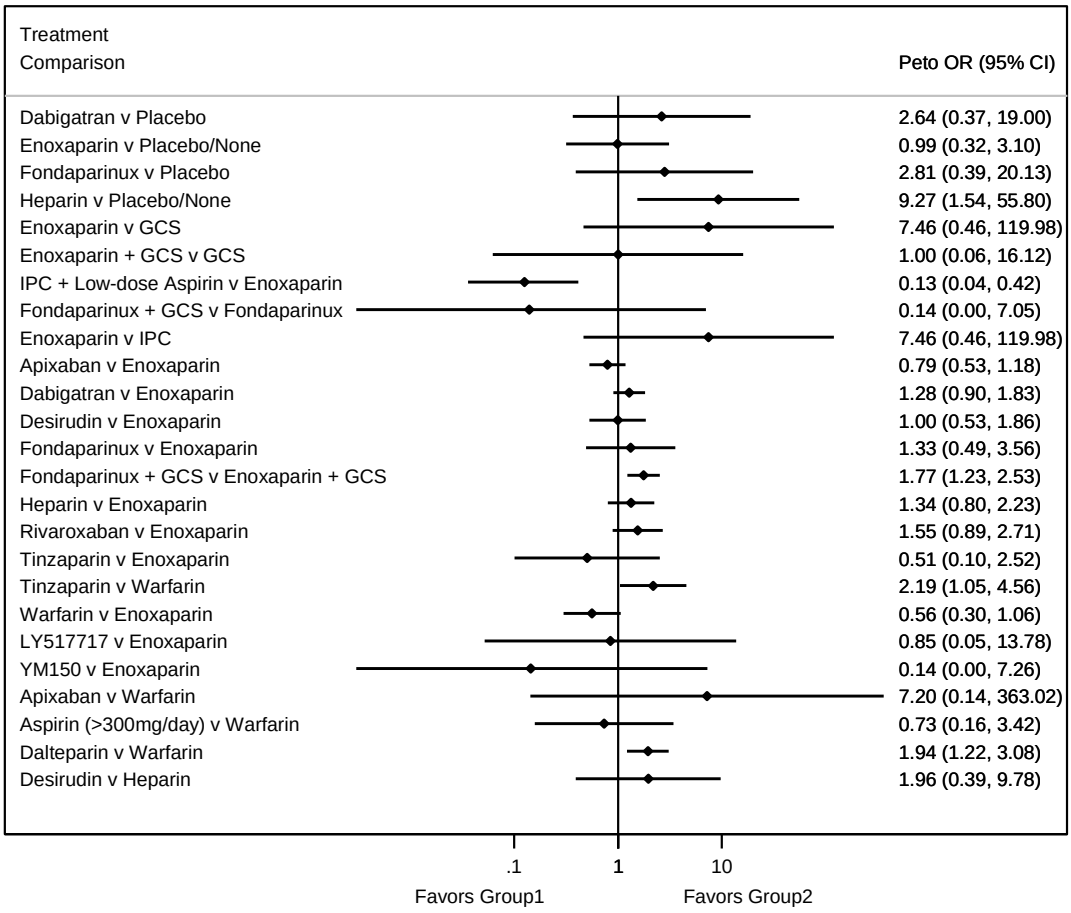


Figure 6. Major Bleeding Direct Comparisons among Hip Patients

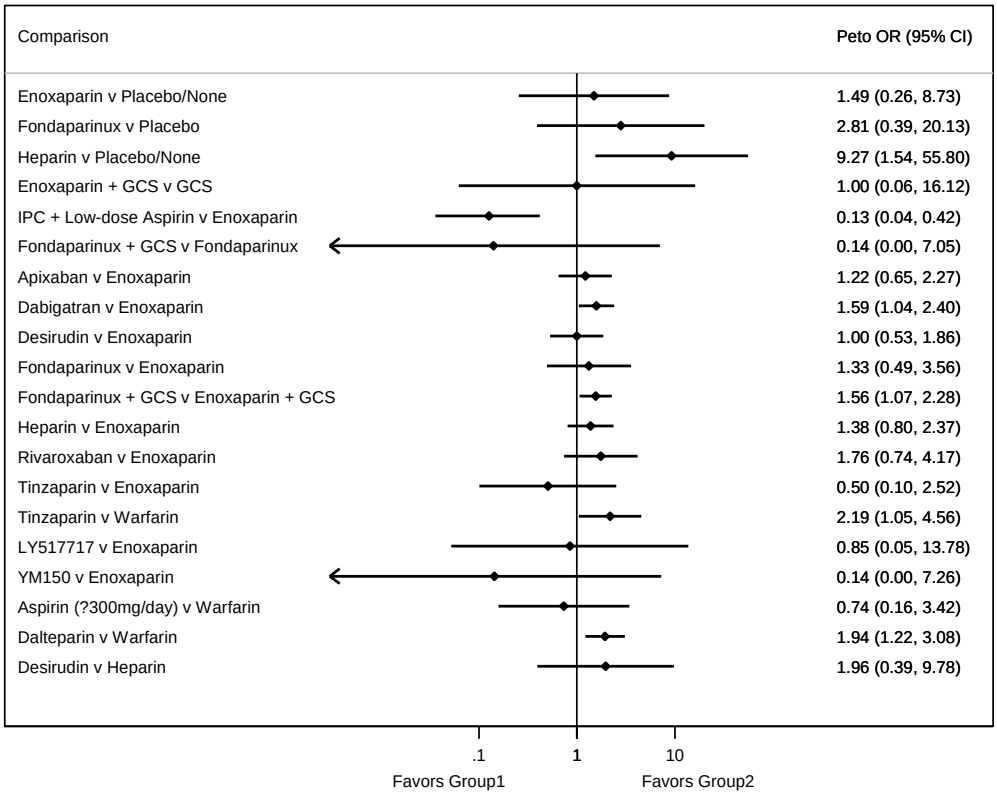


Figure 7. Major Bleeding Direct Comparisons among Knee Patients

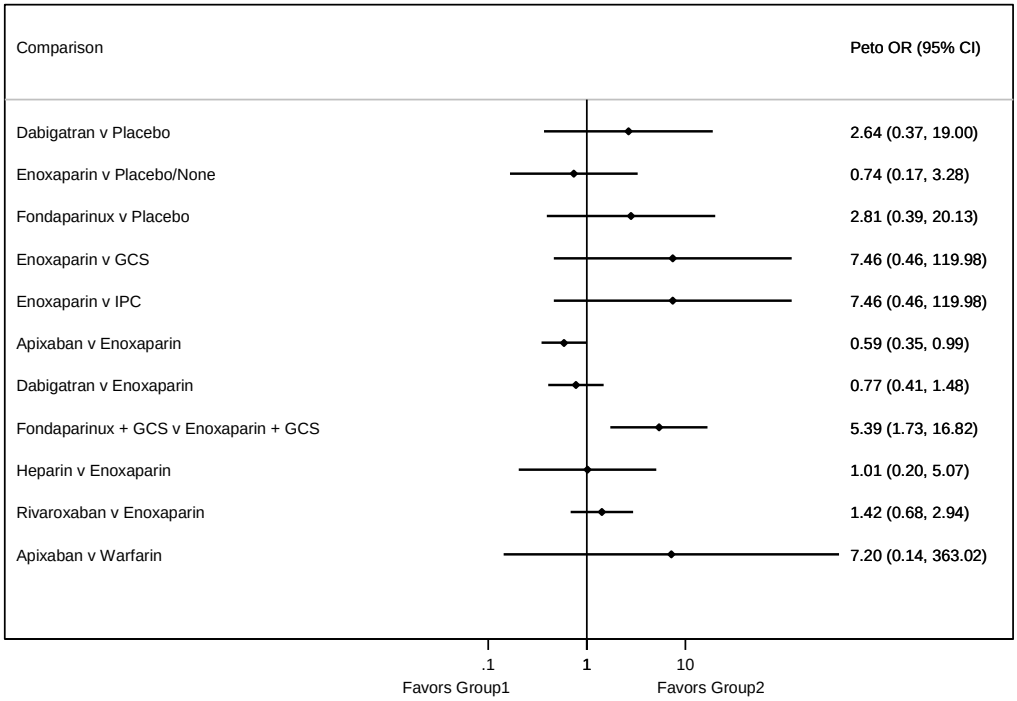


Figure 8. All Cause Mortality Direct Comparisons among Hip and Knee Patients

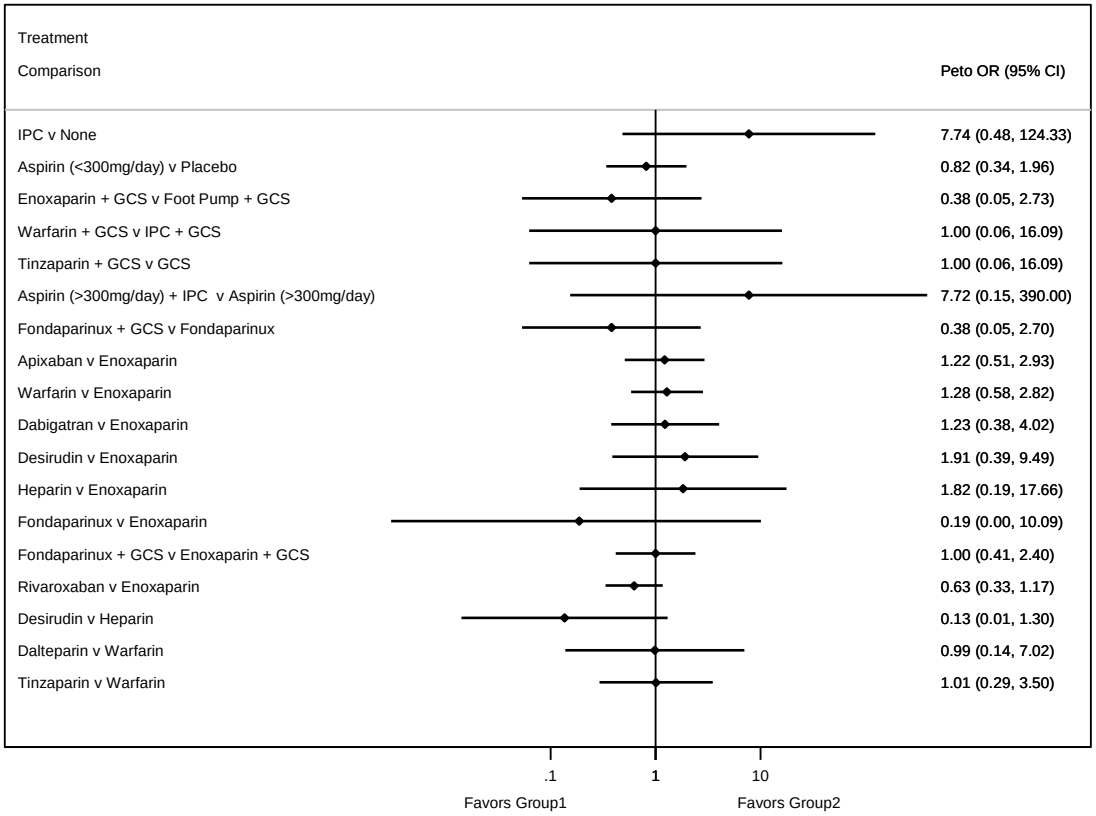


Figure 9. All Cause Mortality Direct Comparisons among Hip Patients

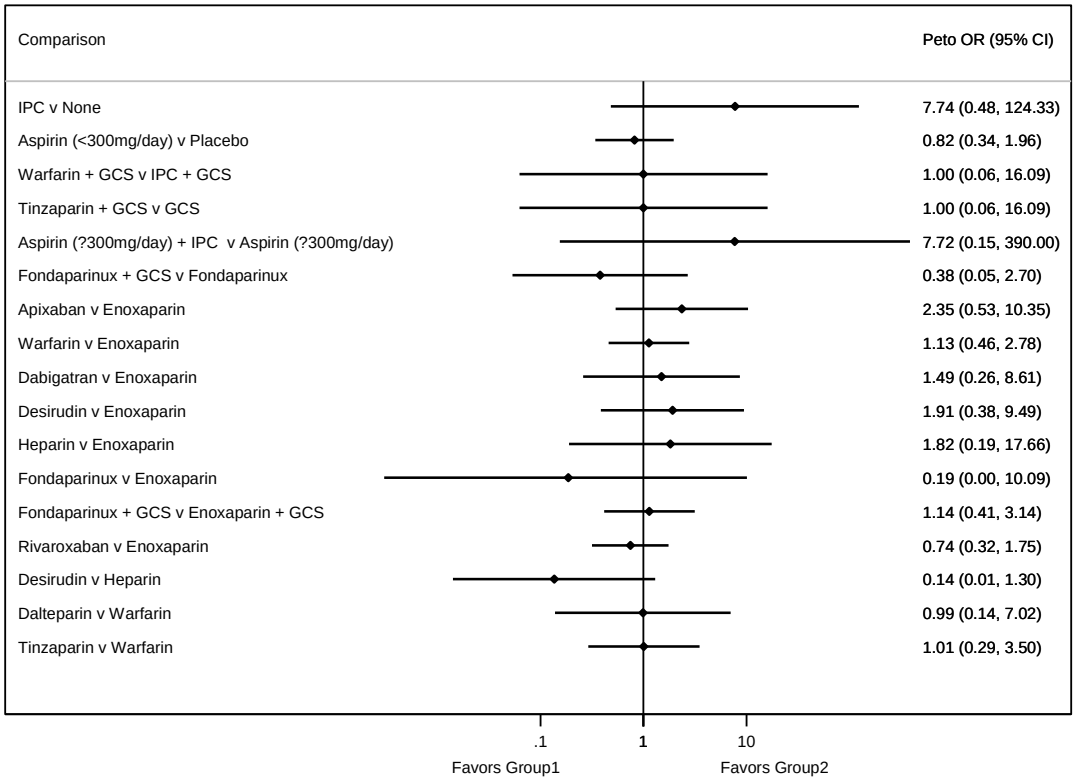


Figure 10. All Cause Mortality Direct Comparisons among Knee Patients

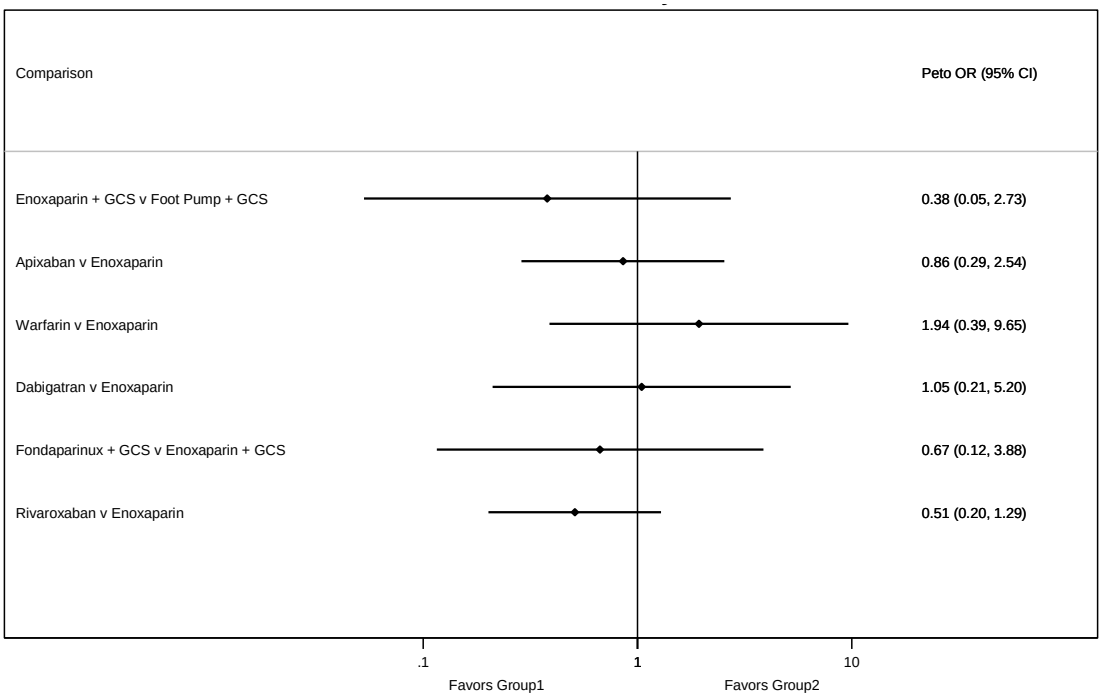


Figure 11. Symptomatic Deep Vein Thrombosis Direct Comparisons among Hip and Knee Patients

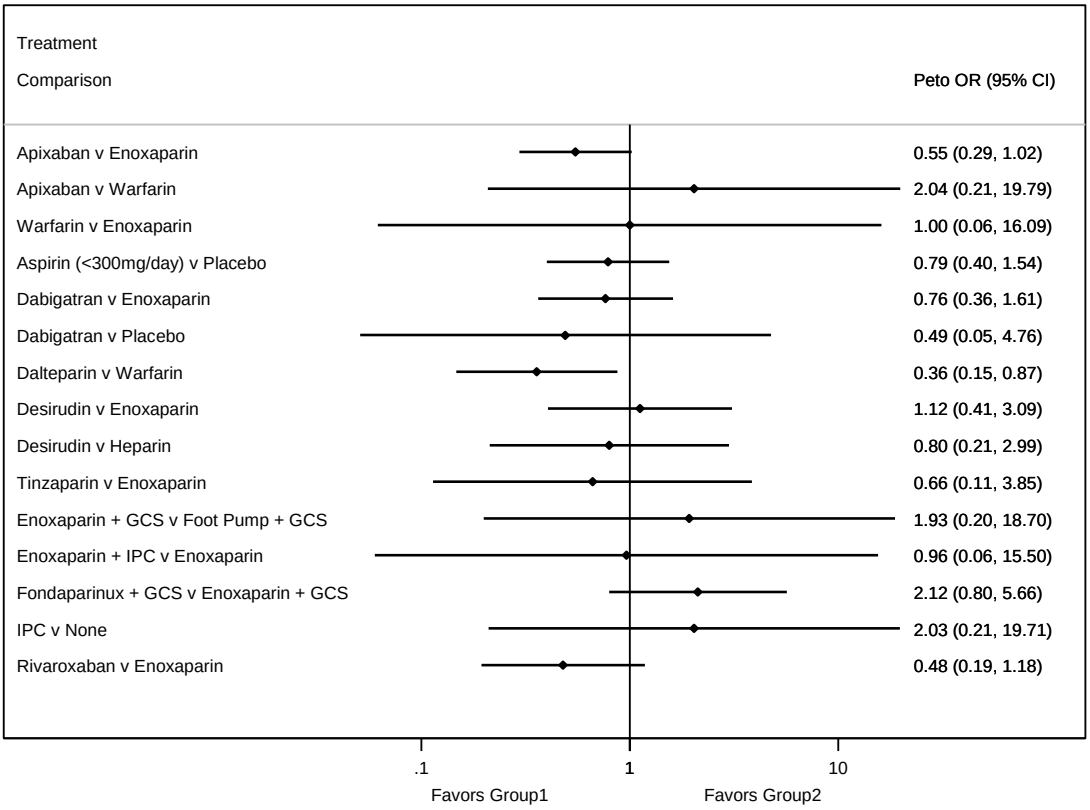


Figure 12. Symptomatic Deep Vein Thrombosis Direct Comparisons among Hip Patients

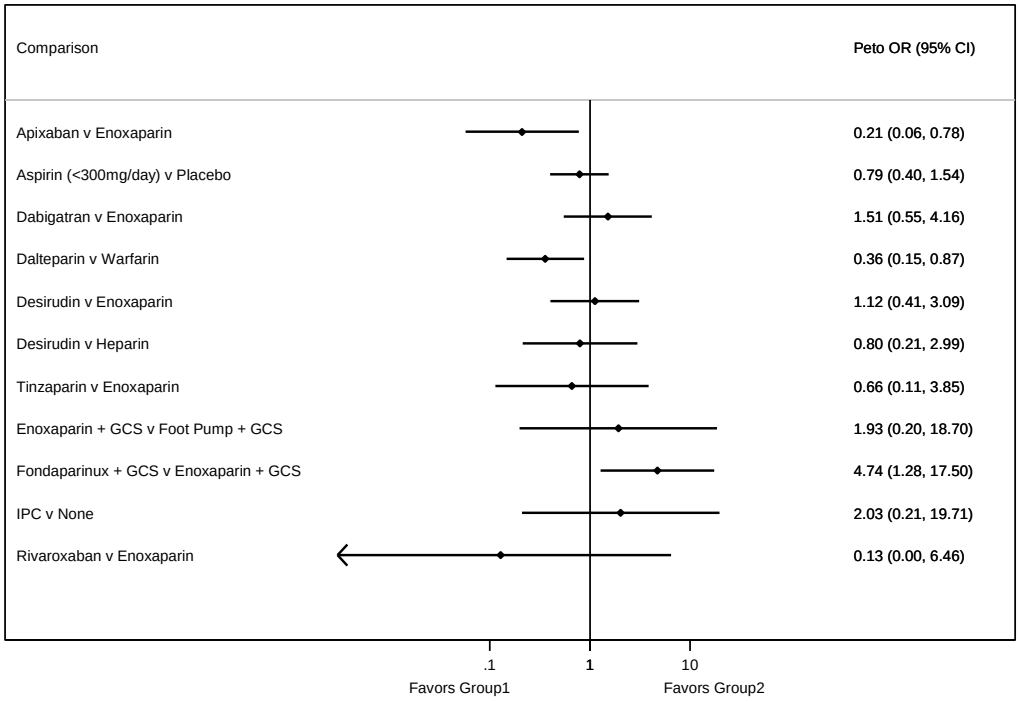


Figure 13. Symptomatic Deep Vein Thrombosis Direct Comparisons among Knee Patients

