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Steven B. Haas

The Hospital for Special Surgery

Robert L. Barrack

Washington University School of Medicine in St. Louis

Geoffrey Westrich

The Hospital for Special Surgery

Paul F. Lachiewicz

University of North Carolina at Chapel Hill

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Venous Thromboembolic Disease After Total Hip and Knee Arthroplasty

By Steven B. Haas, MD, MPH, Robert L. Barrack, MD, Geoffrey Westrich, MD, and Paul F. Lachiewicz, MD

An Instructional Course Lecture, American Academy of Orthopaedic Surgeons

Thromboembolic disease continues to pose a major threat to patients undergoing total hip and knee arthroplasty. Despite a great deal of research, there is still controversy concerning the best prophylactic regimen. This lecture outlines the various methods of mechanical and pharmacologic prophylaxis, describes the pros and cons of the American College of Chest Physicians (ACCP) guidelines for prevention of deep venous thrombosis, and presents the American Academy of Orthopaedic Surgeons (AAOS) clinical guidelines for prevention of symptomatic pulmonary embolism in patients undergoing total hip and total knee arthroplasty.

Prophylactic Modalities: Mechanical and Pharmacologic

The ideal prophylaxis modality for the high-risk population of patients undergoing total hip or knee arthroplasty would be clinically effective without side effects, be practical and easy to use, require no monitoring, and be cost-effective. Unfortunately, this ideal method of prophylaxis does not exist. The use of anticoagulants requires constant balancing of the risk of clots against the risk of bleeding. Some of these issues can be overcome with a multimodal approach, which is the closest to an “ideal” method that is currently available.

Pharmacologic Prophylaxis

Parenteral heparin, fondaparinux, oral warfarin, and oral acetylsalicylic acid are the major existing pharmacologic prophylaxis agents. Desirudin, a hirudin derivative, has also been approved by the U.S. Food and Drug Administration (FDA) for the prevention of venous thromboembolism. There are many more medications in various stages of development, including oral heparin and direct thrombin inhibitors of factors IIa, IXa, and Xa such as indraparinux, dabigatran, apixaban, and rivaroxaban.

Parenteral Heparin

Three different types of parenteral or low-molecular-weight heparin have been approved by the FDA. Enoxaparin (Lovenox) is the most commonly used and has been approved for patients undergoing total hip or knee arthroplasty. In addition, ardeparin (Normiflo) has been approved for patients undergoing total knee arthroplasty, and dalteparin (Fragmin) has been approved for patients undergoing total hip arthroplasty.

Look for this and other related articles in *Instructional Course Lectures, Volume 58*, which will be published by the American Academy of Orthopaedic Surgeons in February 2009:

- **“Prevention of Symptomatic Pulmonary Embolism in Patients Undergoing Total Hip and Total Knee Arthroplasty: Clinical Guidelines of the American Academy of Orthopaedic Surgeons,” by Paul F. Lachiewicz, MD**

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Low-molecular-weight heparin has many advantages, including rapid antithrombotic action. There is limited variability in its effects among different individuals, and prothrombin time and activated partial thromboplastin time have little influence. The drug has linear pharmacokinetics and a half-life of four and a half hours. No monitoring is required, allowing more practical outpatient use, and the drug can be effective when given every twelve or twenty-four hours.

The major disadvantages are the cost and risks of complications and bleeding. At our institution, low-molecular-weight heparin therapy costs \$31 per day, compared with \$9 per day for subcutaneous unfractionated heparin or less than \$1 per day for warfarin. The presence of an epidural catheter is a contraindication to the use of low-molecular-weight heparin, as such catheters increase the possibility of epidural hematomas and neurological deficits associated with regional anesthesia. The evidence regarding the greater risk of bleeding complications is inconclusive, although it is still a cause for concern. One trial¹ demonstrated a higher prevalence of bleeding complications, and another² showed increased blood loss associated with low-molecular-weight heparin therapy. A large randomized prospective study³ showed that the overall prevalences of symptomatic deep venous thrombosis and pulmonary embolism in patients with unilateral primary hip arthroplasty were similar in a group that received low-molecular-weight heparin and a group treated with warfarin, with most patients having received the study medication for one to seven days. Just over 1% (eighteen) of 1516 patients who received enoxaparin and 0.5% (eight) of 1495 patients who received warfarin had major bleeding events. The prevalence of minor bleeding events was significantly higher ($p = 0.021$) in the patients treated with enoxaparin (140 of 1516, 9.2%) than it was in those treated with warfarin (106 of 1495, 7.1%). Francis et al.⁴ reported that the prevalence of bleeding complications at the operative site and the rate of postoper-

ative transfusions in patients treated with low-molecular-weight heparin were significantly higher ($p = 0.03$ and $p = 0.001$, respectively) than the prevalences in patients treated with warfarin, but they did not find any significant differences between the groups with respect to the decrease in the hematocrit, intraoperative or postoperative blood loss, or the prevalence of major bleeding complications.

Oral Warfarin

The pharmacologic agent most commonly used for anticoagulation is warfarin (Coumadin). The widely accepted and extensively proven efficacy of this compound and the low risk of bleeding complications are major benefits. It is also effective for secondary prophylaxis, even in patients in whom clots developed while warfarin was being used as the primary prophylaxis⁵. The oral administration allows easy continued use in the outpatient setting.

Limitations of warfarin include the still-present risk of bleeding complications and possible inferiority of its effectiveness for primary prevention of thrombosis compared with that of low-molecular-weight heparin¹. It also requires monitoring to ensure therapeutic but safe international normalized ratios. Previous findings⁶⁻⁸ indicate that an international normalized ratio of between 2.0 and 2.5 is associated with the lowest rates of bleeding complications, with retention of efficacy. The prevalence of deep venous thrombosis after total knee arthroplasty in patients treated with warfarin alone remains as high as 35% to 55%⁹, indicating that warfarin on its own is not sufficient for clot prevention. A number of studies have shown that warfarin is more effective for prophylaxis against proximal deep venous thrombosis than it is for prevention of distal deep venous thrombosis in patients treated with total hip replacement¹⁰⁻¹².

Acetylsalicylic Acid

Acetylsalicylic acid, commonly known as aspirin, is a simple, inexpensive oral anticoagulant that does not require monitoring. It is extremely safe and has the added benefit of reducing hetero-

topic ossification. Most studies have shown it to be less effective than both low-molecular-weight heparin and warfarin^{9,13}, but it may provide sufficient prophylaxis against thromboembolic disease when it is used in combination with mechanical prophylaxis. Westrich et al.¹⁴ conducted a randomized prospective study comparing treatment with low-molecular-weight heparin and a calf mechanical compression device with treatment with acetylsalicylic acid and the same device in patients undergoing total knee arthroplasty. The rates of deep venous thrombosis, as assessed with ultrasonography, were not significantly different between the two groups, showing that aspirin in combination with mechanical compression may be as effective as, and safer than, more aggressive anticoagulant therapy.

Oral Heparin

One promising new pharmacologic agent that is being developed for anticoagulation is oral heparin. The goal of this new formulation is to attain the highly effective clot-prevention ability of parenteral heparin with an easily administered oral form of the drug. This could be achieved by combining unfractionated heparin and a carrier molecule, sodium N-(8[2-hydroxybenzoyl]amino) caprylate, allowing greater gastrointestinal absorption. A recent multicenter, randomized, double-blind Phase-III study¹⁵ showed that oral heparin decreased the prevalence of postoperative thrombi with a low frequency of bleeding complications in a large population of patients treated with total hip arthroplasty.

Other Agents

The other major focus of new research is the development of compounds that are able to directly or indirectly inhibit factors IIa (thrombin), IXa, or Xa in the coagulation pathway.