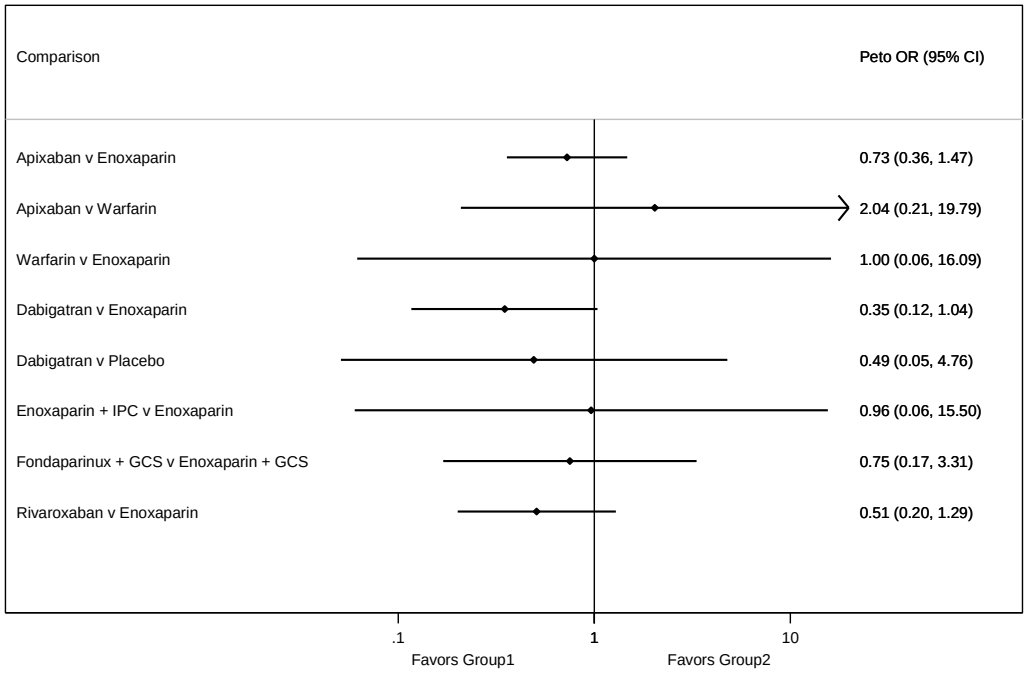
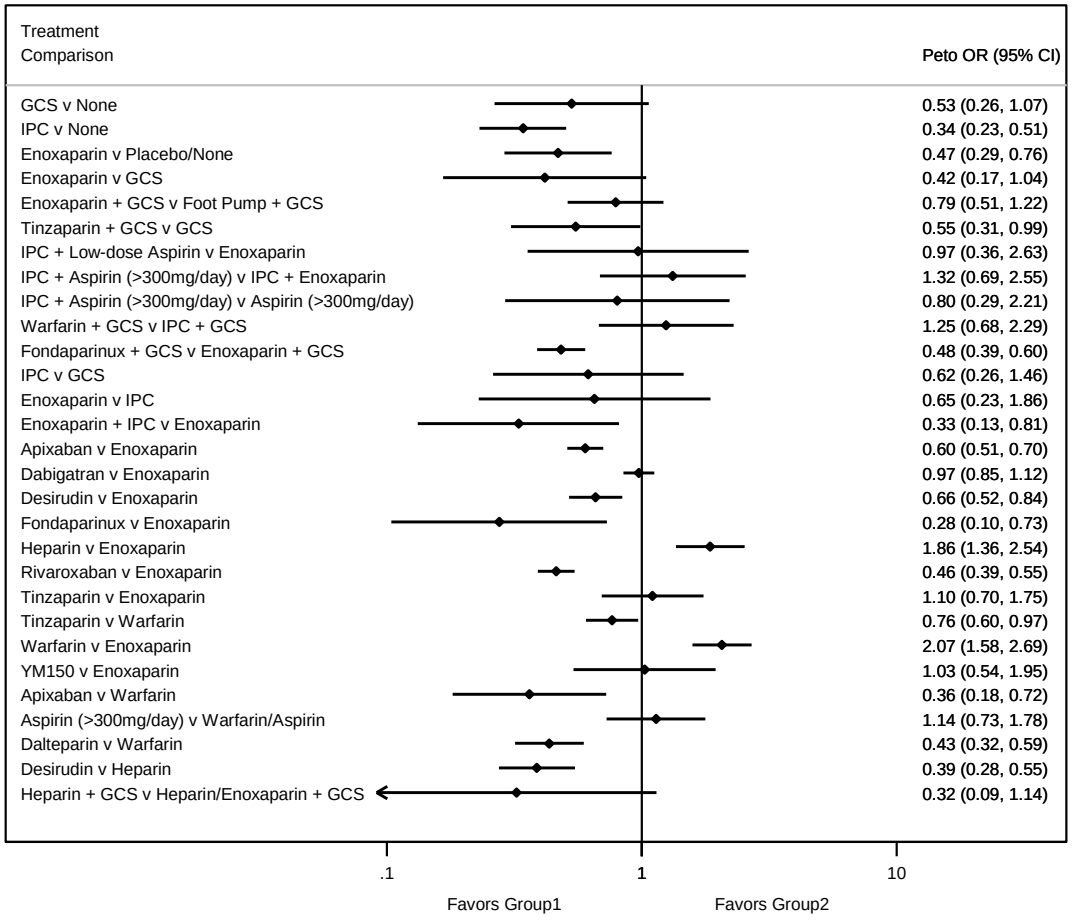


Figure 14. Deep Vein Thrombosis Direct Comparisons among Hip and Knee Patients



Note: For all figures and tables in this recommendation, the outcome Deep Vein Thrombosis (DVT) refers to any DVT: symptomatic or asymptomatic.

Figure 15. Deep Vein Thrombosis Direct Comparisons among Hip Patients

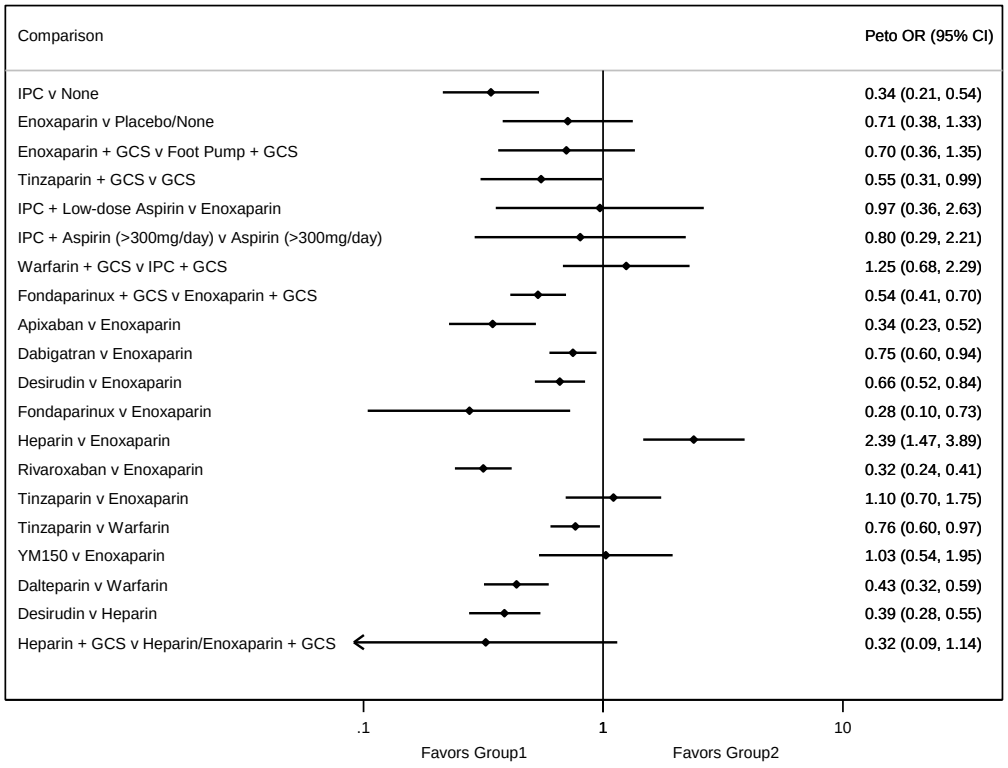


Figure 16. Deep Vein Thrombosis Direct Comparisons among Knee Patients

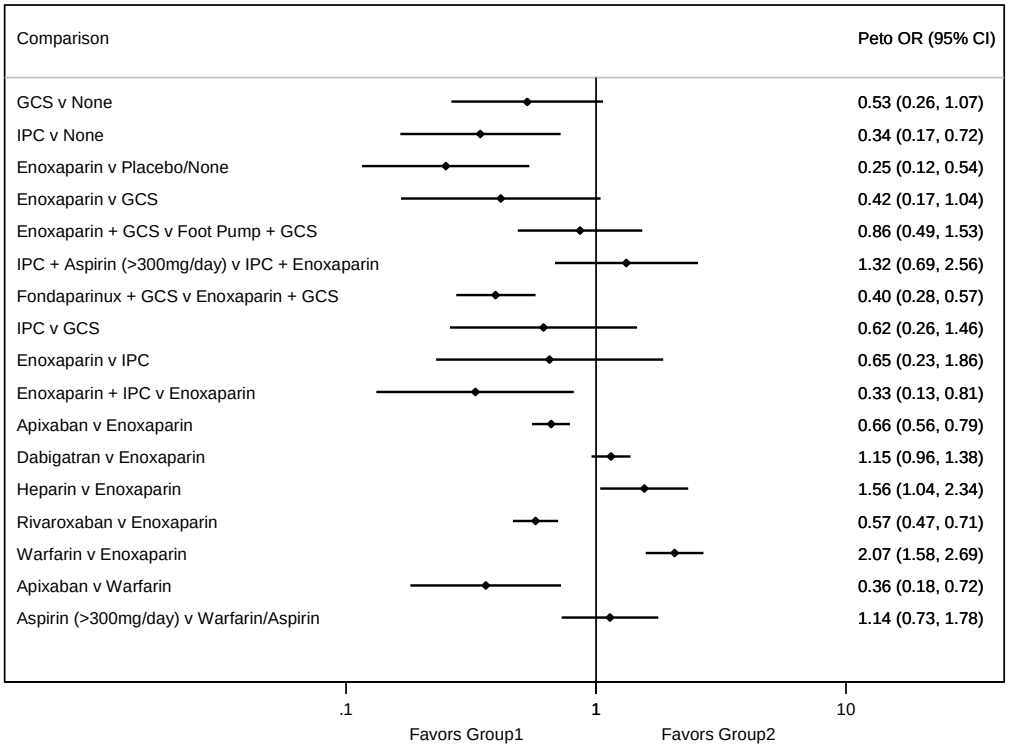


Figure 17. Proximal DVT Direct Comparisons among Hip and Knee Patients

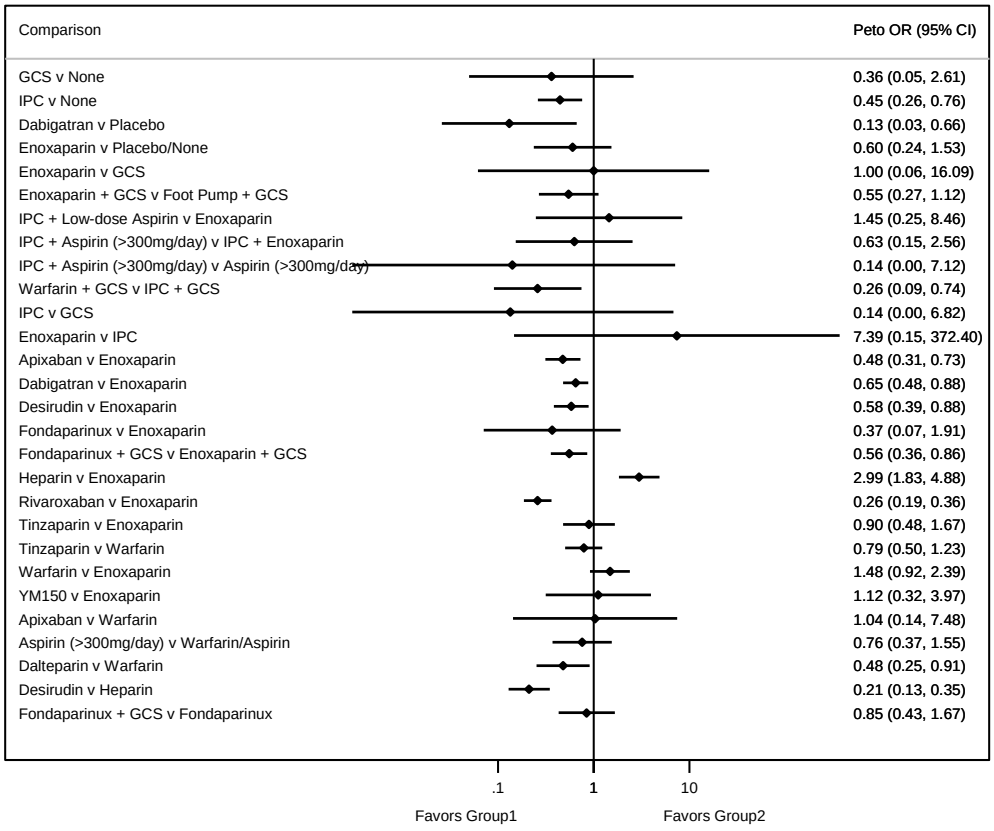


Figure 18. Proximal DVT Direct Comparisons among Hip Patients

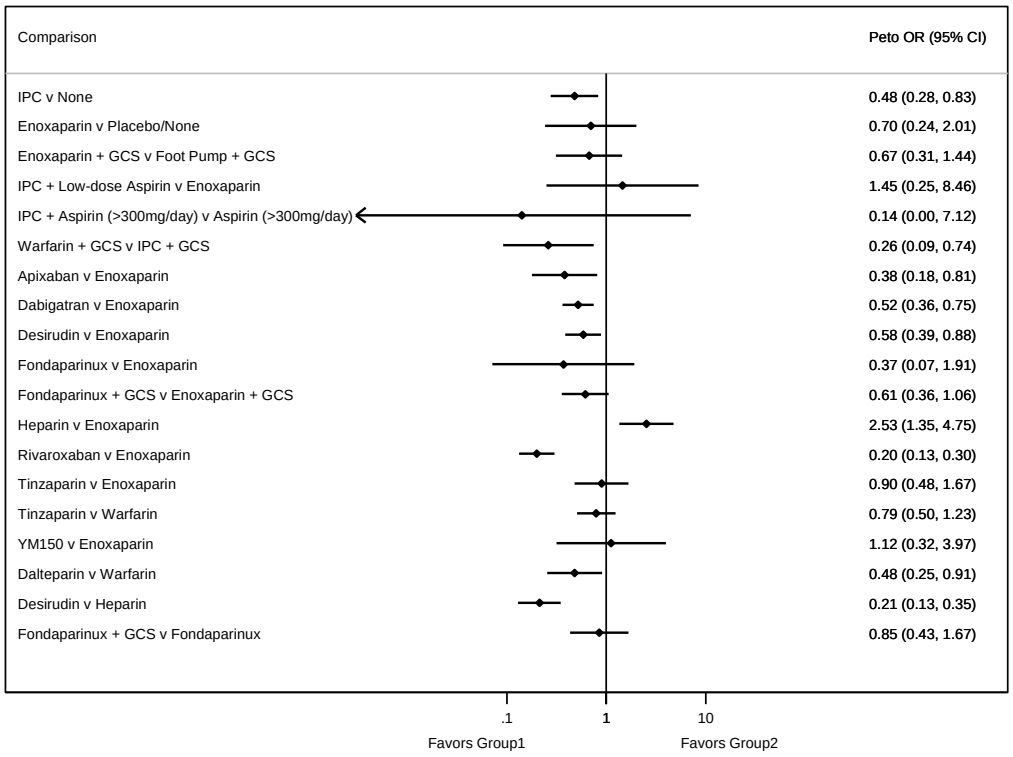
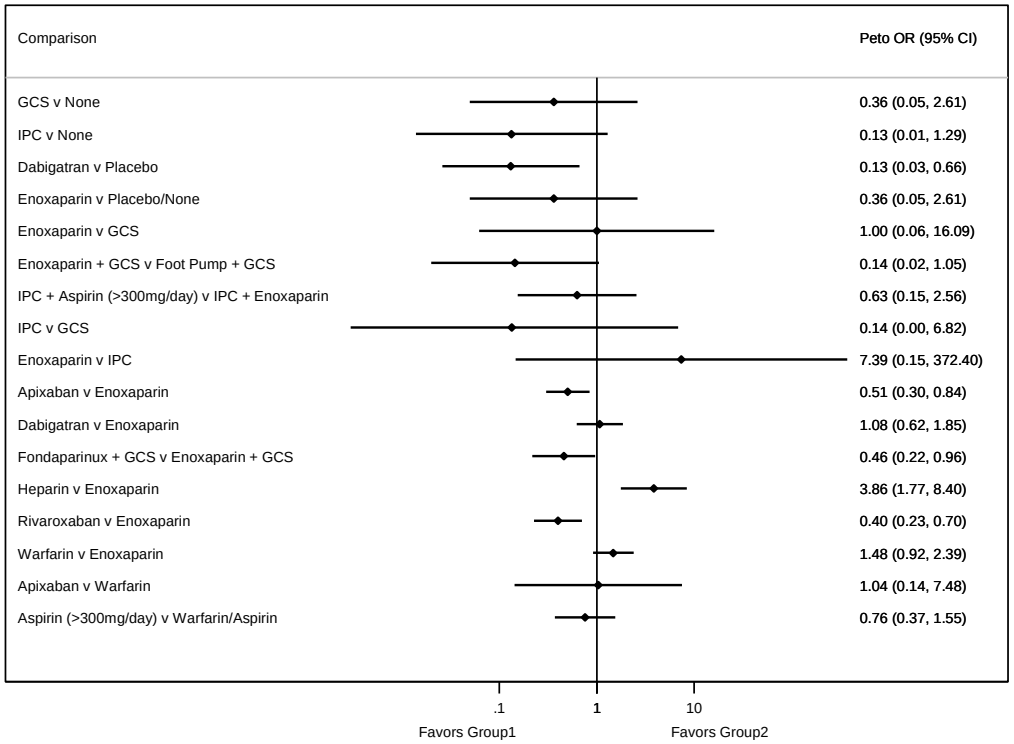


Figure 19. Proximal DVT Direct Comparisons among Knee Patients

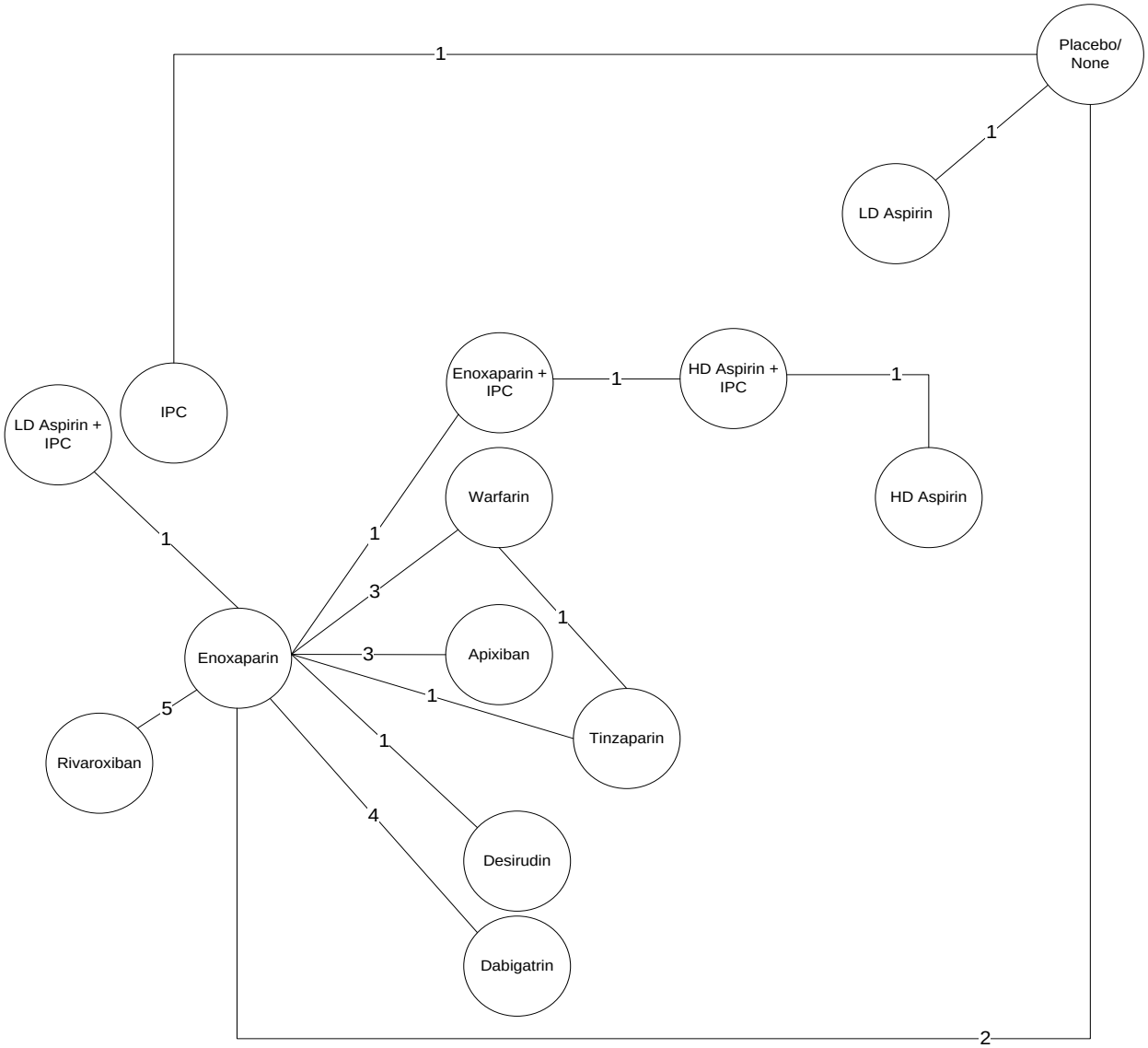


NETWORK META-ANALYSES

MODELS

This section depicts our final models. Please see Appendix XV for the models depicting our sensitivity analyses.