Ximelagatran (Exanta and Exarta), an oral direct factor-IIa inhibitor, initially showed promise, but marketing and foreign-distribution efforts in the United States were halted in 2006 because of unacceptable levels of hepatotoxicity. Prior to this, conflicting effi-

cacy results had been shown. Cohen et al.¹⁶ found no overall advantage of ximelagatran over low-molecular-weight heparin in patients treated with hip or knee surgery, but Colwell et al.¹⁷ found the efficacy of ximelagatran to be superior to that of warfarin. Although ximelagatran had unacceptable serious side effects, there may be other direct thrombin inhibitors that can be effective with fewer side effects.

Recombinant hirudin and its derivative desirudin (Iprivask) are direct factor-IIa inhibitors in an injectable form. Hirudin naturally occurs as a peptide in the salivary glands of medicinal leeches. Early research showed that the prevalence of deep venous thrombosis associated with desirudin was lower than that associated with enoxaparin¹⁸ or unfractionated heparin¹⁹ and that the bleeding risks were similar^{18,19}. Desirudin is currently approved for use for the prevention of thromboembolic disease.

Dabigatran etexilate (Rendix and Pradaxa), an oral direct factor-IIa inhibitor, is currently being assessed in Phase-III trials. Completed Phase-II research studies²⁰ comparing dabigatran etexilate, started one to four hours postoperatively, with enoxaparin, started twelve hours preoperatively, showed that the rates of pulmonary embolism and deep venous thrombosis associated with the highest doses of dabigatran were significantly lower than those associated with the enoxaparin ($p = 0.0007$). The risk of serious bleeding complications increased in a dose-dependent manner. The overall efficacy with regard to the prevention of venous thromboembolism and the risk of bleeding events were similar to those associated with enoxaparin.

Fondaparinux (Arixtra) is the first synthetic inhibitor of factor Xa. It is a single chemical entity created through a total chemical synthesis process, which enables batch-to-batch consistency. It has a single molecular target within the coagulation cascade, and there is no risk of pathogen contamination. It is administered subcutaneously in daily doses. Bauer et al.²¹ carried out a

multicenter, randomized, double-blind trial comparing fondaparinux (2.5 mg once daily) with enoxaparin (30 mg twice daily). The primary outcome was the development of venous thromboembolism, which was assessed up to eleven days postoperatively in 724 patients. The patients who received fondaparinux had a significantly lower prevalence of thromboembolic complications ($p < 0.001$), although their risk of major bleeding was significantly higher ($p = 0.006$). Fondaparinux is FDA-approved and currently available.

Idraparinux is a hypermethylated fondaparinux derivative. As an indirect inhibitor of factor Xa, it requires antithrombin as a cofactor. Idraparinux is administered subcutaneously once a week. A Phase-II study²² demonstrated a treatment effect similar to that of warfarin, with less bleeding than warfarin at a dose of 2.5 mg but an unacceptable risk of major bleeding at a dose of 10 mg. Further Phase-III research is in progress.

Oral factor-Xa inhibitors are also being developed. One of these, apixaban, is currently being evaluated in Phase-III trials to compare it with acetylsalicylic acid and warfarin for the prevention of stroke and systemic embolism²³. A previous study on apixaban therapy in patients treated with total knee replacement showed a promising risk-benefit profile when the drug was given at dosages of 2.5 mg twice a day and 5 mg once a day²⁴.

Rivaroxaban (Xarelto) is another oral factor-Xa inhibitor. It has a rapid onset, high oral bioavailability, and predictable pharmacokinetics²⁵. Phase-II studies showed it to be well tolerated and effective in the prevention of thromboembolic disease following orthopaedic surgery²⁵⁻²⁷. A Phase-III study of patients treated with total knee replacement showed it to be significantly superior to enoxaparin in terms of efficacy ($p = 0.01$), with a similar risk of bleeding²⁵. Currently, four separate trials are being carried out to assess rivaroxaban: two involving patients treated with total hip replacement and two involving patients treated with total knee replacement.