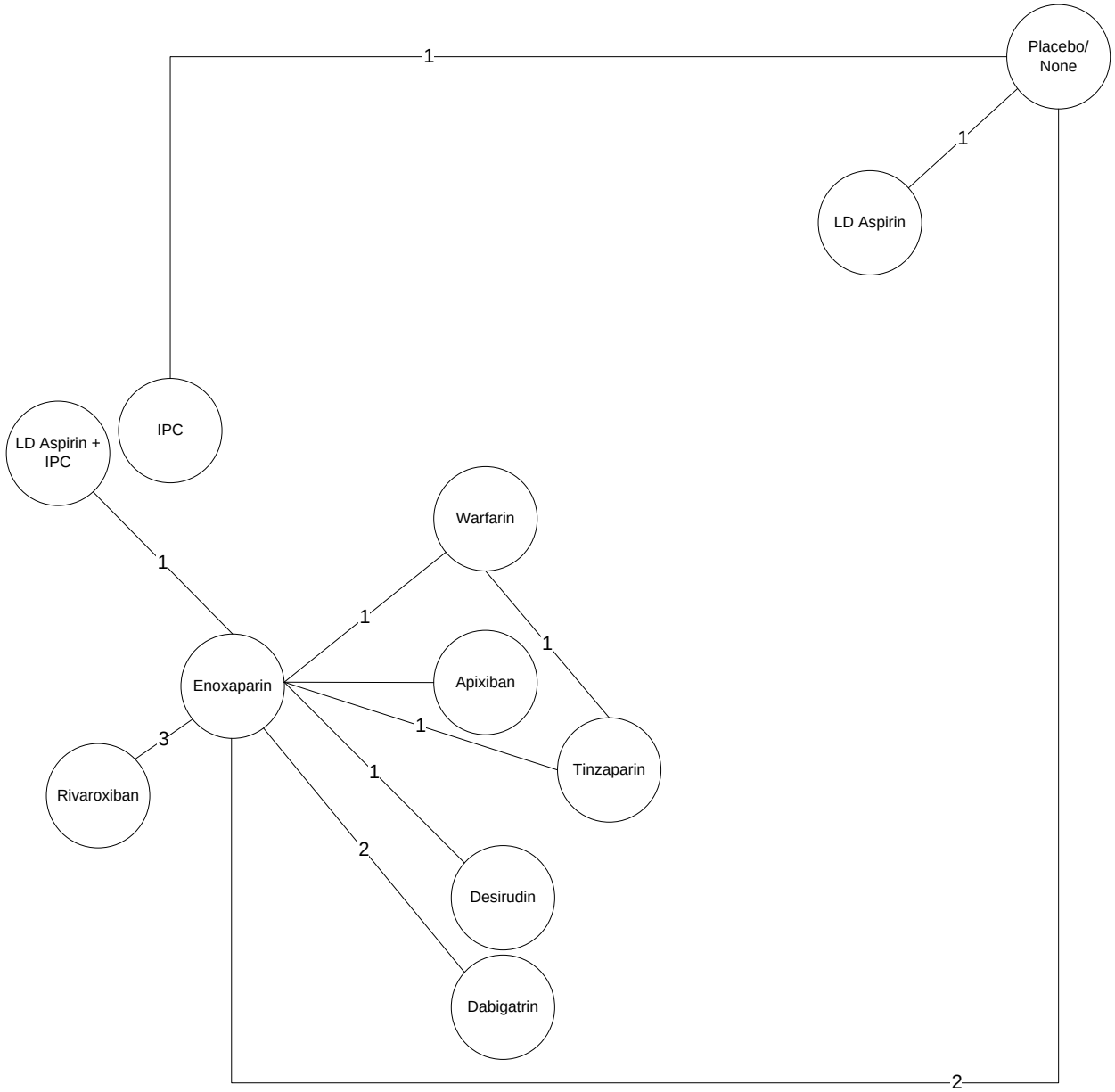
Figure 20. Final Pulmonary Embolism Model (with continuity correction, without heparin or multi-arm trials)



The model depicted in the figure is the final model for pulmonary embolism. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes data from patients who received a hip arthroplasty and those who received a total knee arthroplasty. It does not include trials of heparin and trials with > 2 arms. Circles denote the treatments studied. Lines between circles denote treatment

comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

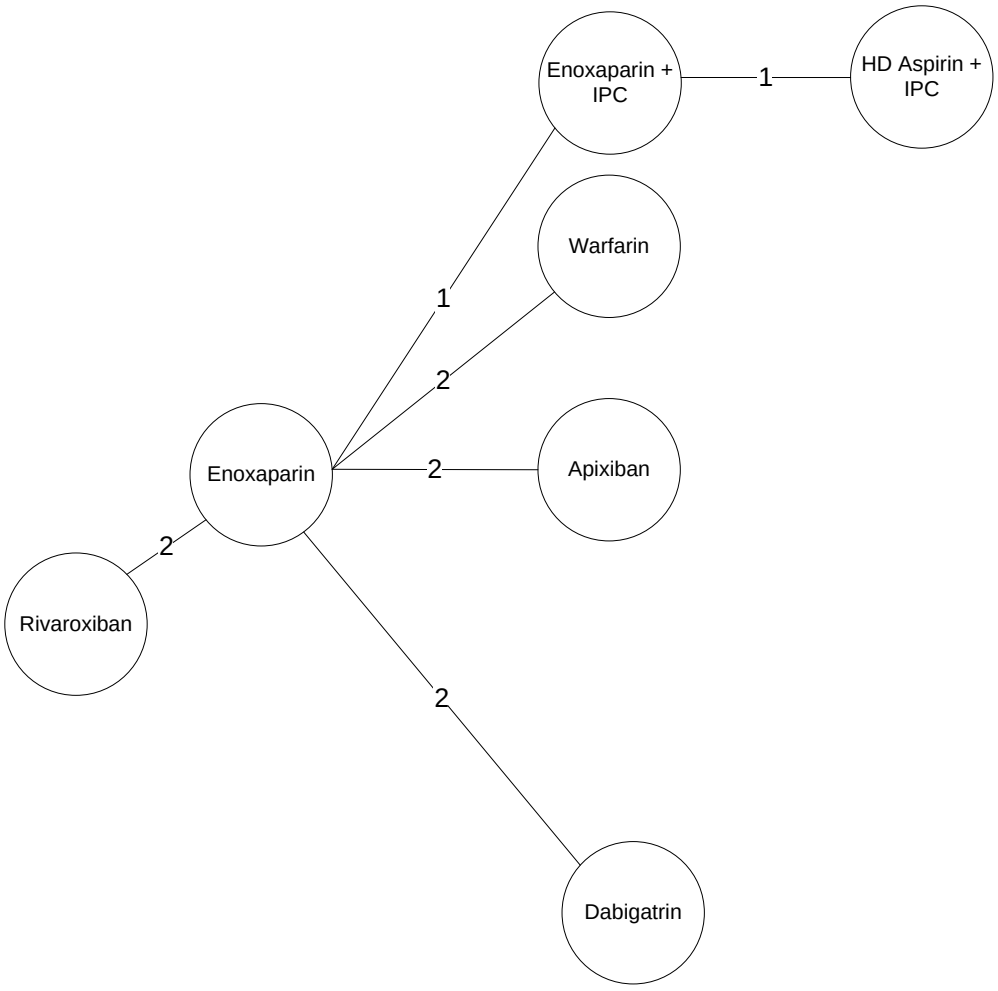
Figure 21. Final Pulmonary Embolism Model (with continuity correction, without heparin, or multi-arm trials, H**ip patients only**



The model depicted in the figure is a model for pulmonary embolism. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a hip arthroplasty. It does not include trials of heparin or trials with >2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers

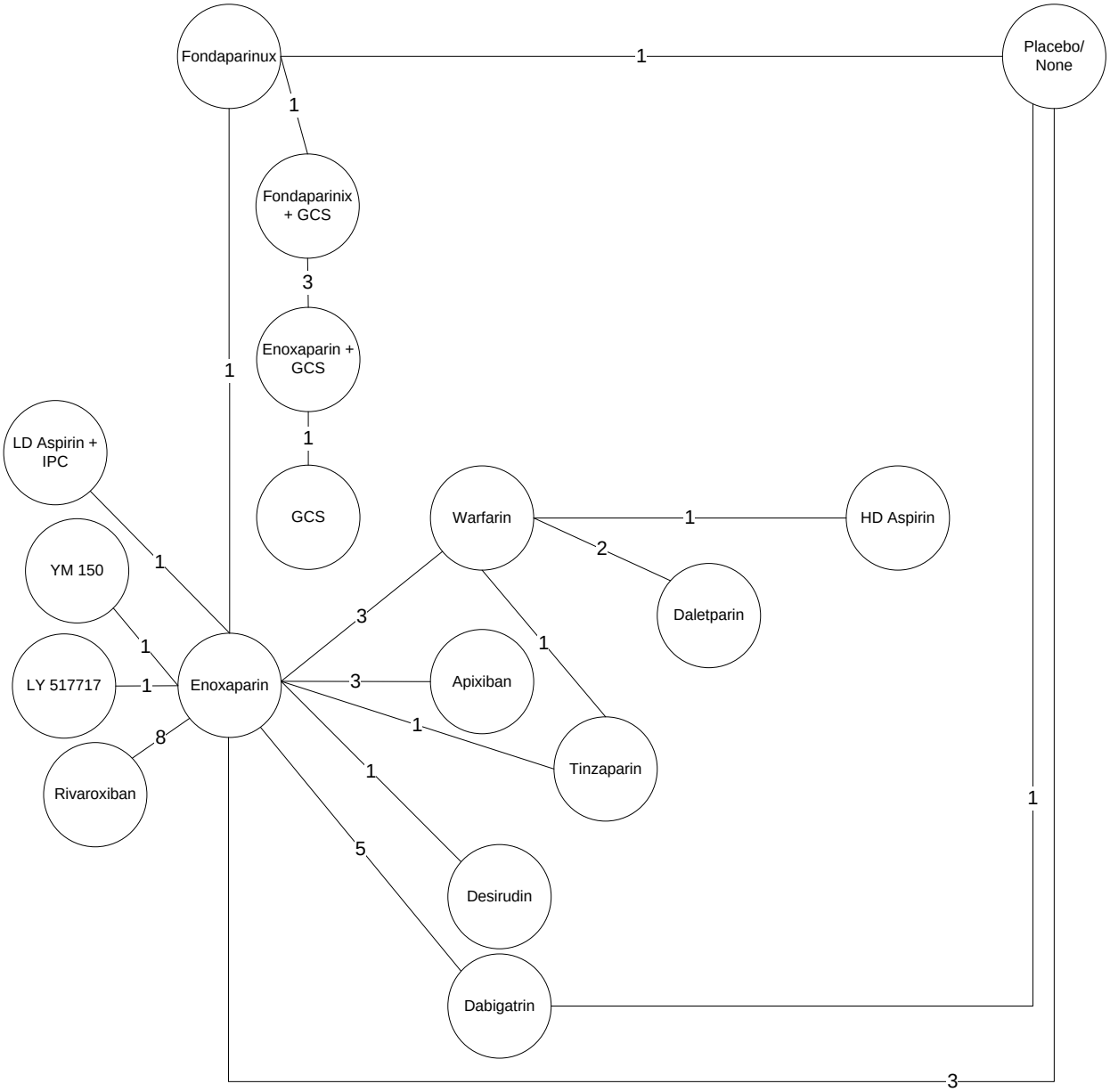
on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 22. Final Pulmonary Embolism Model (with continuity correction, without heparin, or multi-arm trials, Knee patients only



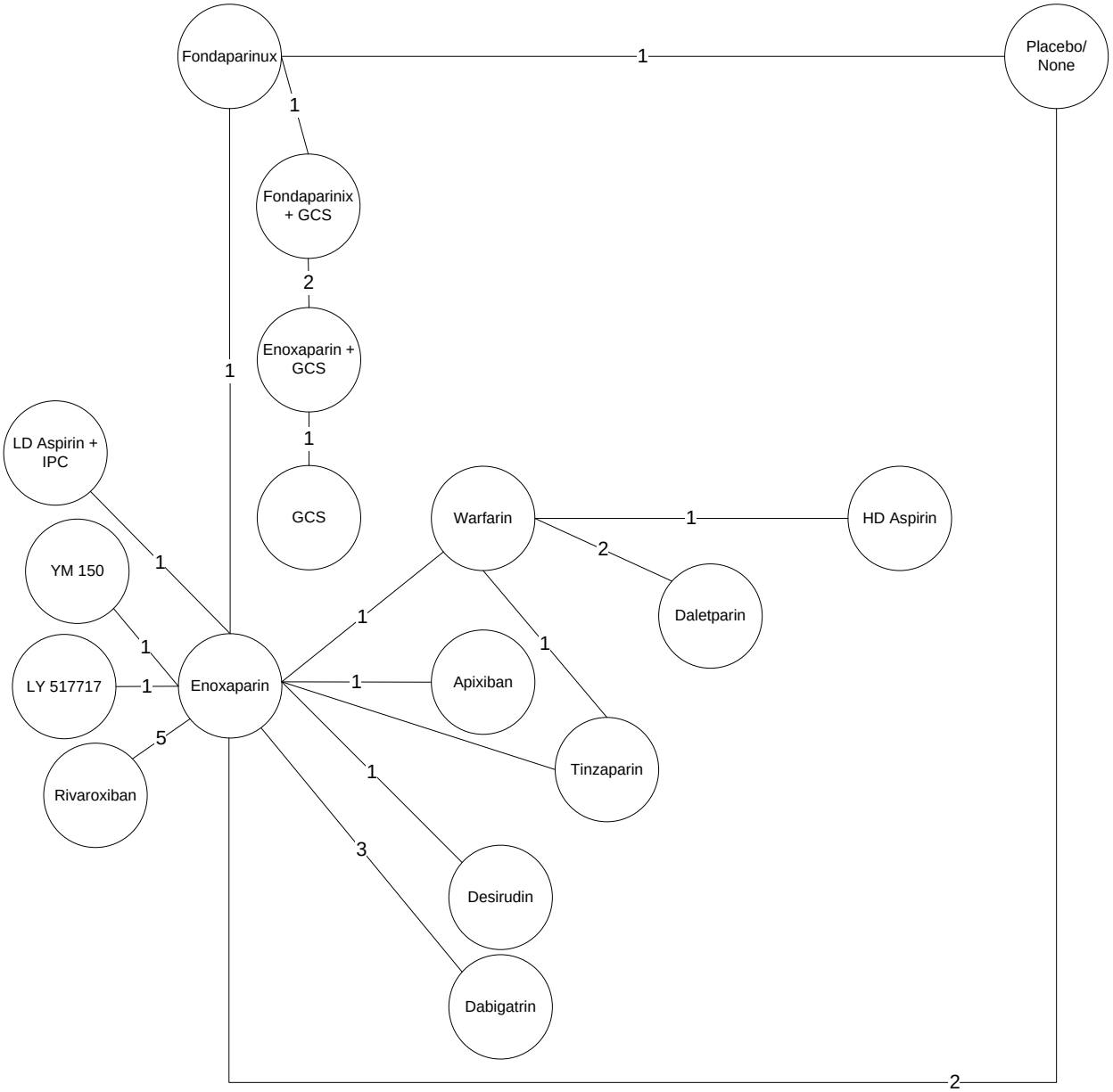
The model depicted in the figure is a model for pulmonary embolism. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a knee arthroplasty. It does not include trials of heparin or trials with >2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 23. Final Major Bleeding Model (with continuity correction, without heparin or multi-arm trials)



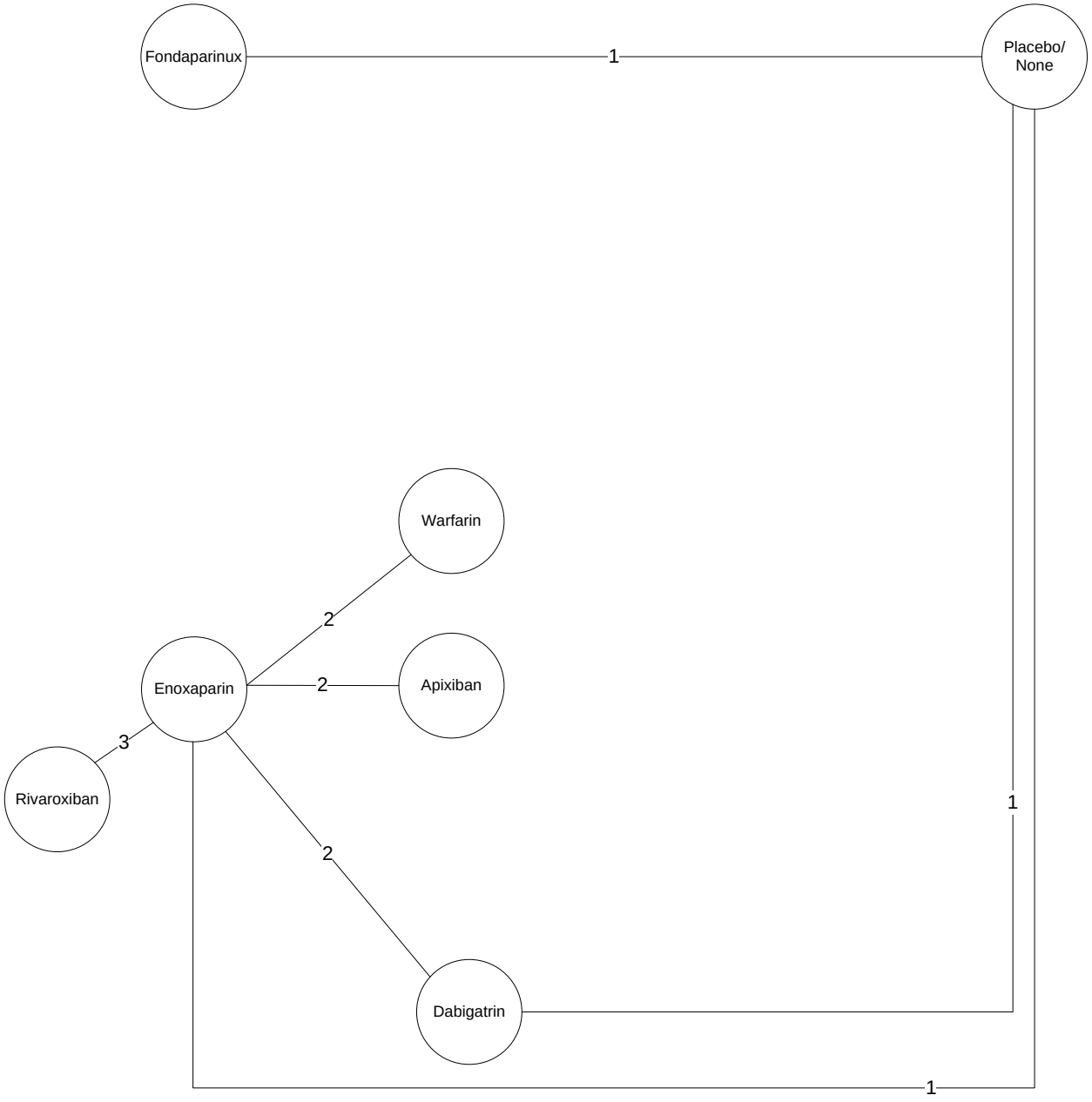
The model depicted in the figure is the final model for major bleeding. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes data from patients who received a hip arthroplasty and those who received a total knee arthroplasty. It does not include trials of heparin and trials with > 2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 24. Final Major Bleeding Model (with continuity correction, without heparin, or multi-arm trials, Hip patients only