Mechanical Prophylaxis

Mechanical devices help to prevent venous thromboembolic disease by increasing fibrinolysis and decreasing stasis with accelerated venous emptying. Their efficacy has been proven in the fields of general surgery and neurosurgery as well as orthopaedic surgery. Foot pumps, calf pumps, and calf/thigh pumps are the three major types of mechanical prophylaxis devices. The type of pneumatic compression also varies. It may be standard pneumatic compression, sequential, or rapid inflation. Although these compression devices are associated with extremely low complication rates, compliance issues may decrease their effectiveness. Research on these devices has been less extensive than that on pharmacologic agents, but a number of studies have been conducted to compare the prophylaxis efficacy and compliance rates associated with different device types and compression types.

In a randomized prospective study by Westrich and Sculco²⁸, the combination of pneumatic plantar compression and acetylsalicylic acid was compared with acetylsalicylic acid alone for prophylaxis for patients treated with total knee replacement. The trial included 164 knees in 121 patients (seventy-eight treated with a unilateral total knee arthroplasty and forty-three, with a bilateral total knee arthroplasty). The rate of deep venous thrombosis in the group treated with compression and acetylsalicylic acid (27%, twenty-two of eighty-one) was significantly lower ($p < 0.001$) than that in the group treated with acetylsalicylic acid alone (59%, forty-nine of eighty-three). There was also a direct relationship between compliance with use of the mechanical compression device and the efficacy of the device with regard to prevention of deep venous thrombosis, as assessed with venography (or, if a venogram was unattainable or contraindicated, venous Doppler ultrasound). In another recent randomized prospective study²⁹, Ryan et al. compared the efficacy of an impulse mechanical compression device with that of prophylactic stockings for prevention of pelvic and proximal deep

venous thrombosis, as assessed with magnetic resonance venography, in 100 patients treated with total hip replacement. The mechanical compression led to a significantly lower rate of deep venous thrombosis (8%, four of fifty) compared with that associated with the use of prophylactic stockings (22%, eleven of fifty) ($p < 0.05$).

In 2004, Lachiewicz et al.³⁰ conducted a randomized prospective study of 423 patients who had a total of 472 knee replacements. The patients were randomized to treatment with either a rapid-inflation asymmetrical compression device or a sequential circumferential compression device. The prevalence of thrombi in the patients treated with the rapid-inflation asymmetrical compression device (6.9%, sixteen of 206) was significantly lower ($p = 0.007$) than that in the patients treated with the sequential circumferential compression device (15.0%, thirty-six of 217).

The hemodynamics in patients treated with total hip or total knee arthroplasty were examined in two other studies^{31,32}. One³¹, in patients who underwent total knee replacement, tested three calf-and-thigh pump designs, two foot pump designs, one foot-and-calf pump design, and one calf pump design. The greatest increase in venous volume and velocity (below the saphenous vein) was found in the patients treated with a device that incorporated rapid calf compression. In the other study³², involving patients who underwent total hip replacement, three calf-and-thigh pump designs, two foot pump designs, one foot-and-calf pump design, and one calf pump design were tested. The greatest increase in peak venous velocity occurred with pulsatile calf and calf-and-foot pneumatic compression with a rapid inflation time. The final key finding was that, because of compliance issues, simple and easy-to-apply efficacious devices have the greatest chance of success.

A prospective study³³ of 100 patients showed that the rate of compliance with the use of a foot-pump pneumatic compression device (Plexi-Pulse) after total knee arthroplasty was

90.1%. Patients found the device to be relatively comfortable and easy to apply and remove, and nurses rated this device highly in comparison with other pneumatic compression devices. Because a device is effective only when it is used as directed, it is important to consider ease of use and likelihood of staff and patient compliance, not just "ideal" use, when evaluating different types of mechanical compression devices.

Inferior Vena Cava Filters

Inferior vena cava filters do not prevent deep venous thrombosis, but they can prevent pulmonary embolization. They are often inserted in patients with a history of venous thromboembolic disease and those with substantial traumatic injuries before other prophylaxis methods can be initiated. Inferior vena cava filters are recommended if pharmacologic anticoagulant therapy is clearly contraindicated or if the patient has had thromboembolic complications despite adequate anticoagulation in the past³⁴. The cost of these filters is substantial, and the application is an invasive procedure that requires the use of contrast agents, exposing the patient to a risk of complications³⁵. A promising development has been the introduction of retrievable inferior vena cava filters, which may decrease the risks of complications associated with permanent filter placement. Early data have shown that retrievable filters are effective in preventing pulmonary embolism, with a low rate of insertion-related complications^{36,37}. These filters can be left in place permanently or removed when they are no longer needed; however, because of clots lodged in the filter or difficulty with capturing the filter, planned removal may not always be possible³⁸.

Multifactorial Approach

A review³⁹ of fifty studies involving a total of 10,929 patients who had undergone total hip replacement revealed deep venous thrombosis rates of 48% in patients treated with a placebo, 31% in those treated with acetylsalicylic acid, 23% in those treated with warfarin, 21% in those treated with pneumatic com-

pression, and 18% in those treated with low-molecular-weight heparin. The lowest rate of distal deep venous thrombosis was in the pneumatic compression group, and this rate was significantly lower than that in the aspirin group and the warfarin group ($p = 0.0007$ and $p = 0.0001$, respectively). Proximal deep venous thrombosis was significantly less common in the warfarin group and the low-molecular-weight heparin group ($p = 0.0004$ and $p = 0.0059$, respectively) than it was in the pneumatic compression group. The overall prevalence of symptomatic pulmonary embolism was $<1\%$ in the low-molecular-weight heparin, warfarin, and pneumatic compression groups, but the aspirin group had a significantly higher rate of symptomatic pulmonary embolism than the warfarin and low-molecular-weight heparin groups ($p < 0.0083$).

In another extensive review article⁴⁰, the authors examined twenty-three trials that included 6001 patients treated with total knee replacement. They found a deep venous thrombosis rate of 53% in association with aspirin therapy, 45% in association with warfarin, 29% in association with low-molecular-weight heparin, and 17% in association with pneumatic compression. This study did not include a placebo group, and the rates of proximal and distal deep venous thrombosis were not examined separately. Patients who received low-molecular-weight heparin or pneumatic compression were significantly less likely to have a deep venous thrombosis than were patients who received aspirin ($p < 0.0001$) or warfarin ($p < 0.0001$). The patients treated with aspirin had a significantly higher rate of pulmonary embolism than the patients who received any other means of prophylaxis ($p < 0.05$). In both of the meta-analyses, the rates of deep venous thrombosis with the use of each singular modality were substantially higher than rates that have been associated with a combination of chemical and mechanical means. Trials of the use of compression devices in conjunction with postoperative aspirin therapy have shown this combination to be as effective as low-molecular-weight heparin

for the prevention of proximal and distal deep venous thrombosis, with a decreased risk of major bleeding complications^{9,39,40}.

Our institution uses and advocates a multifactorial approach to prevent venous thromboembolism that has been validated by extensive research^{14,35,40-42}. The protocol includes a combination of preoperative, intraoperative, and postoperative prophylaxis techniques. Preoperative assessment involves a full medical evaluation with special attention paid to coagulation risk factors such as a current malignant tumor, a history of pulmonary embolism or deep venous thrombosis, estrogen therapy, oral contraceptive use, and tobacco use. Patients must discontinue the use of any procoagulant medication prior to admission. Autologous blood donation is also encouraged because it has been proven to significantly reduce the prevalence of deep venous thrombosis after total hip and total knee arthroplasty ($p = 0.003$ and $p < 0.01$, respectively)^{43,44}.