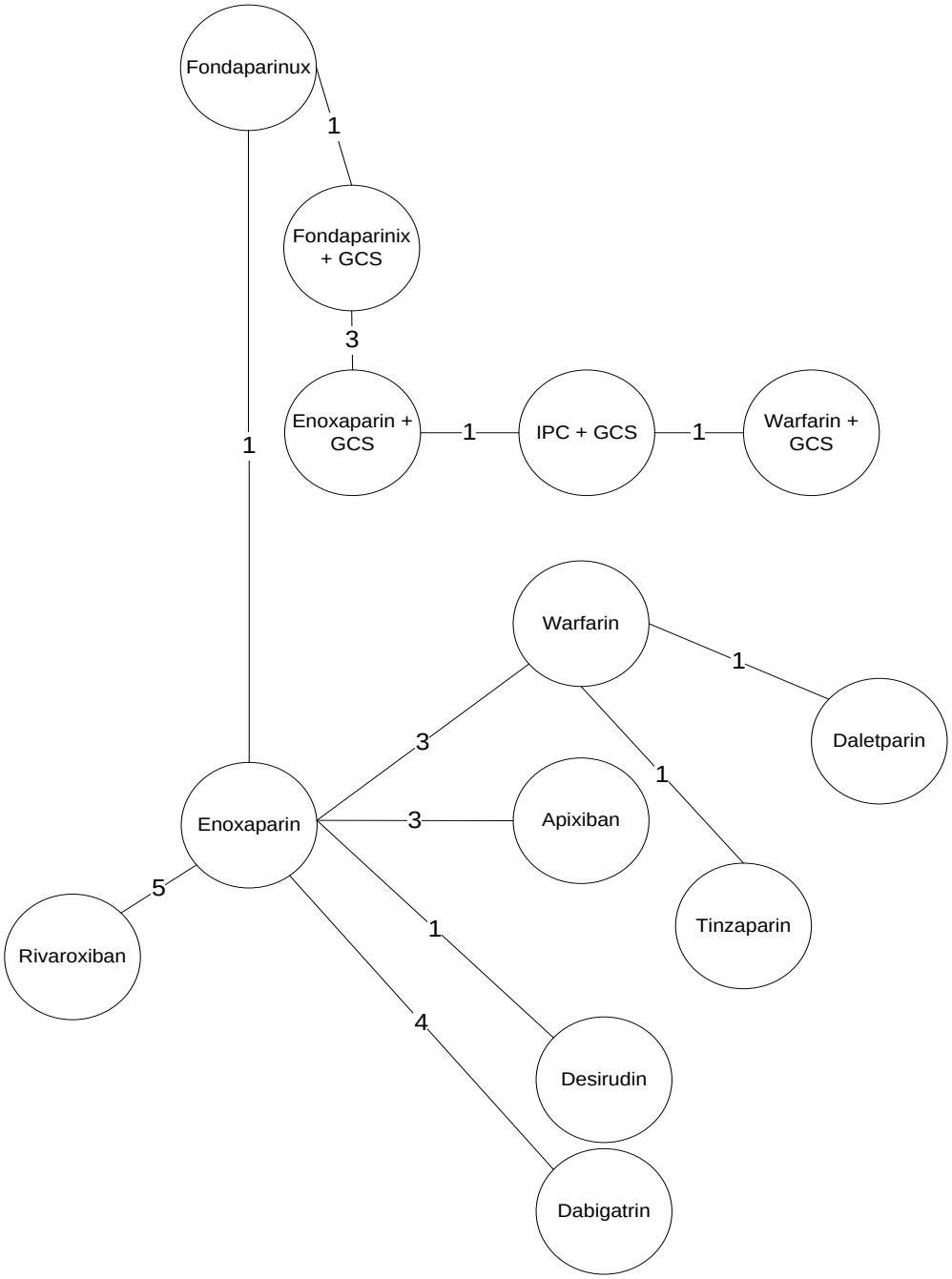
The model depicted in the figure is a model for major bleeding. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a hip arthroplasty. It does not include trials of heparin or trials with >2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 25. Final Major Bleeding Model (with continuity correction, without heparin, or multi-arm trials, Knee patients only



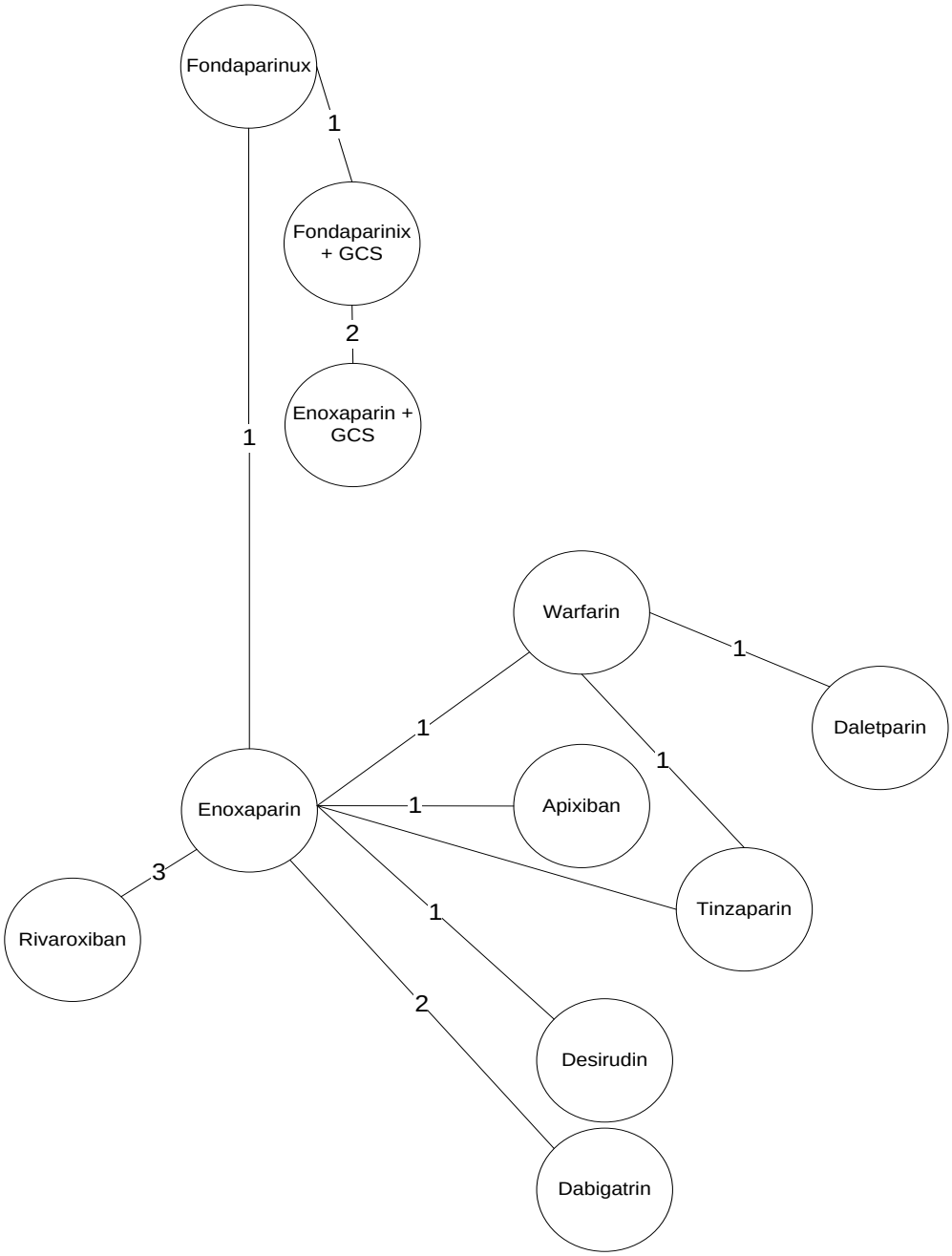
The model depicted in the figure is a model for major bleeding. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a knee arthroplasty. It does not include trials of heparin or trials with >2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 26. Final All Cause Mortality Model (with continuity correction, without heparin or multi-arm trials)



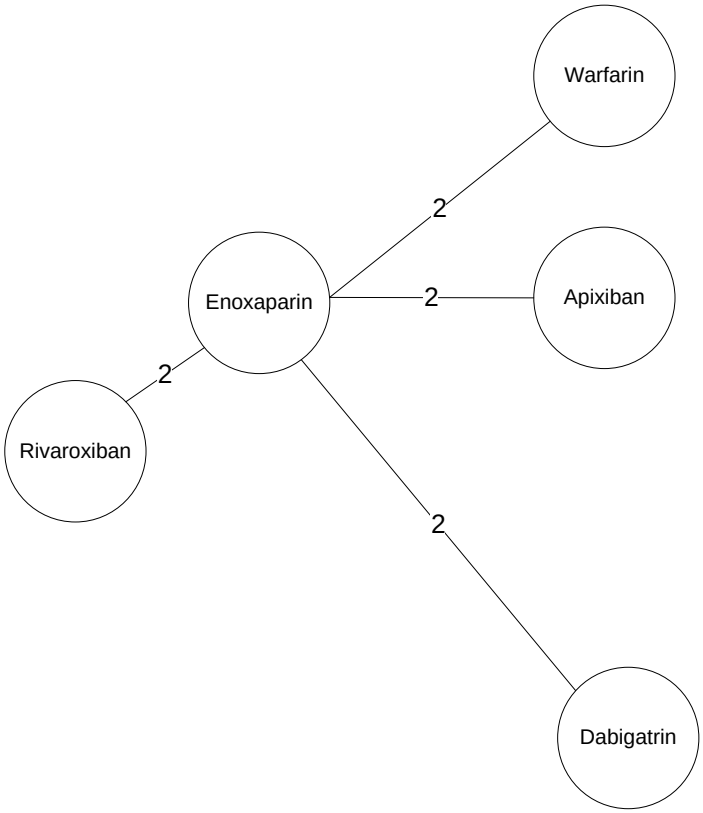
The model depicted in the figure is the final model for all cause mortality. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes data from patients who received a hip arthroplasty and those who received a total knee arthroplasty. It does not include trials of heparin and trials with > 2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 27. Final All Cause Mortality Model (with continuity correction, without heparin, or multi-arm trials, Hip patients only



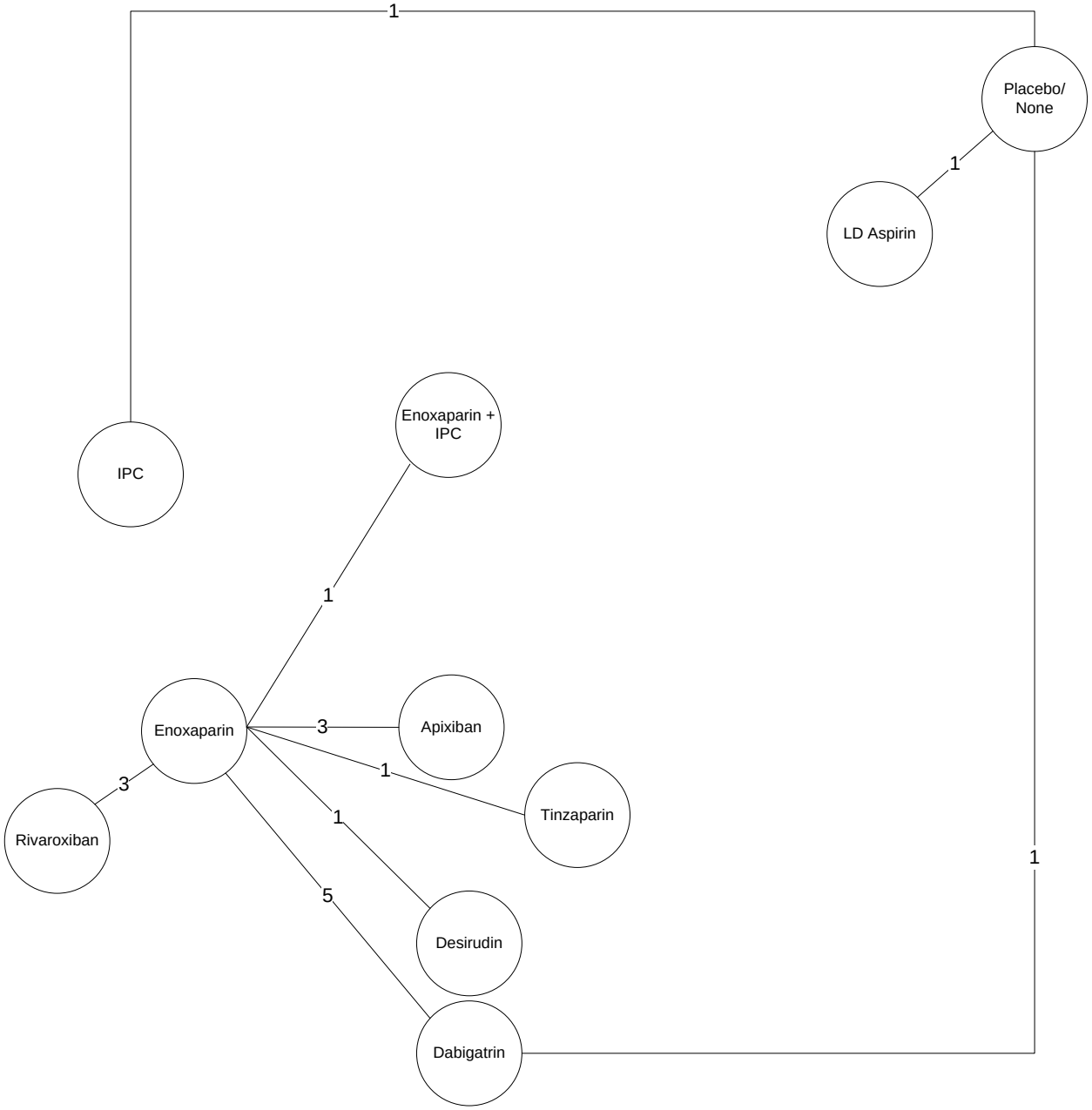
The model depicted in the figure is a model for all cause mortality. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a hip arthroplasty. It does not include trials of heparin or trials with >2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 28. Final All Cause Mortality Model (with continuity correction, without heparin, or multi-arm trials, Knee patients only



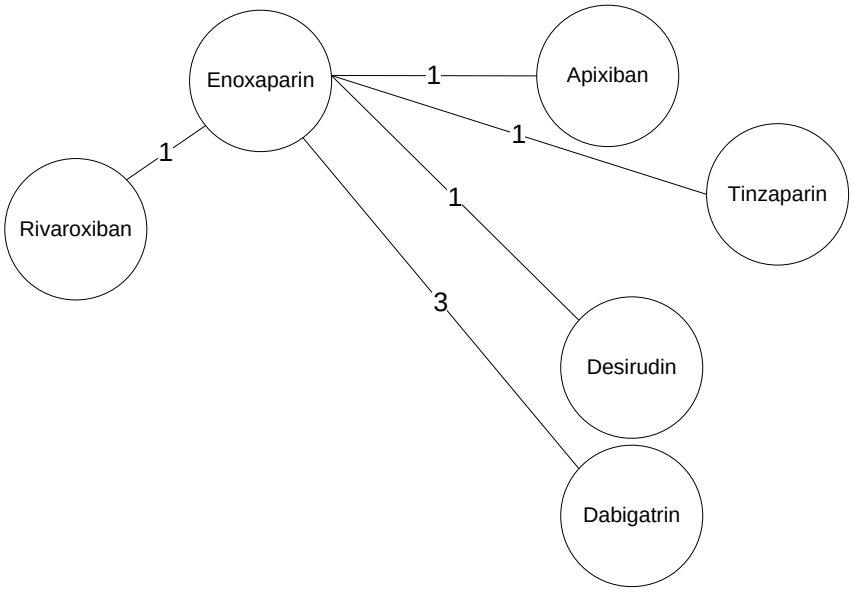
The model depicted in the figure is a model for all cause mortality. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a knee arthroplasty. It does not include trials of heparin or trials with >2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 29. Final Symptomatic DVT Model (with continuity correction, without heparin, or multi-arm trials.



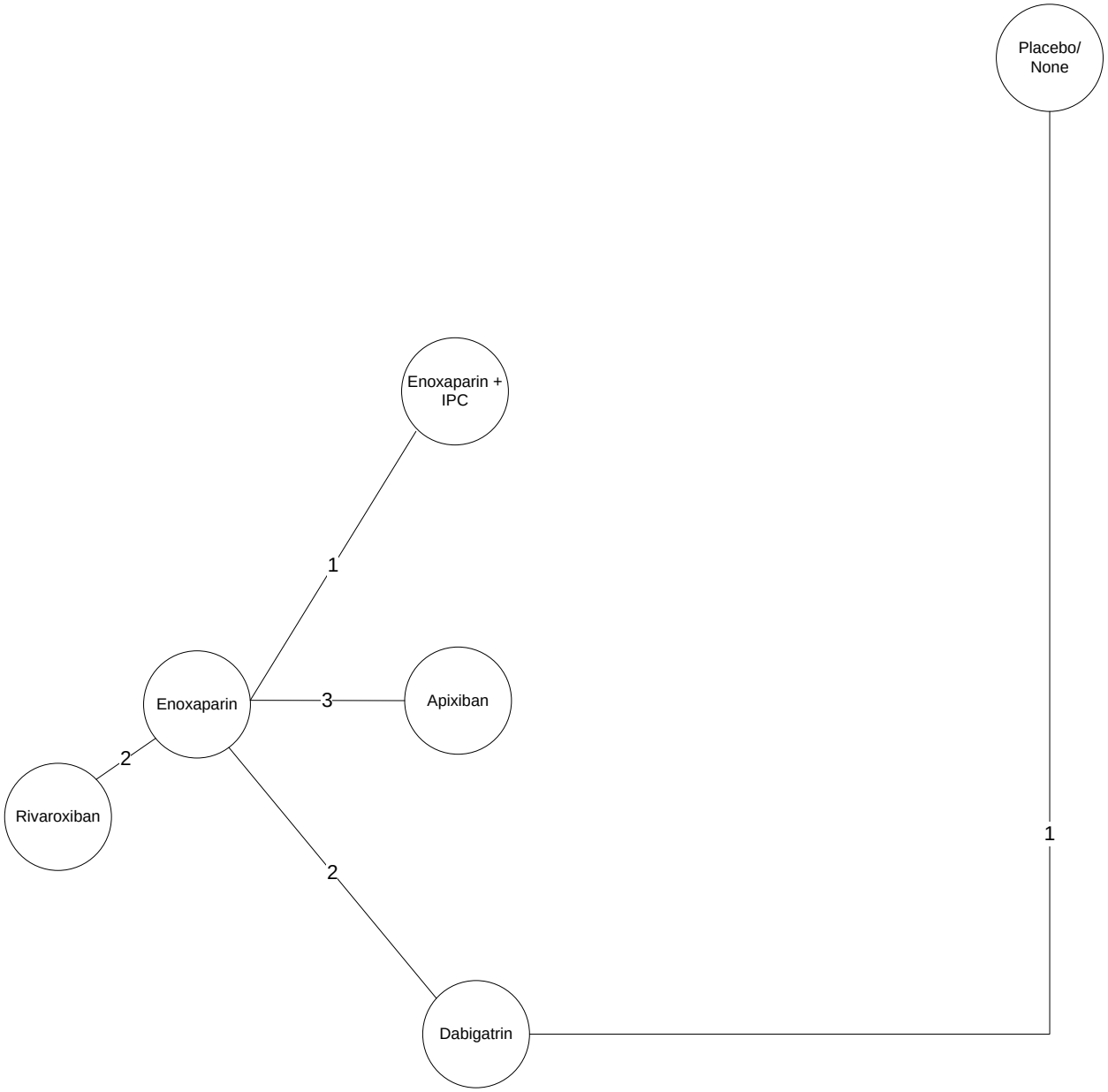
The model depicted in the figure is the final model for symptomatic DVT that omits studies for which a continuity correction was required, studies of heparin, and studies with > 2 arms. The model includes data from patients who received a hip arthroplasty and those who received a total knee arthroplasty. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles. None of the included studies required a continuity correction, so this is the same model as for the model without continuity corrected studies.

Figure 30. Final Symptomatic DVT Model (with continuity correction, without heparin, or multi-arm trials, Hip patients only



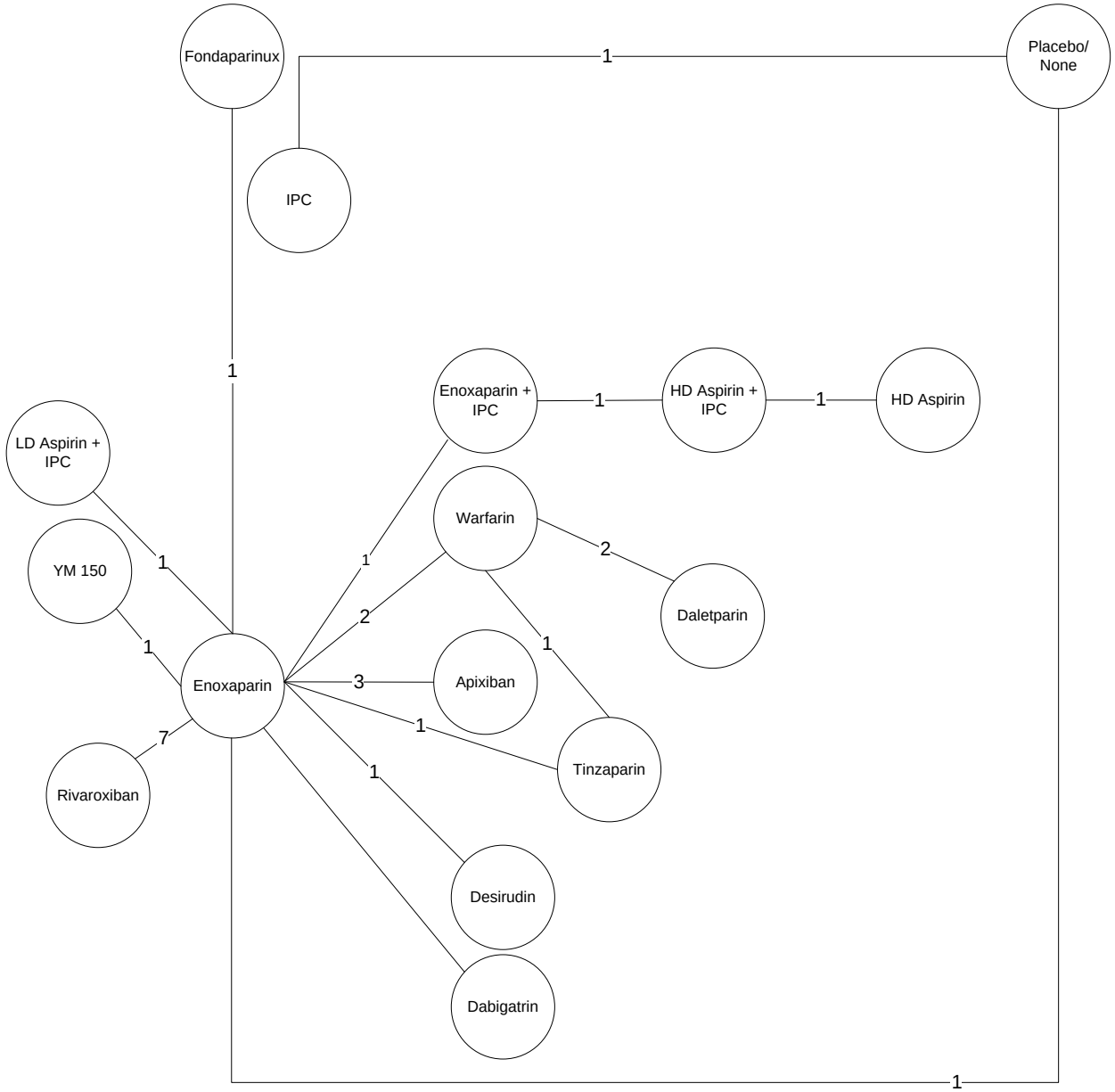
The model depicted in the figure is a model for symptomatic DVT. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a hip arthroplasty. It does not include trials of heparin or trials with >2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 31. Final Symptomatic DVT Model (with continuity correction, without heparin, or multi-arm trials, Knee patients only