There are intraoperative techniques that may reduce the risk of thromboembolic complications. Using regional anesthesia decreases blood loss and the rate of deep venous thrombosis, and intraoperative pneumatic compression decreases venous stasis and the risk of clotting⁴⁵⁻⁴⁷. A surgical duration of less than seventy minutes also decreased the rate of deep venous thrombosis in patients treated with total knee arthroplasty⁴⁸. A single intraoperative dose of unfractionated heparin may decrease the rate of deep venous thrombosis after total hip arthroplasty, but the data with regard to total knee arthroplasty are less conclusive^{9,49}.

The standard inpatient postoperative prophylaxis includes intermittent pneumatic compression and pharmacologic prophylaxis (usually warfarin, or aspirin if warfarin is contraindicated). Furthermore, it is important for prophylaxis to continue following discharge from the hospital and for the patient to be aware of the symptoms of venous thromboembolism postdischarge. Pellegrini et al.⁵ found that secondary prophylaxis with extended warfarin

therapy reduced the rates of readmission for the treatment of pulmonary embolism, deep venous thrombosis, or bleeding after total knee replacement, and they recommended that patients continue to take warfarin following discharge. Another recent study¹³ showed that, even if screening tests reveal negative findings, discharging patients without continuing prophylaxis after a total hip or knee arthroplasty is not cost-effective.

In a large study from our institution, González Della Valle et al.⁴¹ found that a multimodal approach of preoperative and intraoperative measures combined with pneumatic compression, knee-high elastic stockings, early mobilization, and chemoprophylaxis with acetylsalicylic acid (83% of patients) or warfarin (17%) for four to six weeks following total hip arthroplasty was safe and efficacious. The study included 1947 consecutive patients (2032 total hip arthroplasties) who were observed prospectively for three months. The first 171 patients had a 6.4% prevalence of asymptomatic deep venous thrombosis as assessed with ultrasound, and the other 1776 patients had a 2.5% prevalence of clinical deep venous thrombosis. Nonfatal symptomatic pulmonary embolism occurred in 0.6% (twelve) of the 1947 patients. The low rates of thromboembolic complications in this high-risk population are evidence that routine anticoagulation with chemoprophylactic agents that may increase the risk of bleeding, such as low-molecular-weight heparin, is unnecessary. The authors of a review of prophylaxis following total knee arthroplasty concurred³⁵, finding that “no one method of prophylaxis has been shown to be ideal and there is little doubt that more than one modality focusing on both mechanical and chemical means of prevention need to be employed.”

Pros and Cons of the ACCP Guidelines for Prophylaxis Against Deep Venous Thrombosis After Total Joint Replacement

In 2004, the recommendations of the Seventh ACCP Conference on Antith-

rombotic and Thrombolytic Therapy for prophylaxis against deep venous thrombosis were published⁵⁰. These recommendations were based on a systematic review of the literature by experts in the field, with use of strict, well-defined criteria for inclusion of studies. Since the recommendations of the ACCP are frequently utilized as a standard, it is important to understand the methodology as well as the advantages and disadvantages of these guidelines⁵¹. The criteria for inclusion of studies that form the basis of the recommendations included a defined patient population that was identified as belonging to the group at risk, a sample size of at least ten patients in each group, and an identifiable end point normally consisting of the prevalence of deep venous thrombosis as demonstrated by contrast venography. Only randomized clinical trials were assessed for the determination of prophylaxis efficacy. Final recommendations were based on comments from five to ten external reviewers. The rationale for prophylaxis for hospitalized patients was based on the high prevalence of venous thromboembolism, the adverse consequence of sequelae of deep venous thrombosis, and the efficacy and effectiveness of thromboprophylaxis. Patients undergoing total joint replacement were considered to be either at high risk or at the highest risk depending on their age, the presence of additional risk factors, and the high-risk nature of arthroplasty surgery.