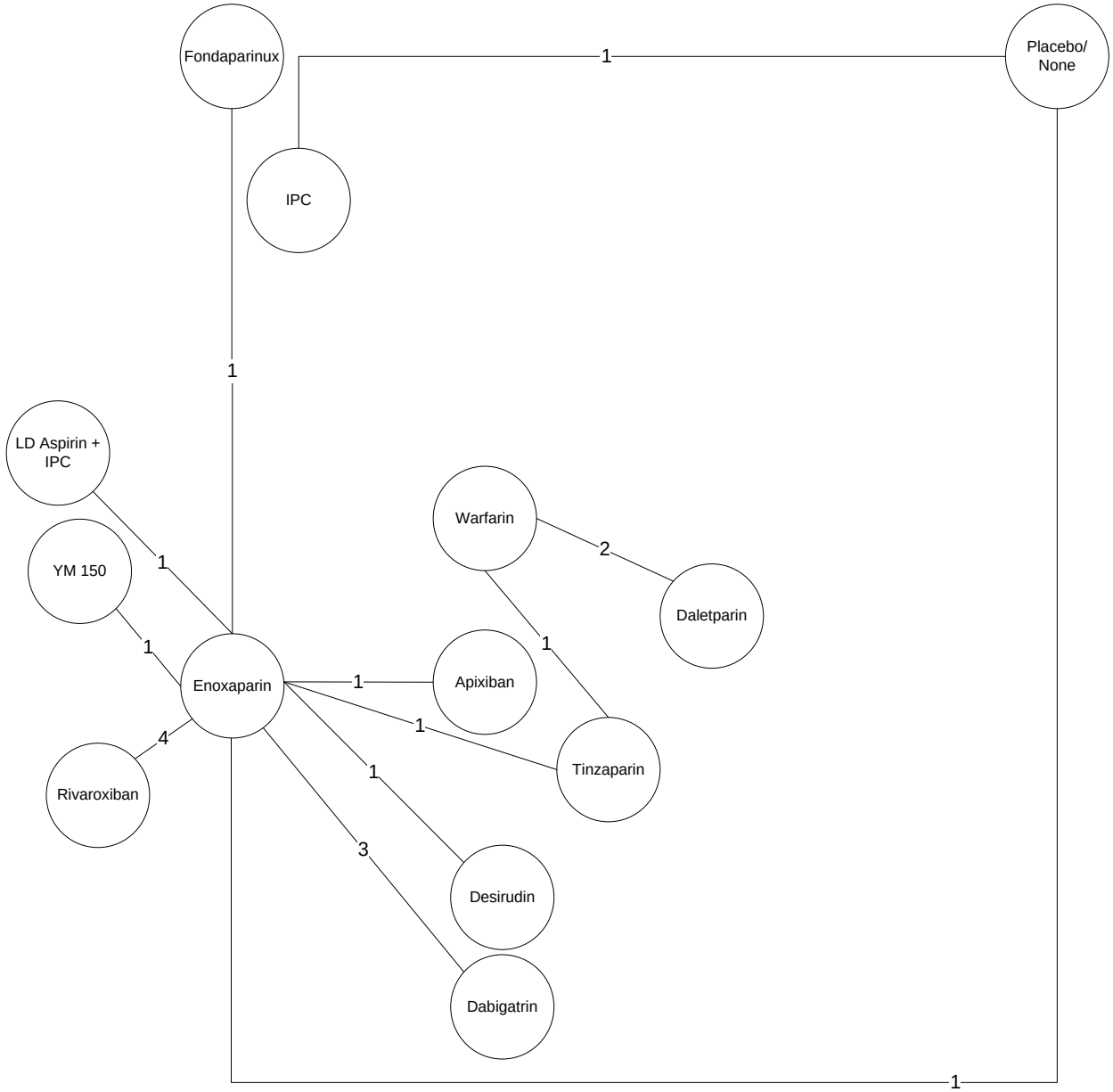
The model depicted in the figure is a model for symptomatic DVT. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a knee arthroplasty. It does not include trials of heparin or trials with >2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 32. Final DVT Model (with continuity correction, without heparin or multi-arm trials)



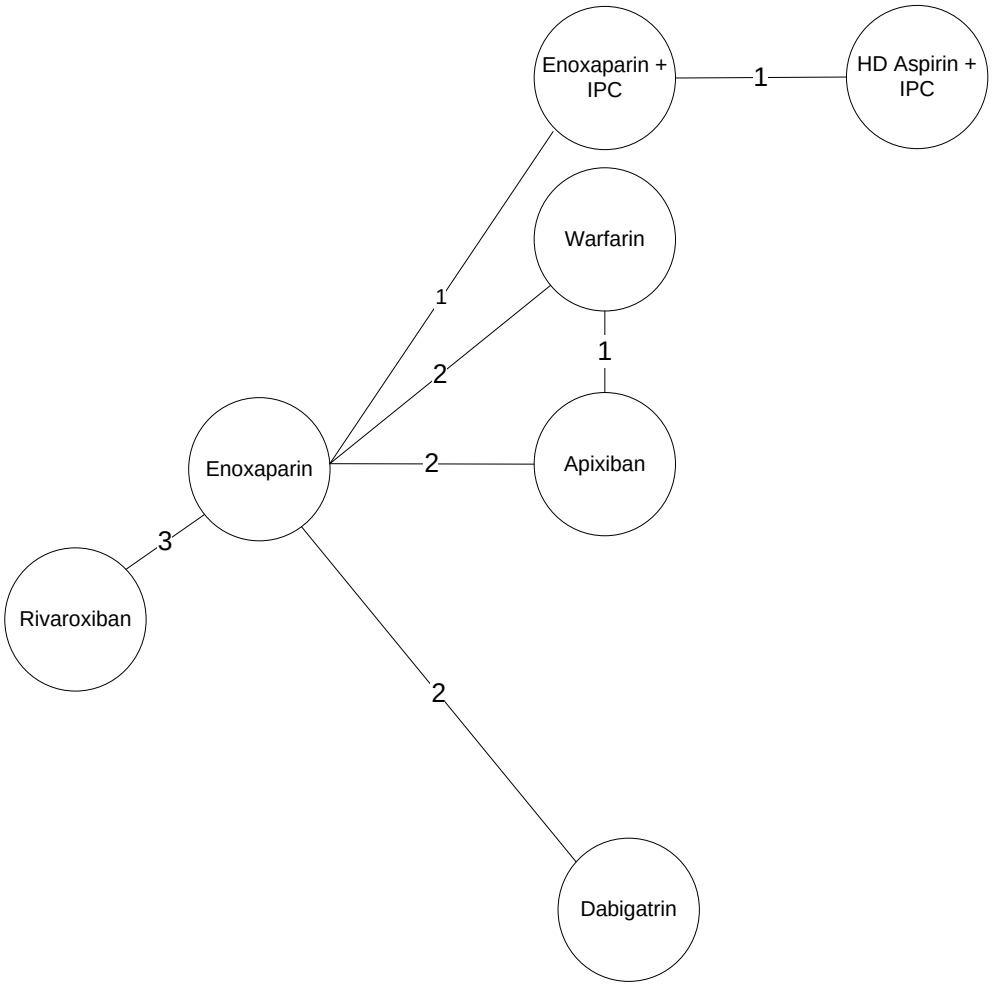
The model depicted in the figure is the final model for DVT that omits studies for which a continuity correction was required, studies of heparin, and studies with > 2 arms. The model includes data from patients who received a hip arthroplasty and those who received a total knee arthroplasty. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles. None of the included studies required a continuity correction, so this is the same model as for the model without continuity corrected studies.

Figure 33. Final DVT Model (with continuity correction, without heparin or multi-arm trials), Hip patients only



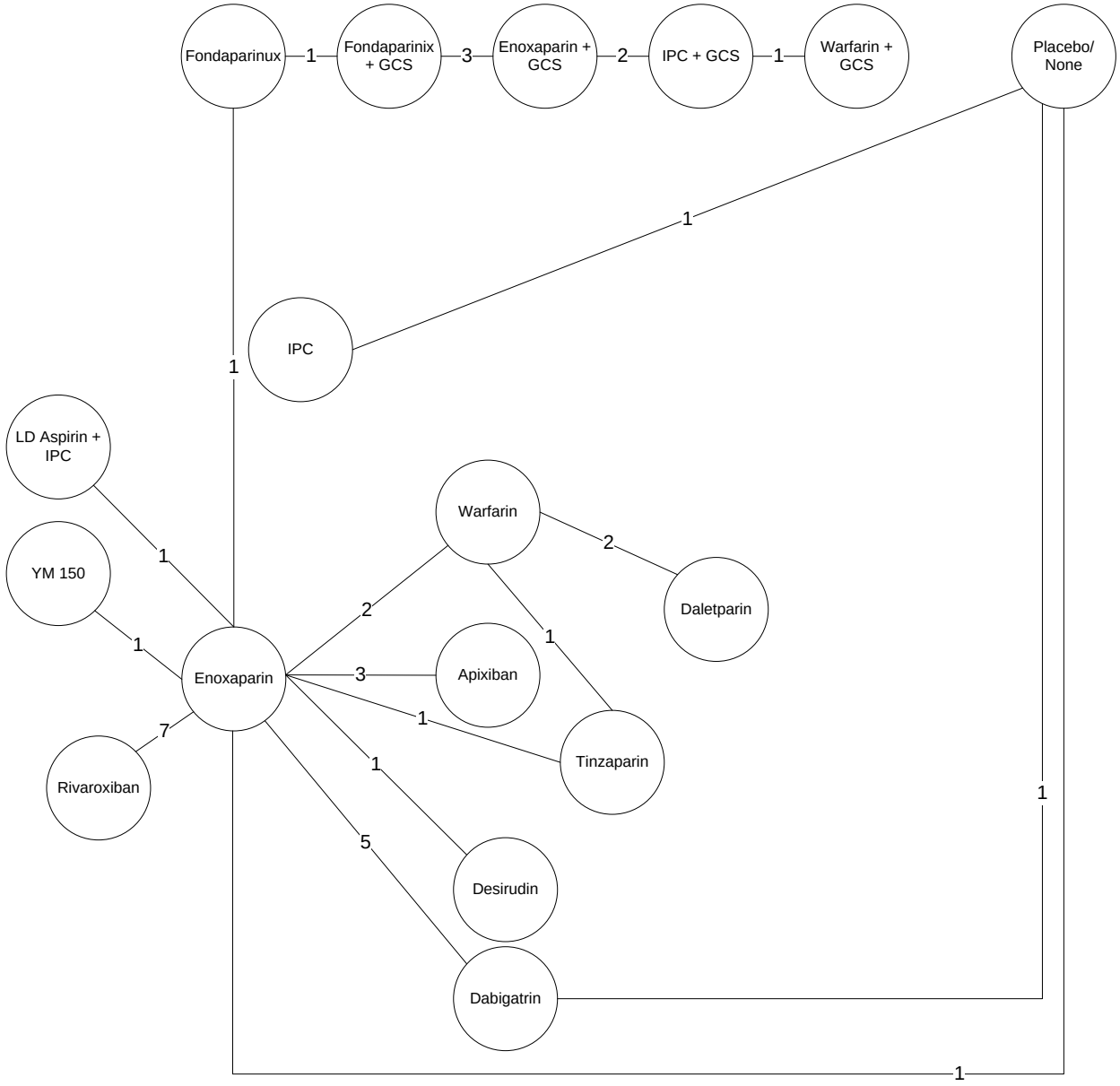
The model depicted in the figure is a model for DVT. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a hip arthroplasty. It does not include trials of heparin or trials with >2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 34. Final DVT Model (with continuity correction, without heparin or multi-arm trials), Knee patients only



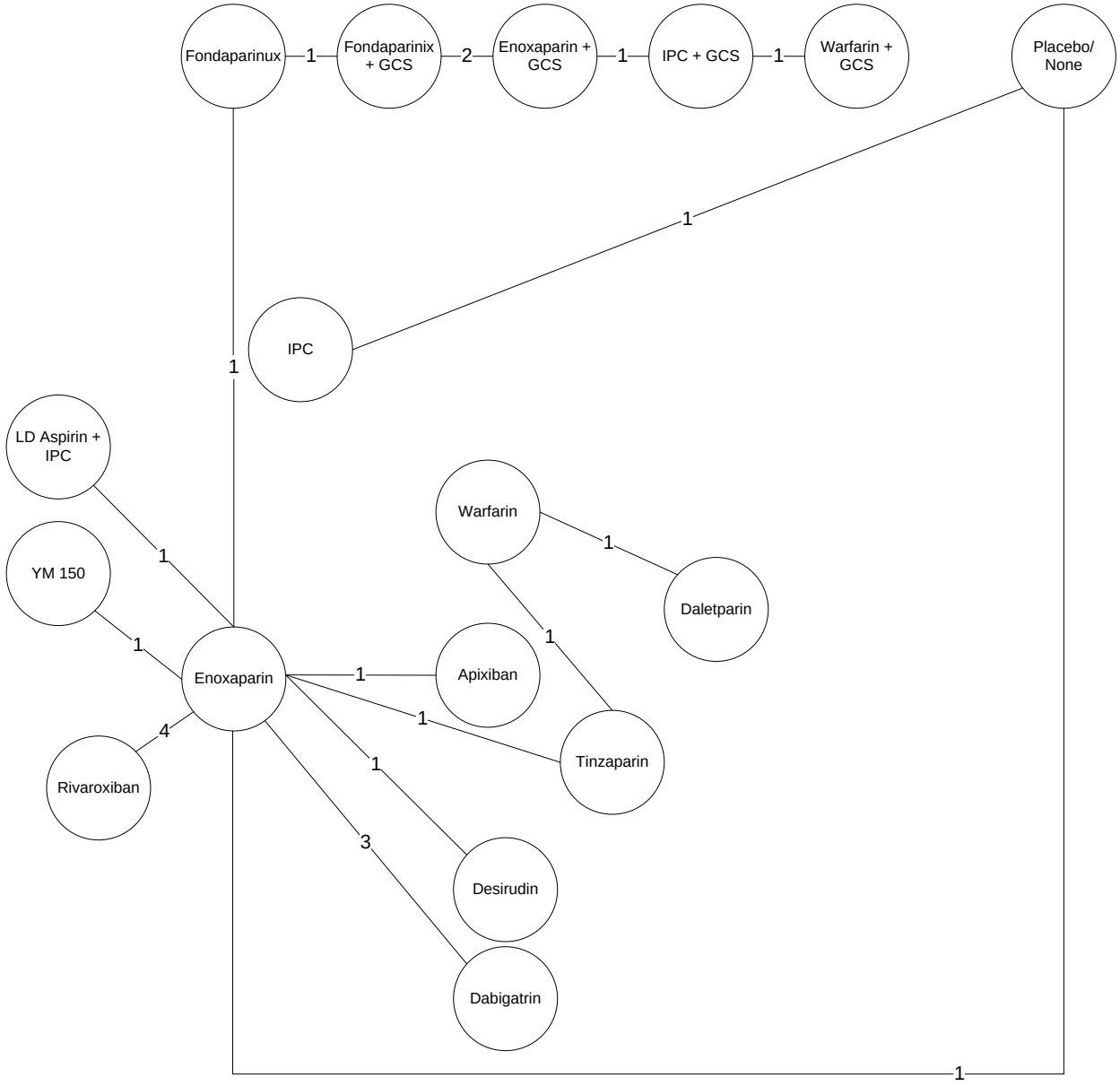
The model depicted in the figure is a model for DVT. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a knee arthroplasty. It does not include trials of heparin or trials with >2 arms. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 35. Final Proximal DVT Model (with continuity correction, without heparin or multi-arm trials)



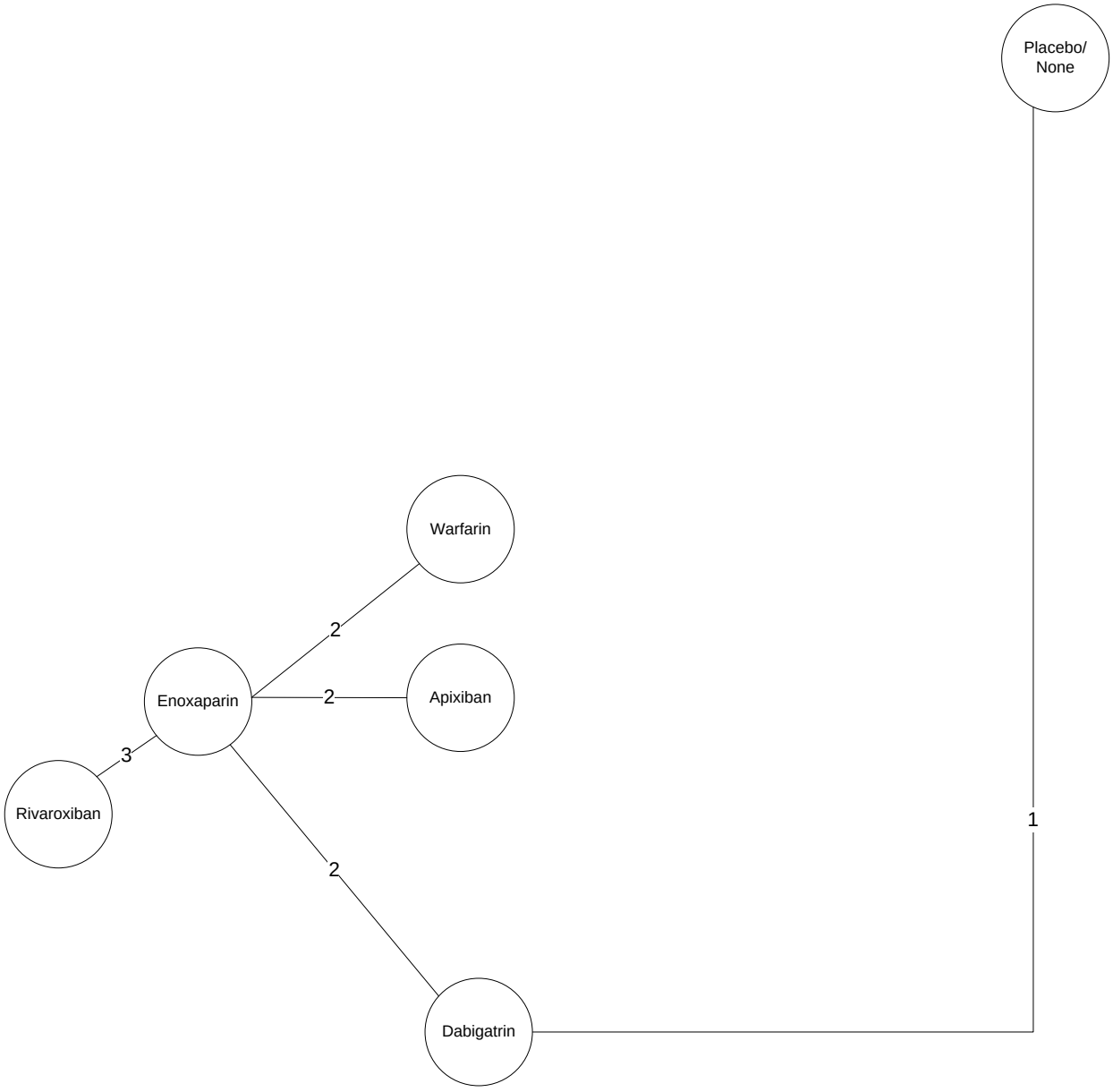
The model depicted in the figure a model for proximal DVT. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes data from patients who received a hip arthroplasty and those who received a knee arthroplasty. Trials of heparin and trials with >2 arms are not included. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 36. Final Proximal DVT Model (with continuity correction, without heparin or multi-arm trials), Hip patients only



The model depicted in the figure a model for proximal DVT. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a hip arthroplasty. Trials of heparin and trials with >2 arms are not included. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

Figure 37. Final Proximal DVT Model (with continuity correction, without heparin or multi-arm trials), Knee patients only



The model depicted in the figure a model for proximal DVT. All trials that observed at least one event in one of its groups are included. A continuity correction was employed for trials that observed no events at least one of its groups. The model includes only data from patients who received a knee arthroplasty. Trials of heparin and trials with >2 arms are not included. Circles denote the treatments studied. Lines between circles denote treatment comparisons that are addressed by direct evidence. The numbers on these lines show the number of trials that compared the two treatments denoted in the circles.

NETWORK META-ANALYSIS RESULTS

The results of the network meta-analyses for each of the six outcomes are shown in the figures below. Here, we present our final models, which exclude trials with > 2 arms (multi-arm trials) and heparin trials. It includes patients who received a total hip arthroplasty and patients who received a total knee arthroplasty. The two multi-arm trials each had zero events in at least two study arms for major bleeding and pulmonary embolism. In this analysis, we added a continuity correction factor to studies with zero events in one arm of the trial.

In addition to the results presented in the figures below, Appendix XV presents the results of the final model for each outcome with each treatment in the model ranked relative to each other.

Appendix XV presents the results of our sensitivity analyses, first by excluding trials with zero events in one arm of a trial, making the use of the continuity correction unneccesary. Then we excluded trials of heparin and, finally, we also excluded multi-arm trials. The results of these sensitivity analyses were not significantly different than the results of our final model.

The results of our consistency checks appear in Appendix XV. Our final models were consistent.

Goodness-of-fit statistics are also presented in Appendix XV. These results suggest that our model fits the available data.

Results are presented in terms of the odds ratio of each treatment as compared to no treatment. However, for all-cause mortality, results are presented as compared to enoxaparin because there are no trials compared to no treatment for this outcome. In Appendix XV, results are presented as compared to enoxaparin for all models; in addition, results are presented as compared to no treatment for the models using the continuity correction when the data allow.

PULMONARY EMBOLISM

Figure 38. Pumonary Embolism among Hip and Knee Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

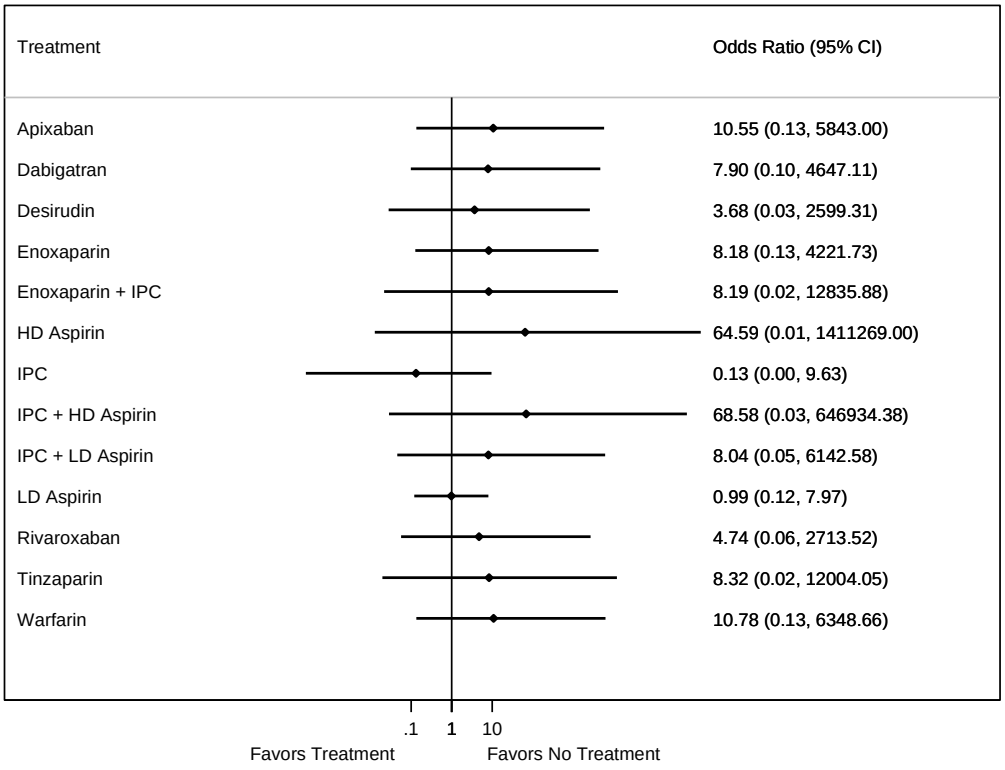


Figure 39. Pumonary Embolism among Hip Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

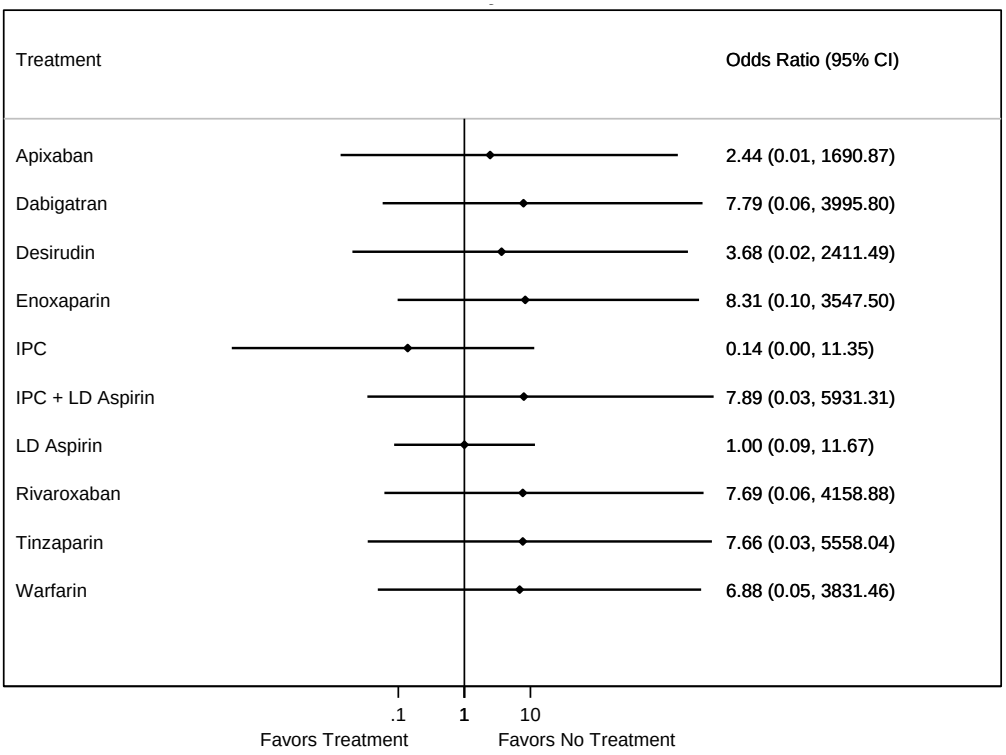


Figure 40. Pumonary Embolism among Knee Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

No studies in the model with no treatment as a comparator

MAJOR BLEEDING

Figure 41. Major Bleeding among Hip and Knee Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

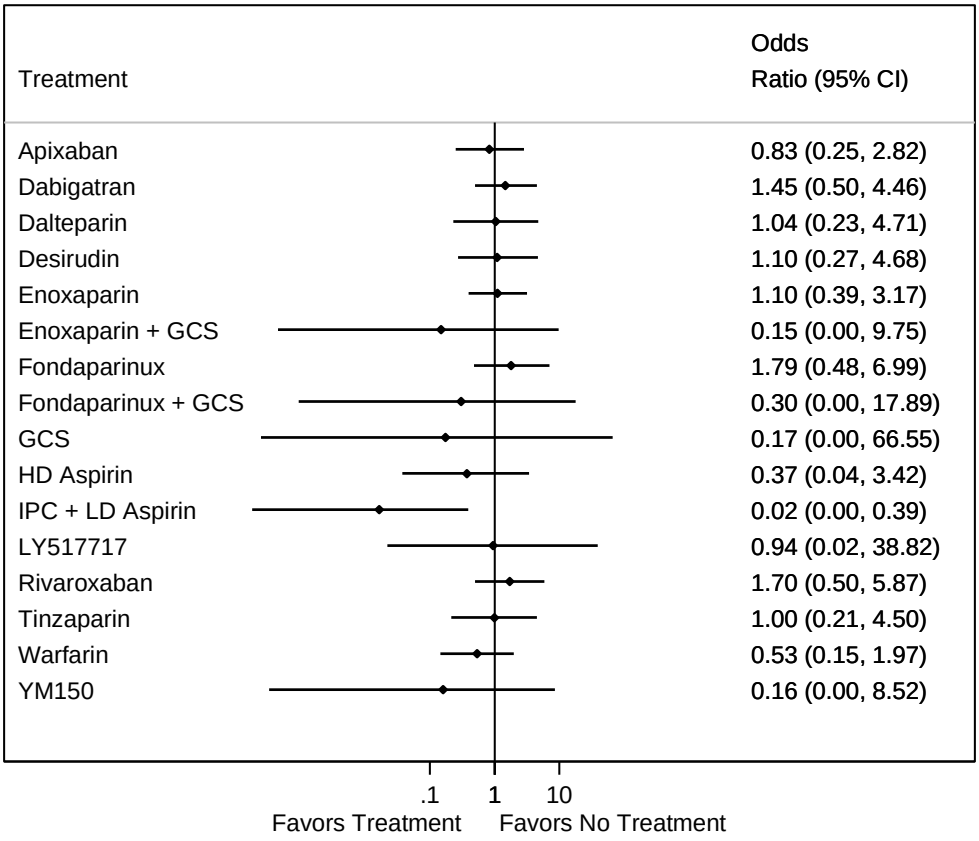


Figure 42. Major Bleeding among Hip Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

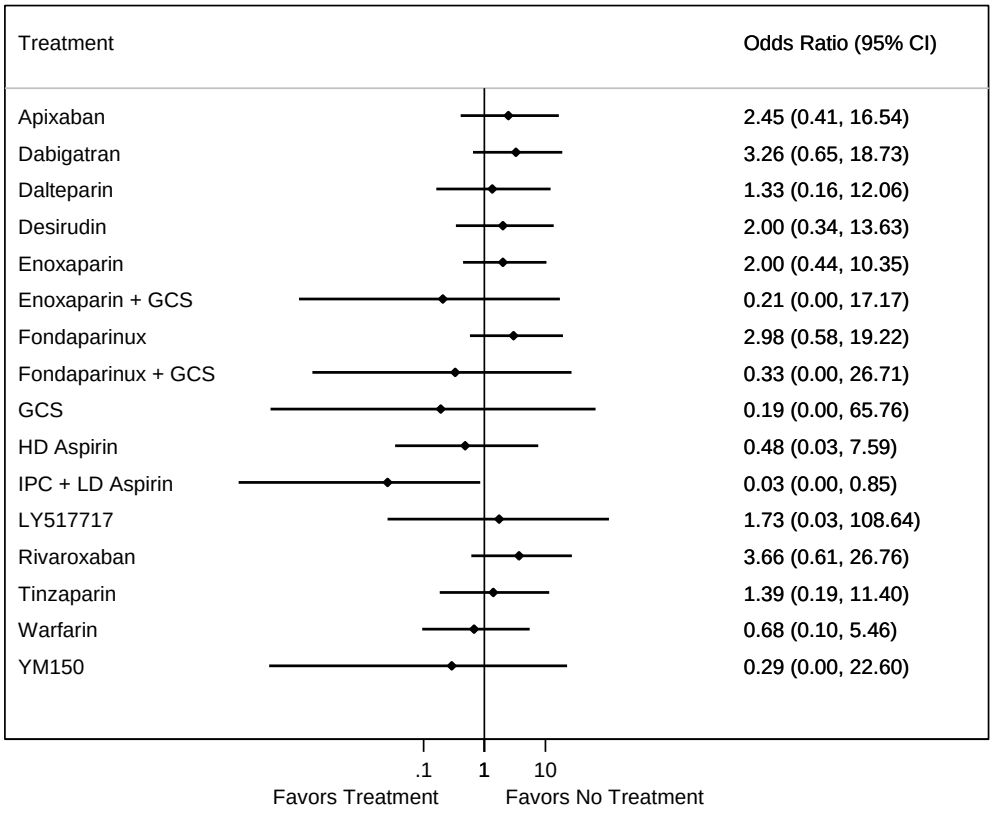
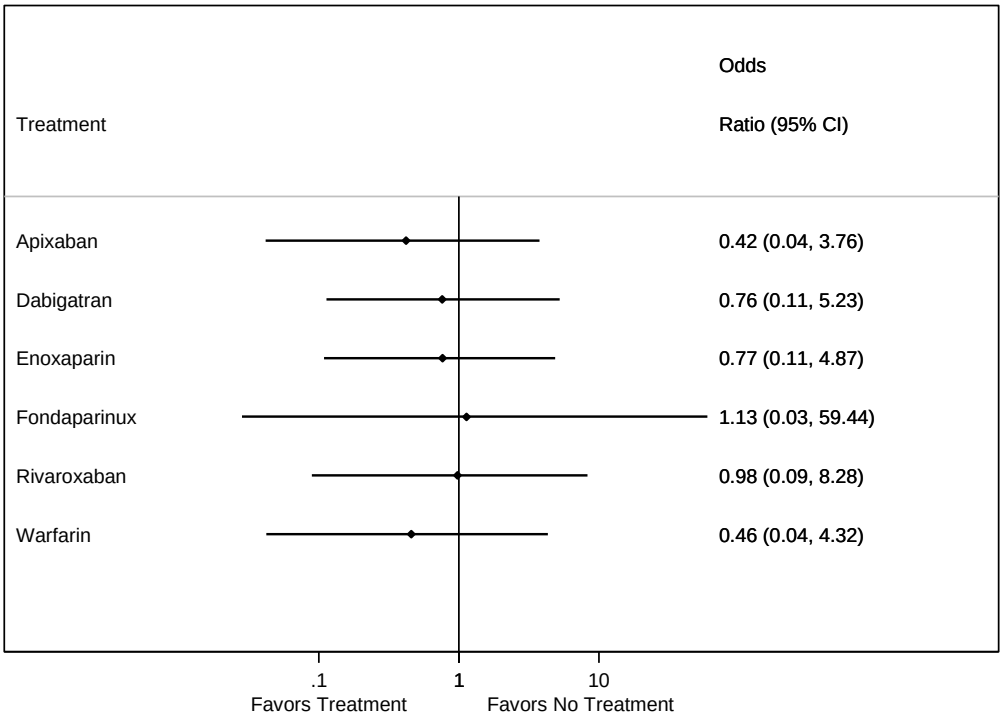


Figure 43. Major Bleeding among Knee Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)



ALL CAUSE MORTALITY

Note: For this outcome, results are only presented compared to enoxaparin because there are no trials with a no treatment arm.

Figure 44. All Cause Mortality among Hip and Knee Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. Enoxaparin)

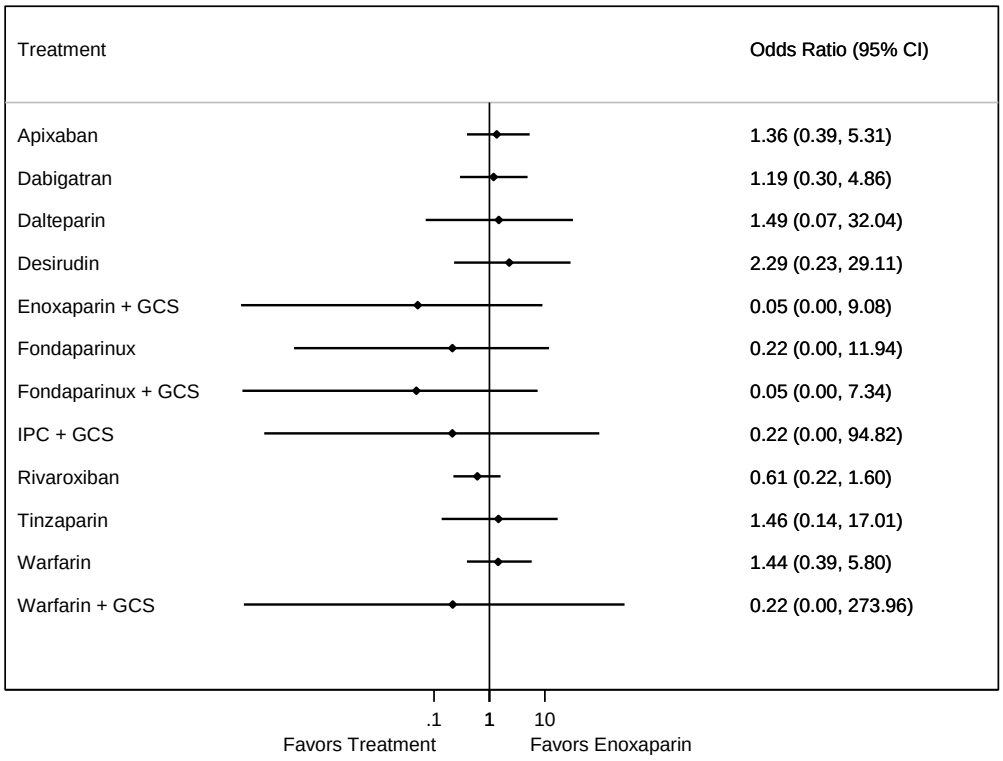


Figure 45. All Cause Mortality among Hip Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. Enoxaparin)

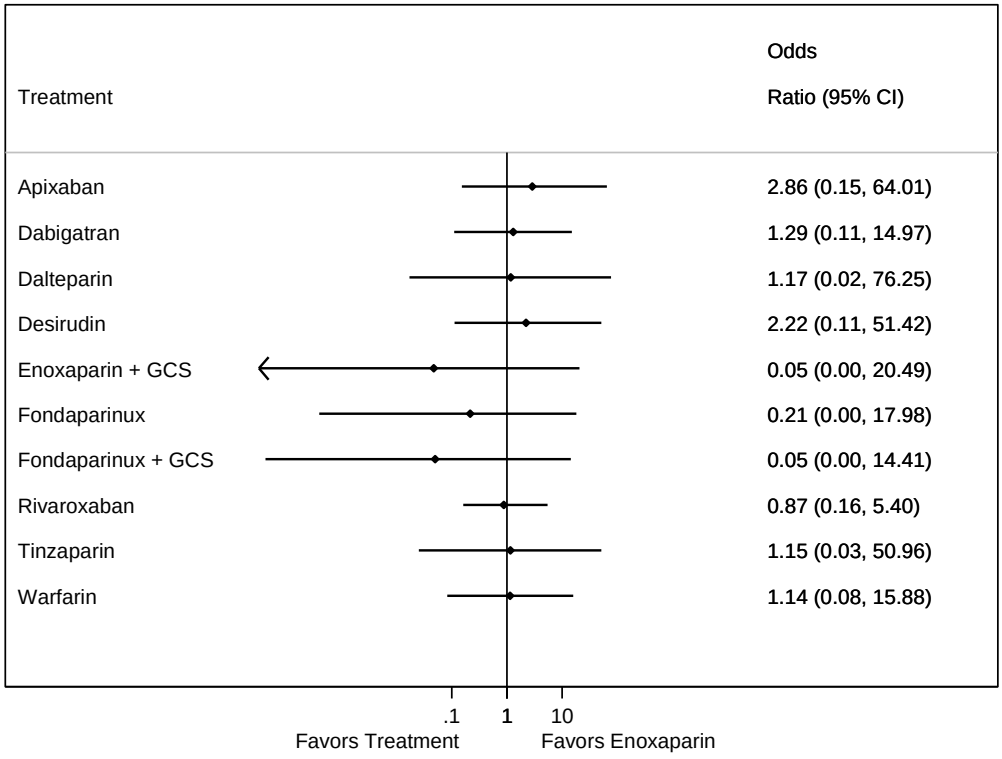
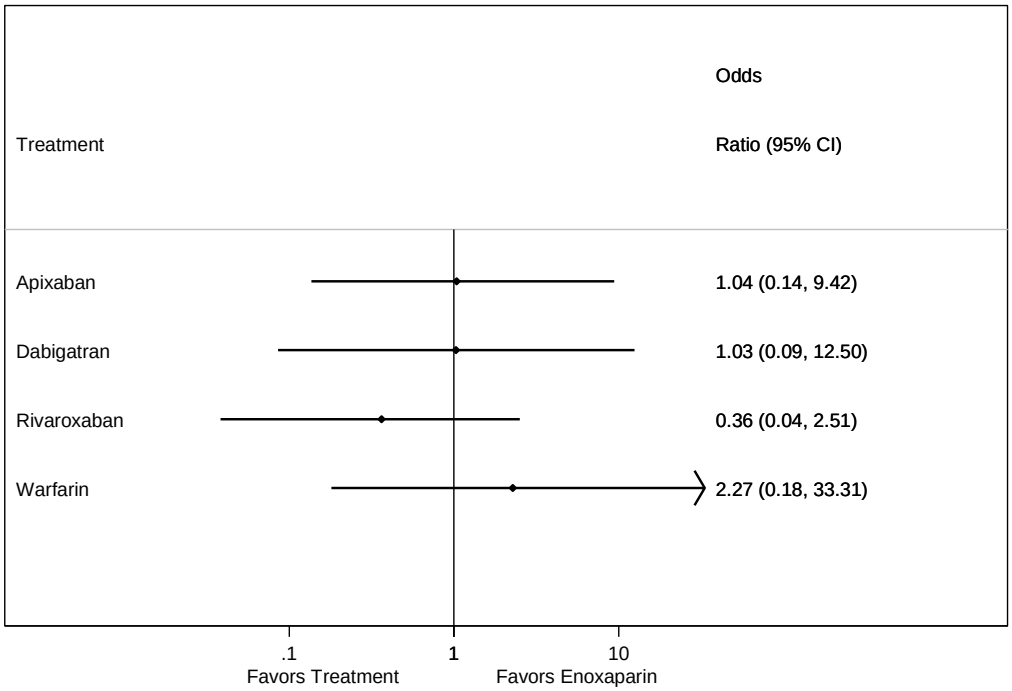


Figure 46. All Cause Mortality among Knee Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. Enoxaparin)



SYMPTOMATIC DEEP VEIN THROMBOSIS

Figure 47. Symptomatic DVT among Hip and Knee Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

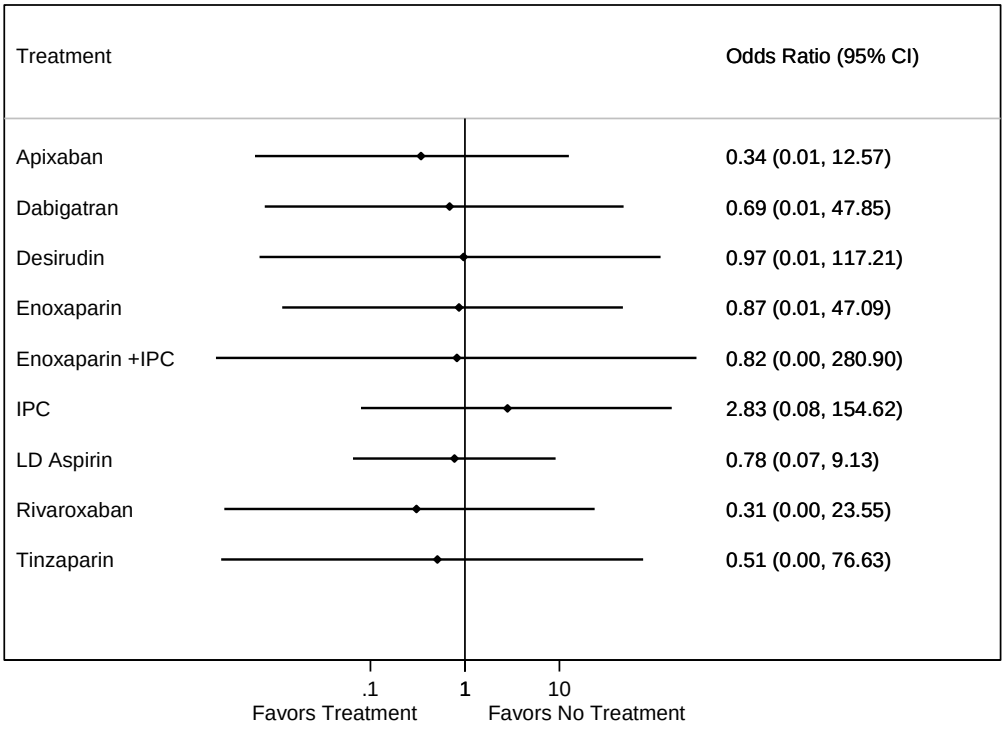
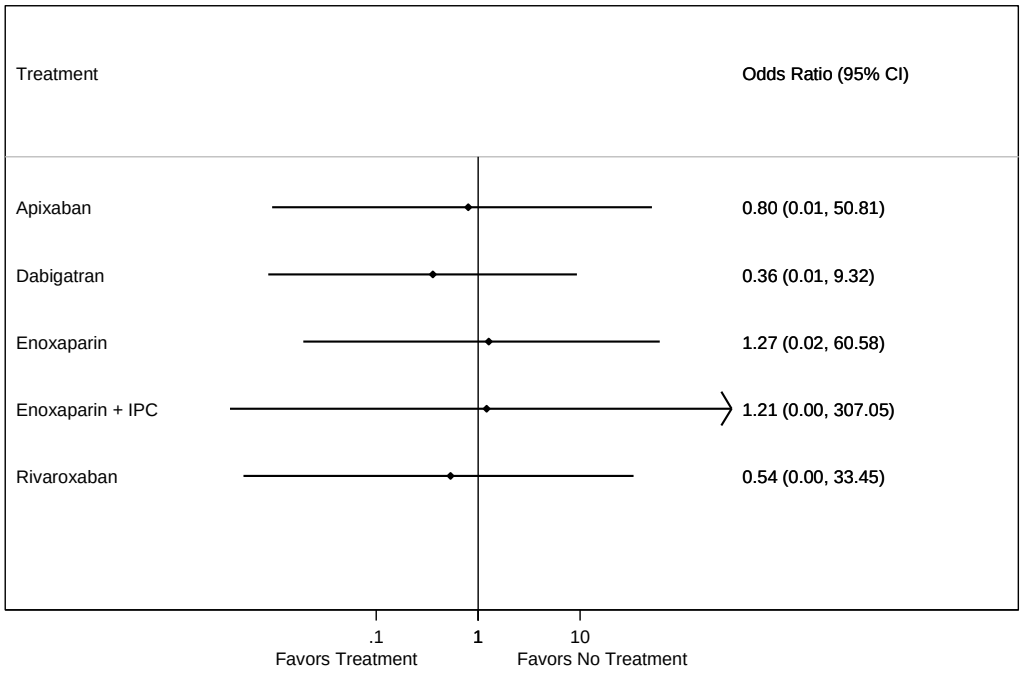


Figure 48. Symptomatic DVT among Hip Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

No studies in the model with no treatment as a comparator

Figure 49. Symptomatic DVT among Knee Patients - Network Meta-Analysis Results with Continuity Correction Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)



DEEP VEIN THROMBOSIS

Figure 50. Deep Vein Thrombosis among Hip and Knee Patients - Network Meta-Analysis Results Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

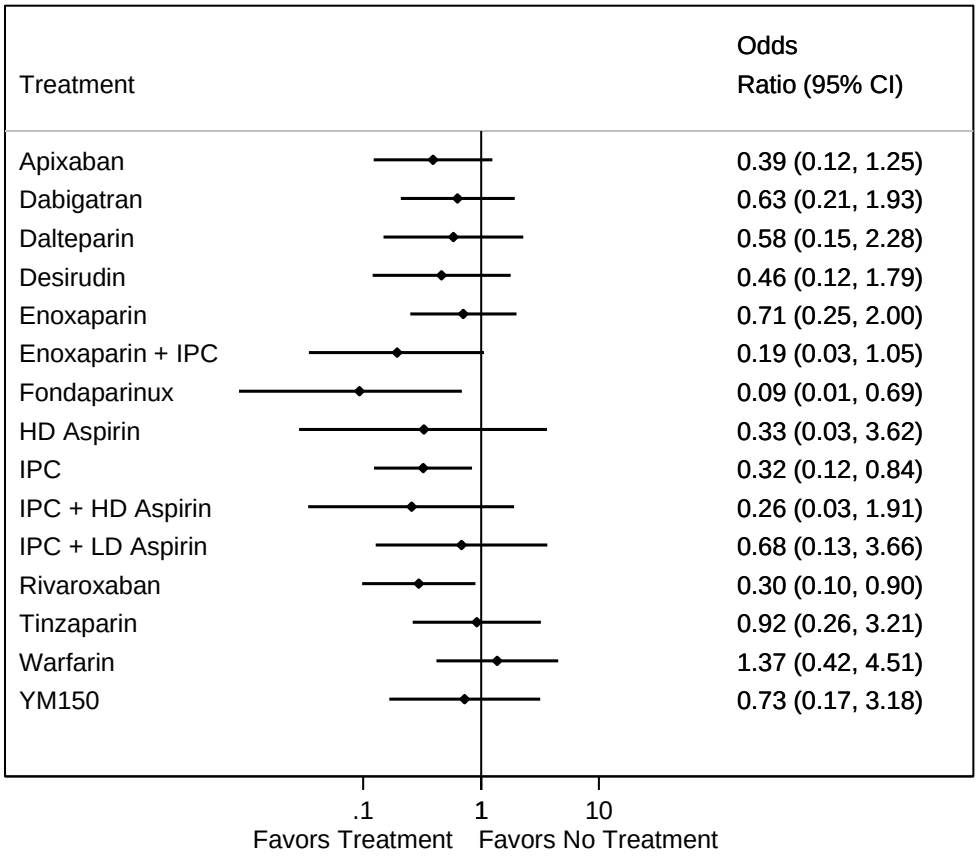


Figure 51. Deep Vein Thrombosis among Hip Patients - Network Meta-Analysis Results Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

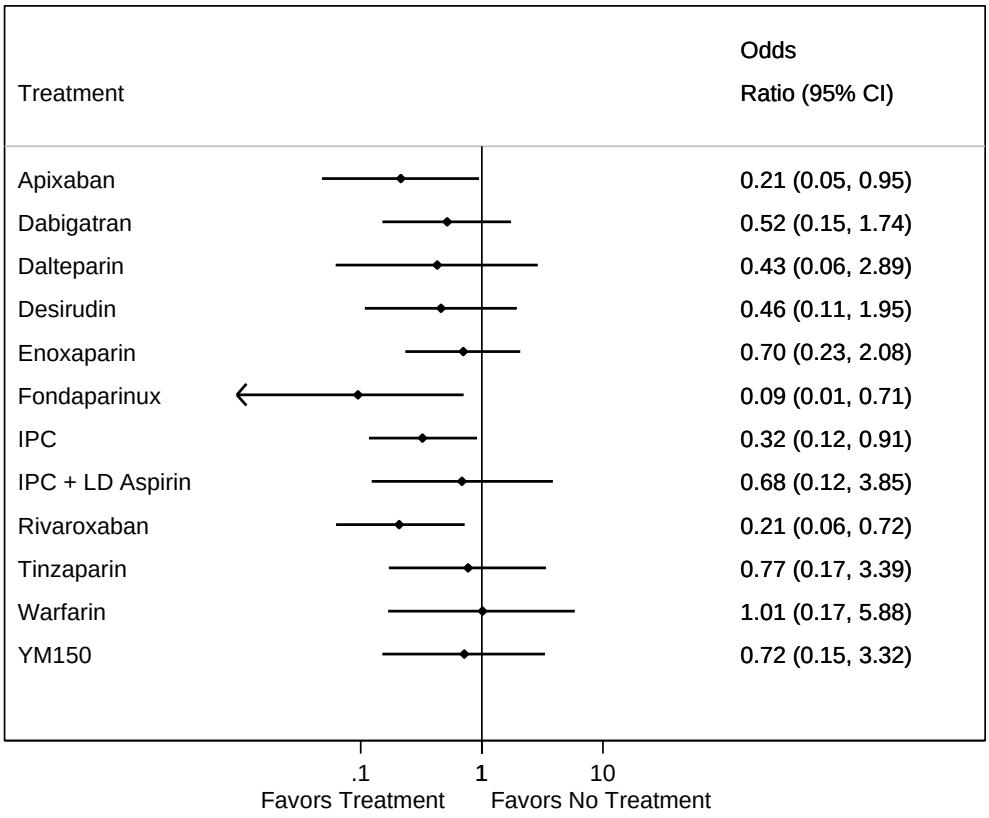


Figure 52. Deep Vein Thrombosis among Knee Patients - Network Meta-Analysis Results Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

No studies in the model with no treatment as a comparator

PROXIMAL DEEP VEIN THROMBOSIS

Figure 53. Proximal Deep Vein Thrombosis among Hip and Knee Patients - Network Meta-Analysis Results Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

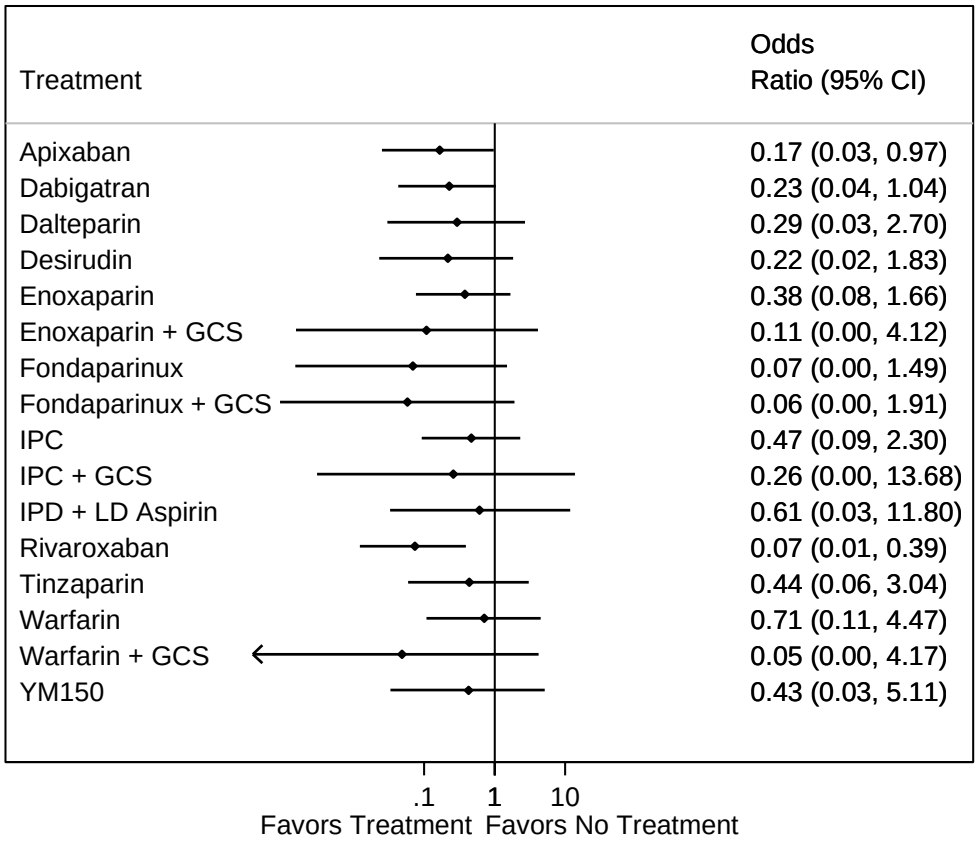


Figure 54. Proximal Deep Vein Thrombosis among Hip Patients - Network Meta-Analysis Results Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)

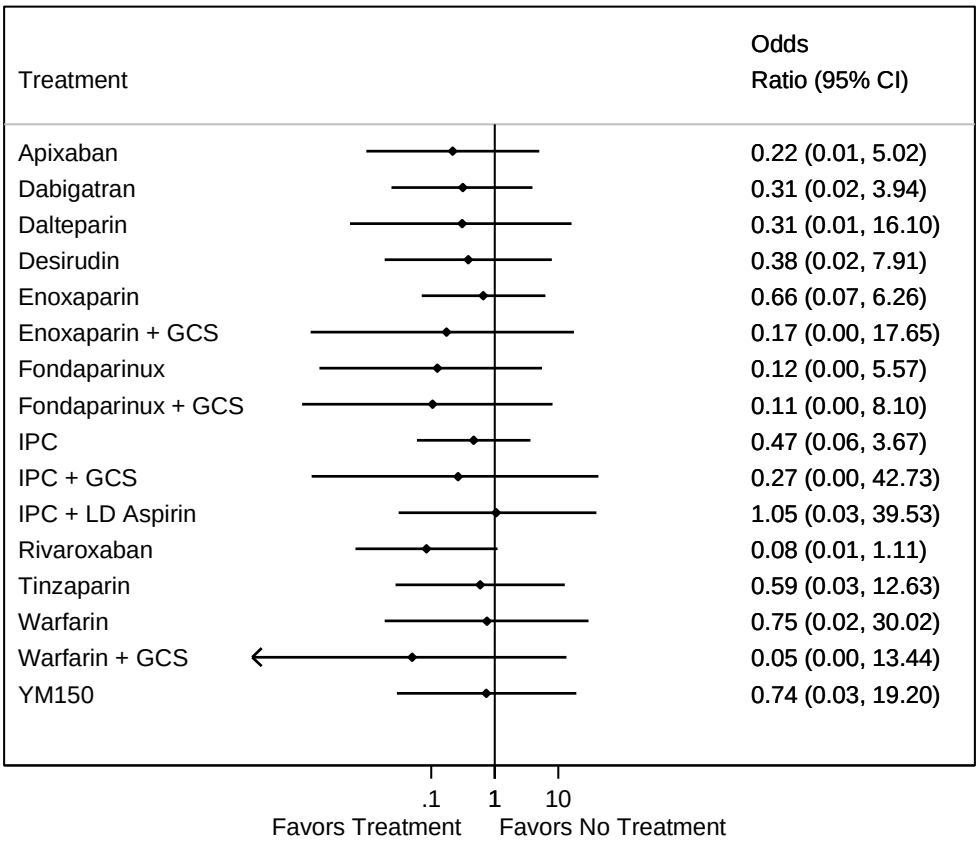
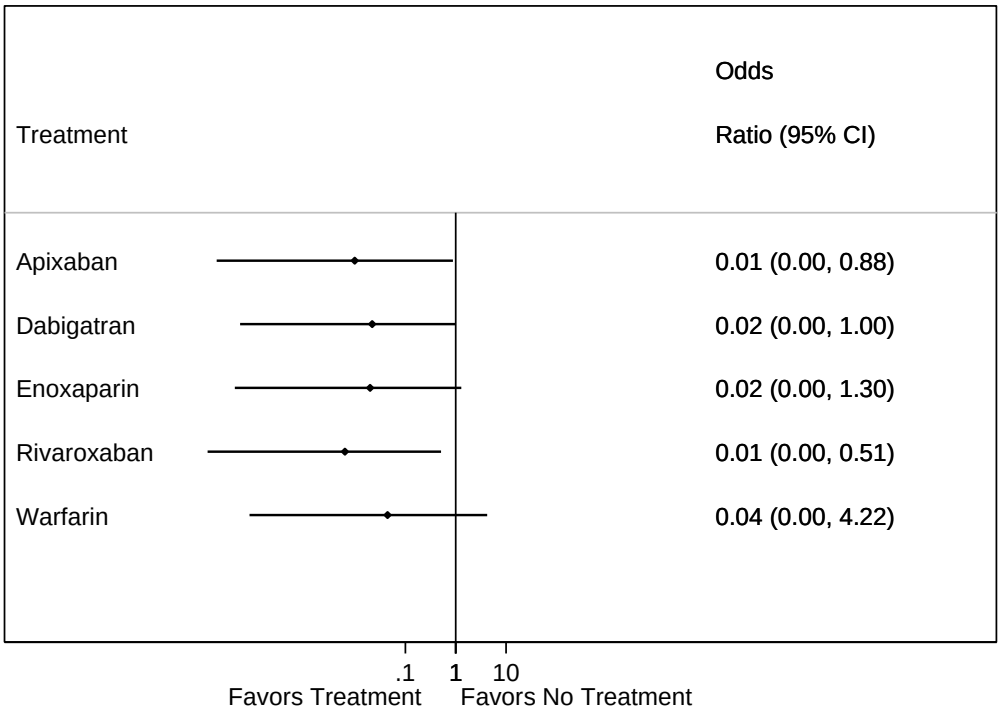


Figure 55. Proximal Deep Vein Thrombosis among Knee Patients - Network Meta-Analysis Results Without Heparin Trials and Without Trials with > 2 Arms (vs. No Treatment)



NETWORK META-ANALYSIS PAIRWISE COMPARISONS

All significant pairwise comparisons from the final network meta-analysis are listed in the tables below. There were no significant comparisons for pulmonary embolism, symptomatic DVT, or all cause mortality. All pairwise comparisons from all network meta-analyis models are presented in Appendix XV.

Table 32. Major Bleeding Significant Pairwise Comparisons - Final Model

Comparison	Patient Populations with Significant Comparison
Enoxaparin + GCS favored over Fondaparinux + GCS	Hip and Knee
IPC + LD Aspirin favored over Apixaban	Hip and Knee, and Hip Only
IPC + LD Aspirin favored over Dabigatran	Hip and Knee, and Hip Only
IPC + LD Aspirin favored over Dalteparin	Hip and Knee, and Hip Only
IPC + LD Aspirin favored over Desirudin	Hip and Knee, and Hip Only
IPC + LD Aspirin favored over Enoxaparin	Hip and Knee, and Hip Only
IPC + LD Aspirin favored over Fondaparinux	Hip and Knee, and Hip Only
IPC + LD Aspirin favored over No Treatment	Hip and Knee, and Hip Only
IPC + LD Aspirin favored over Rivaroxaban	Hip and Knee, and Hip Only
IPC + LD Aspirin favored over Tinzaparin	Hip and Knee, and Hip Only
IPC + LD Aspirin favored over Warfarin	Hip and Knee
Warfarin favored over Dabigatran	Hip and Knee, and Hip Only
Warfarin favored over Rivaroxaban	Hip and Knee, and Hip Only

Table 33. DVT Significant Pairwise Comparisons - Final Model

Comparison	Patient Populations with Significant Comparison
Apixaban favored over Enoxaparin	Hip and Knee, and Hip Only
Apixaban favored over No Treatment	Hip Only
Apixaban favored over Warfarin	Hip and Knee, and Knee Only
Dabigatran favored over Warfarin	Hip and Knee
Dalteparin favored over Warfarin	Hip and Knee, and Hip Only
Desirudin favored over Warfarin	Hip and Knee
Enoxaparin + IPC favored over Dabigatran	Knee Only
Enoxaparin + IPC favored over Enoxaparin	Knee Only
Enoxaparin + IPC favored over Tinzaparin	Hip and Knee
Enoxaparin + IPC favored over Warfarin	Hip and Knee, and Knee Only
Enoxaparin favored over Warfarin	Hip and Knee, and Knee Only
Fondaparinux favored over Dabigatran	Hip and Knee
Fondaparinux favored over Enoxaparin	Hip and Knee, and Hip Only
Fondaparinux favored over No Treatment	Hip and Knee, and Hip Only
Fondaparinux favored over Tinzaparin	Hip and Knee, and Hip Only
Fondaparinux favored over Warfarin	Hip and Knee, and Hip Only
Fondaparinux favored over YM150	Hip and Knee, and Hip Only
HD Aspirin + IPC favored over Warfarin	Knee Only
IPC favored over No Treatment	Hip and Knee, and Hip Only
Rivaroxaban favored over Dabigatran	Hip and Knee, and Hip Only
Rivaroxaban favored over Enoxaparin	Hip and Knee, Hip Only, and Knee Only
Rivaroxaban favored over No Treatment	Hip and Knee, and Hip Only
Rivaroxaban favored over Tinzaparin	Hip and Knee, and Hip Only
Rivaroxaban favored over Warfarin	Hip and Knee, Hip Only, and Knee Only

Table 34. Proximal DVT Significant Pairwise Comparisons - Final Model

Comparison	Patient Populations with Significant Comparison
Apixaban favored over No Treatment	Hip and Knee, and Knee Only
Apixaban favored over Warfarin	Hip and Knee
Rivaroxaban favored over Dabigatran	Hip and Knee
Rivaroxaban favored over Enoxaparin	Hip and Knee, and Hip Only
Rivaroxaban favored over No Treatment	Hip and Knee, and Knee Only
Rivaroxaban favored over Tinzaparin	Hip and Knee
Rivaroxaban favored over Warfarin	Hip and Knee

INDIVIDUAL STUDY RESULTS

Individual study results for each of the six outcomes analyzed in a network meta-analysis, as well as for other outcomes reported by the included studies, can be found in Appendix XV. Details of each study can also be found in Appendix XV.

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Deep Vein Thrombosis

Joint replacement surgery, especially in the lower extremities, is becoming more common. Orthopaedic surgeons performed about 520,000 hip replacements and about 581,000 knee replacements in 2006 (Source: National Center for Health Statistics; Centers for Disease Control and Prevention; 2006 National Hospital Discharge Survey.) The vast majority of these surgeries are very successful, and patients go on to live fuller, more active lives without pain.

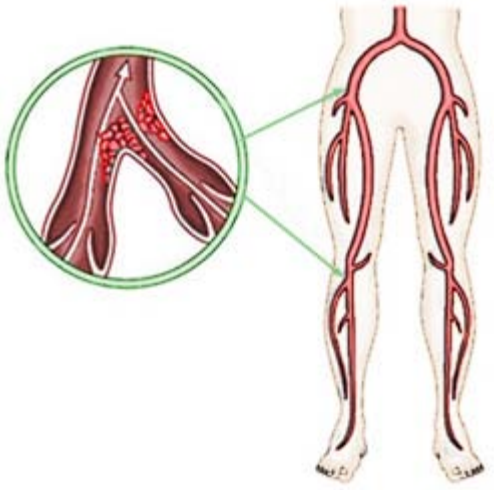
But no operation is without risks. One of the major risks facing patients who undergo surgery in the lower extremities is a complication called deep vein thrombosis, a form of venous thromboembolic disease.

Cause

Deep vein thrombosis (DVT) refers to the formation of a thrombus (blood clot) within a deep vein, commonly in the thigh or calf.

Contributing Factors

Although venous thromboembolic disease can develop after any major surgery, people who have surgery on the lower extremities are especially vulnerable.



Deep vein thrombosis is the formation of a thrombus (blood clot) within a deep vein, commonly in the thigh or calf.

Three factors contribute to formation of clots in veins:

1. Stasis, or stagnant blood flow through veins
This increases the contact time between blood and vein wall irregularities. It also prevents naturally occurring anticoagulants from mixing in the blood. Prolonged bed rest or immobility promotes stasis.

2. Coagulation
Coagulation is encouraged by the presence of tissue debris, collagen or fats in the veins. Orthopaedic surgery often releases these materials into the blood system. During hip replacement surgery, reaming and preparing the bone to receive the prosthesis can also release chemical substances (antigens) that stimulate clot formation into the blood stream.

3. Damage to the vein walls

This can occur during surgery as the physician retracts soft tissues as part of the procedure. This can also break intercellular bridges and release substances that promote blood clotting.

Other factors that may contribute to the formation of thrombi in the veins include:

- Age
- Previous history of DVT or PE
- Metastatic malignancy
- Vein disease (such as varicose veins)
- Smoking
- Estrogen usage or current pregnancy
- Obesity
- Genetic factors

Consequences

The formation of blood clots can have two serious consequences:

1. If the thrombus partially or completely blocks the flow of blood through the vein, blood begins to pool and build-up below the site. Chronic swelling and pain may develop. The valves in the blood vessels may be damaged, leading to venous hypertension. A person's ability to live a full, active life may be impaired.

2. If the thrombus breaks free and travels through the veins, it can reach the lungs, where it is called a pulmonary embolism (PE). A pulmonary embolism is a potentially fatal condition that can kill within hours.

Symptoms

After hip surgery, thrombi often form in the veins of the thigh. These clots are more likely to lead to PE. After knee surgery, most thrombi occur in the calf. Although less likely to lead to PE, these clots are more difficult to detect.

Fewer than one third of patients with DVT present with the classic signs of calf discomfort, edema, distended veins, or foot pain.

Diagnosis

Diagnosing DVT is difficult. Current diagnostic techniques have both advantages and disadvantages. The most commonly used diagnostic tests include venography, duplex or Doppler ultrasonography, and magnetic resonance imaging (MRI).

Venography

Venography uses a radiographic material injected into a vein on the top of the foot. The material mixes with blood and flows toward the heart. An X-ray of the leg and pelvis will then show the calf and thigh veins and reveal any blockages.

Although venography is very accurate and can detect blockages in both the thigh and the calf, it is also costly and cannot be repeated often. In addition, the injected material may

actually contribute to the creation of thrombi.

Duplex Ultrasonography

Duplex ultrasonography can also be very accurate in identifying clogged veins. Projected sound waves bounce off structures in the leg and create images that reveal abnormalities. The addition of color Doppler imaging improves accuracy.

This test is noninvasive and painless, requires no radiation, can be repeated regularly, and can reveal other causes for symptoms. It also costs substantially less than venography. However, it is technically demanding and requires a skilled, experienced operator to obtain the most accurate results.

Ultrasonography is less sensitive in detecting thrombi in the calf and it has limited ability to directly image the deep veins of the pelvis.

Magnetic Resonance Imaging

Magnetic resonance imaging is particularly effective in diagnosing DVT in the pelvis, and as effective as venography in diagnosing DVT in the thigh. This technique is being increasingly used because it is noninvasive and allows simultaneous visualization of both legs.

However, an MRI is expensive, not always readily available, and cannot be used if the patient has certain implants, such as a pacemaker. In addition, the patient can experience claustrophobia.

Prevention

Both DVT and PE may be asymptomatic and difficult to detect. Thus, physicians focus on preventing their development by using mechanical or drug therapies. Without this preventive treatment, as many as 80 percent of orthopaedic surgical patients would develop DVT, and 10 percent to 20 percent would develop PE. Even with these preventative therapies, DVT and subsequent PE remain the most common cause for emergency readmission and death following joint replacement.

Prevention is a three-pronged approach designed to address the issues of stasis and coagulation. Usually, several therapies are used in combination. For example, a patient may be fitted with graded compression elastic stockings and an external compression device upon admittance to the hospital; movement and rehabilitation begin the first day after surgery and continue for several months; anticoagulant therapy may begin the night before surgery and continue after the patient is discharged.

Early Movement and Rehabilitation

With hospital stays averaging just four to seven days after an arthroplasty on the lower extremity, early movement is imperative as well as beneficial. Physical therapy, including joint range of motion, gait training and isotonic/isometric exercises, usually begins on the first day after the operation. Pain relievers administered intravenously also facilitate early mobilization.

Mechanical Prophylaxis

Mechanical preventatives are usually used in combination with other therapies. They include:

- Lower extremity exercises such as simple leg lifts, elevating the foot of the bed, and

active and passive ankle motion to increase blood flow through the femoral vein.

- Graded compression elastic stockings, which are more effective in preventing thrombi formation in the calf than in the thigh.
- Continuous passive motion, which is a logical treatment, but has not been proven effective in preventing the development of DVT.
- External pneumatic compression devices that apply pulsing pressures similar to those that occur during normal walking. They can help reduce the overall rate of DVT occurrence when used with other therapies, but they are difficult to apply and patient compliance is often a problem.
- In rare cases, a filter device may be placed in one of the large veins to prevent migration of clots..

Pharmacologic Prophylaxis

The use of anticoagulant pharmacologic agents includes an inherent risk of increased bleeding, which must be measured against their effectiveness in preventing clot formation. The most common anticoagulants are aspirin, warfarin (also called coumadin), and heparin.

Aspirin

Aspirin is easy to administer, costs little, has few bleeding complications, and does not need to be monitored. However, it has not been proven more effective than other agents and may not be advisable for all patients. Studies have shown that aspirin has a greater protective effect for men than for women.

Warfarin (also called Coumadin)

Warfarin is the most commonly used agent for hip and knee replacement patients. Warfarin interferes with vitamin K metabolism in the liver to prevent formation of certain clotting factors. Because warfarin takes at least 36 hours to start working, and four to five days to reach its maximum effectiveness, it is usually started the day before surgery. Low doses are used because higher doses can cause episodes of bleeding, but the dose response is difficult to predict and warfarin must be administered through an outpatient clinic. Warfarin can cause fetal damage.

Heparin

Heparin is a naturally occurring substance that inhibits the clotting cascade. It can come in high (standard unfractionated heparin) or low (fractionated heparin) molecular weights. Recent emphasis has been on low molecular weight heparins (LMWH) because they are more predictable and effective, with fewer bleeding complications than standard unfractionated heparin. LMWH is effective after both hip and knee joint replacement surgeries, but there is a higher incidence of bleeding when it is used after knee replacement surgery. The most commonly used and researched LMWH are enoxaparin, ardeparin, dalteparin, and fraxiparine. Heparin works much faster than warfarin, so it is often administered initially and followed by warfarin therapy, or administered as a single agent.

Postoperative Treatment

The risk of developing DVT extends for at least three months after joint replacement surgery. The risk is greatest two to five days after surgery; a second peak development

period occurs about 10 days after surgery, after most patients have been discharged from the hospital.

Treatment is the same for both asymptomatic and symptomatic venous thromboembolisms. If the clot is located in the femoropoliteal vein of the thigh, treatment consists of bed rest and five days of heparin therapy followed by three months of warfarin. A clot in the calf veins does not normally require heparin treatment; outpatient warfarin treatment for six to 12 weeks is sufficient. These treatment regimens are designed to prevent the occurrence of a fatal pulmonary embolism and reduce the morbidity associated with DVT.

Research

Recently, the Food and Drug Administration approved the use of the LWMH dalteparin sodium in a once-daily, 14-day dosing regimen to prevent DVT after hip surgery. A common postoperative regimen is five days of heparin followed by three months of warfarin therapy. However, the length of time that therapy should continue after surgery varies, depending on the agent used and individual patient considerations.

Orthopaedic surgeons are continuing to research techniques, such as the use of regional anesthesia and intraoperative heparin, to reduce the risk of DVT formation. Studies have shown that using regional rather than general anesthesia can reduce the overall rate of DVT formation by up to 50 percent.

Research to identify those patients particularly at risk for DVT formation after surgery is also ongoing. Some risk factors such as weight and history have been identified. Based on these risk factors, some physicians use regular surveillance of patients, while others recommend using venography to identify those patients at risk for developing DVT. In general, orthopaedic surgeons would rather avoid extended outpatient prophylaxis for all patients, preferring to focus on those most at risk.

Last reviewed and updated: January 2009

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Venous Thromboembolism in Adult Hospitalizations — United States, 2007–2009

Deep vein thrombosis (DVT) is a blood clot that occurs in a deep vein of the body; pulmonary embolism (PE) occurs when a clot breaks free and enters the arteries of the lungs. DVT and PE comprise venous thromboembolism (VTE), an important and growing public health concern (*1*,*2*). Hospitalization is a major risk factor for VTE, and many VTE events that occur among hospitalized patients can be prevented (*2*,*3*). A new program of the U.S. Department of Health and Human Services (Partnership for Patients: Better Care, Lower Costs) aims to reduce the number of preventable VTE cases in hospitals (*4*). To estimate the number of hospitalizations with VTE each year in the United States, CDC analyzed 2007–2009 data from the National Hospital Discharge Survey (NHDS). The results of that analysis determined that an estimated average of 547,596 hospitalizations with VTE occurred each year among those aged ≥18 years in the United States. DVT was diagnosed in an estimated annual average of 348,558 hospitalizations, and PE was diagnosed in 277,549; both DVT and PE were diagnosed in 78,511 hospitalizations. Estimates of the rates of hospitalizations with VTE were substantially higher among adults aged ≥60 years compared with those aged 18–59 years. These findings underscore the need to promote implementation of evidence-based prevention strategies to reduce the number of preventable cases of VTE among hospitalized patients.

NHDS uses a stratified multistage probability design to obtain a sample of discharges from nonfederal short-stay (average: <30 days) hospitals in the 50 states and District of Columbia (*5*). Medical and demographic information, up to seven listed discharge diagnoses, and disposition (including patient death) are collected for a sample of discharges from each hospital. Data including restricted design variables were accessed through the Research Data Center of CDC's National Center for Health Statistics. For this report, *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes were used to identify hospitalizations of persons aged ≥18 years with discharge diagnoses of DVT or PE. A DVT diagnosis was defined as the presence of any of the ICD-9-CM codes 451.1x, 451.81, 451.83, 453.2, 453.4x, 671.3x, and 671.4x. A PE diagnosis was defined as the presence of any of the ICD-9-CM codes 415.1x and 673.2x. Hospitalizations with codes for either DVT or PE also were counted as having a VTE diagnosis. Whether DVT or PE were present on admission or acquired during the hospital stay could not be determined. Data from 2007–2009 were used in this analysis. Weighted estimates of the average annual number of hospitalizations with a discharge diagnosis of DVT or PE were divided by the 2008 midyear U.S. population estimates to derive rates of hospitalizations with a diagnosis of VTE per 100,000 population overall among adults aged ≥18 years, by sex and selected age groups.

During 2007–2009, an estimated annual average of 547,596 hospitalizations had a diagnosis of VTE for adults aged ≥18 years. Estimates for DVT and PE diagnoses were not mutually exclusive. An estimated annual average of 348,558 adult

INSIDE

Continuing Education examination available at http://www.cdc.gov/mmwr/cme/conted_info.html#weekly.

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What is already known on this topic?

Hospitalized patients are at increased risk for venous thromboembolism (VTE), which consists of deep vein thrombosis (DVT) and pulmonary embolism (PE). Many of the VTEs acquired by hospitalized patients are preventable.

What is added by this report?

During 2007–2009, an estimated annual average of 547,596 adult hospitalizations occurred for which a discharge diagnosis of VTE was recorded; 348,558 of these hospitalizations had a discharge diagnosis of DVT, and 277,549 had a discharge diagnosis of PE. A total of 78,511 had both discharge diagnoses.

What are the implications for public health practice?

VTE is an important public health concern. Greater efforts are needed to identify, develop, and implement VTE prevention strategies and to improve surveillance for VTE cases to reduce morbidity and mortality from VTE.

hospitalizations had a diagnosis of DVT, and 277,549 adult hospitalizations had a diagnosis of PE. An estimated annual average of 78,511 adult hospitalizations (14% of overall VTE hospitalizations) had diagnoses of both DVT and PE.

The estimated average annual number of hospitalizations with VTE was successively greater among older age groups: 54,034 for persons aged 18–39 years; 143,354 for persons aged 40–59 years; and 350,208 for persons aged ≥60 years (Figure). The estimated average annual number of hospitalizations with VTE was comparable for men (250,973) and women (296,623).

The average annual rates of hospitalizations with a discharge diagnosis of DVT, PE, or VTE among adults were 152, 121, and 239 per 100,000 population, respectively (Table). For VTE, the average annual rates were 60 per 100,000 population aged 18–39 years, 143 for persons aged 40–49 years, 200 for persons aged 50–59 years, 391 for persons aged 60–69 years, 727 for persons aged 70–79 years, and 1,134 for persons aged ≥80 years. The rates of hospitalization were similar for men and women, and the point estimates increased for both sexes by age.

On average, 28,726 hospitalized adults with a VTE diagnosis died each year. Of these patients, an average of 13,164 had a DVT diagnosis and 19,297 had a PE diagnosis; 3,735 had both DVT and PE diagnoses.

Reported by

Hussain R. Yusuf, MD, James Tsai, MD, Hani K. Atrash, MD, Sheree Boulet, DrPH, Scott D. Grosse, PhD, Div of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, CDC. ***Corresponding contributor:*** *Hussain Yusuf, hyusuf@cdc.gov, 404-498-3937.*

Editorial Note

The results of this analysis underscore the importance of VTE as a public health concern. Many of the VTE diagnoses reported via NHDS might have occurred during hospitalization, when the risk for VTE is known to be elevated (e.g., because of major surgery, immobility, or comorbid conditions)

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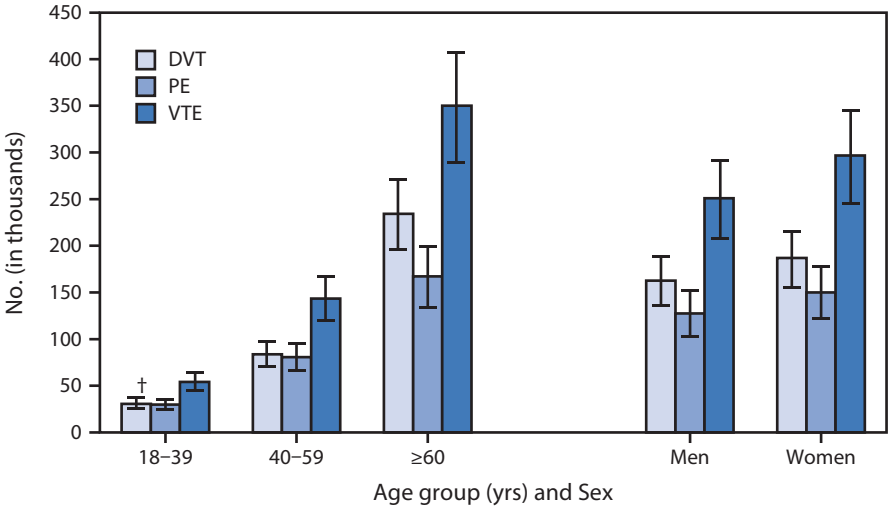
FIGURE. Estimated average annual number of hospitalizations with a diagnosis of deep vein thrombosis (DVT), pulmonary embolism (PE), or venous thromboembolism (VTE), by patient sex and age group — National Hospital Discharge Survey, United States, 2007–2009*



* Diagnoses of DVT and PE are not mutually exclusive; an estimated 78,511 patients received diagnoses of both DVT and PE. VTE estimates include patients with diagnoses of either DVT or PE.
† 95% confidence interval.

(*1–3*). Because VTE cases that occur in hospitals often are preventable, an opportunity exists to reduce disease burden through implementation of evidence-based prevention strategies in hospital settings (*1,2,6*).

The incidence of DVT and PE is known to be much higher among older adults compared with younger persons (*7*). In this analysis, the estimates of hospitalization rates with a discharge diagnosis of DVT, PE, or VTE were successively higher among older age groups. Although DVT and PE affect older hospitalized patients the most, a substantial number of hospitalizations with a diagnosis of VTE occurred among younger patients. Previous research has not clearly demonstrated a consistent difference between the rates of VTE in men and women (*8*). The findings in this report indicate that hospitalization rates with a diagnosis of DVT, PE, or VTE were comparable between men and women.

Many DVT and PE events can be prevented through appropriate administration of prophylaxis, which might include pharmacologic agents (e.g., antithrombotic agents) or mechanical devices. Current use of prophylaxis in hospitalized patients might be suboptimal (*1,9*). CDC is collaborating with partners to promote implementation of evidence-based guidelines for prevention of DVT and PE in hospitalized patients. CDC also is developing a VTE module within the National Healthcare Safety Network, a web-based surveillance system for hospitals and health-care facilities.*

The findings in this report are subject to at least four limitations. First, whether DVT or PE was present on admission or onset occurred during the hospital stay cannot be determined. Second, DVT and PE diagnoses were identified using ICD-9-CM codes available in NHDS data rather than through medical record abstraction. Research suggests that most of the DVT and PE ICD-9-CM codes recorded in discharge records

* Additional information available at http://www.cdc.gov/nhsn.

TABLE. Estimated average annual rate (per 100,000 population) of hospitalizations with a diagnosis of deep vein thrombosis (DVT), pulmonary embolism (PE), or venous thromboembolism (VTE), by patient sex and age group — National Hospital Discharge Survey, United States, 2007–2009*

	DVT			PE			VTE		
Age group (yrs)	Total (95% CI)	Men (95% CI)	Women (95% CI)	Total (95% CI)	Men (95% CI)	Women (95% CI)	Total (95% CI)	Men (95% CI)	Women (95% CI)
Overall	**152 (127–177)**	**146 (122–171)**	**158 (131–185)**	**121 (98–144)**	**115 (91–138)**	**127 (102–153)**	**239 (199–279)**	**226 (187–265)**	**252 (208–296)**
18–39	34 (26–42)	32 (23–40)	36 (27–45)	33 (25–40)	28 (19–36)	38 (28–48)	60 (47–72)	53 (40–65)	67 (52–81)
40–49	81 (63–98)	97 (72–123)	64 (47–81)	82 (63–100)	85 (61–109)	78 (58–99)	143 (114–172)	154 (117–190)	132 (103–161)
50–59	120 (98–143)	144 (113–175)	97 (75–119)	111 (86–135)	124 (91–156)	99 (73–124)	200 (164–237)	226 (180–272)	176 (138–213)
60–69	247 (194–299)	254 (197–311)	241 (181–301)	203 (160–246)	208 (159–257)	199 (150–247)	391 (315–468)	405 (321–490)	379 (293–465)
70–79	487 (389–584)	469 (362–576)	501 (388–614)	349 (264–434)	337 (229–445)	359 (276–442)	727 (582–872)	720 (556–884)	732 (578–885)
≥80	791 (649–934)	821 (635–1,007)	775 (629–921)	500 (392–609)	537 (390–684)	480 (368–592)	1,134 (927–1,340)	1,153 (904–1,402)	1,123 (911–1,336)

Abbreviation: CI = confidence interval.
* Diagnoses of DVT and PE are not mutually exclusive; an estimated 78,511 patients received diagnoses of both DVT and PE. VTE estimates include patients with diagnoses of either DVT or PE.

and used in this study on average have positive predictive values ranging from 75% to 95% (*10*). Third, the unit of analysis in this report was hospitalization and not the number of persons with diagnoses of DVT or PE. Patients hospitalized multiple times for these conditions in a given year would be counted more than once in NHDS data. Finally, NHDS surveys a sample of hospitalizations in the United States; therefore, the findings are subject to sampling variability.

Patients should discuss VTE prevention with their healthcare providers before and during hospitalization and adhere to prescribed therapies, as appropriate. Comprehensive public health efforts also are needed to prevent VTE among hospitalized patients. Development and implementation of evidence-based prevention strategies are important to achieving this goal.

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