Additional rationales for routine thromboprophylaxis for patients undergoing total joint arthroplasty were that most postoperative deep venous thrombi and pulmonary emboli are clinically silent, it is difficult to predict whether symptomatic deep venous thrombosis or pulmonary embolism will develop in a particular patient, and identifying “at risk” patients with either physical examination or screening modalities has proven to be generally ineffective. Also, the cost of diagnosing and treating the sequelae of venous thromboembolic disease is substantial. In addition to the risk and cost of treating a disease that could have been

TABLE I Comparison of Efficacy and Complications with an ACCP Grade-1A Protocol with Previous Results with a Non-ACCP Protocol in Patients Treated with Total Hip Arthroplasty^{50,59}

	ACCP Grade-1A Protocol with Lovenox (Enoxaparin)	Non-ACCP Protocol with Coumadin (Warfarin)	P Value
Major complications	11/129 (9%)	15/705 (2.1%)	<0.001
Symptomatic deep venous thrombosis	9/129 (7%)	11/705 (1.6%)	<0.001
Pulmonary embolism	2/129 (1.6%)	1/705 (0.1%)	<0.01
Hematoma/reoperation	3/129 (2.3%)	2/705 (0.3%)	<0.01
Local wound problems	8/129 (6.2%)	4/705 (0.6%)	<0.001
Heparin-induced thrombocytopenia	1/129 (0.8%)		

prevented, there is an increased future risk of recurrent disease and its sequelae such as chronic post-thrombotic syndrome. The underlying assumptions regarding the effectiveness of thromboprophylaxis include evidence that prophylaxis is very effective in lowering the prevalence of deep venous thrombosis, that prophylaxis can prevent both symptomatic pulmonary embolism and fatal pulmonary embolism, and that prophylaxis against deep venous thrombosis is cost-effective. Also underlying these recommendations are the facts that many cases of symptomatic venous thromboembolic disease occur after discharge, failure to prevent venous thromboembolic disease results in therapeutic anticoagulation with additional substantial risks, and venous thrombi can result in a number of sequelae that are frequently overlooked. These sequelae include post-thrombotic syndrome, which can cause leg swelling, dermatitis, and ulcers; venous insufficiency; and persistent venous occlusion. The clinical diagnosis of venous thromboembolic disease is unreliable,

and routine screening of asymptomatic patients has proven to be not cost-effective. There is a strong case, therefore, for primary prophylaxis on a routine basis. Of all practices reviewed by the Agency for Healthcare Research and Quality (AHRQ) in terms of their ability to reduce adverse events while decreasing overall costs, prophylaxis against deep venous thrombosis has received the highest safety rating.

The end point selected for the clinical trials on thromboprophylaxis by the ACCP was venographically proven deep venous thrombosis. While it is recognized that most asymptomatic deep venous thrombi are not clinically relevant, there is allegedly a strong concordance between the “surrogate” outcome of asymptomatic deep venous thrombosis and clinically important deep venous thrombosis, with a ratio estimated to range from five to one to ten to one. The use of a decrease in mortality or the rate of symptomatic pulmonary embolism alone as an end point has been termed “problematic.”⁵⁰

On the basis of these underlying assumptions and rigorous methodology, evidence-based guidelines, rated as either Grade 1 (defined as strong and indicative of benefits that outweigh risk, burden, and cost) or Grade 2 (defined as being less certain with regard to the magnitude of benefits, risks, and costs), were released. Grade-1 recommendations were subdivided into Grade-1A recommendations, which are based on randomized clinical trials with consistent results that provide unbiased recommendations; Grade-1B recommendations, which are based on randomized clinical trials with inconsistent results or with major methodological weaknesses; and Grade-1C recommendations, which are based on observational studies or on generalization from one group of patients included in randomized clinical trials to a different, but somewhat similar, group of patients who did not participate in those trials⁵². The Grade-1A recommendations for prophylaxis for hip replacement included administration of warfarin with a target international normalized ratio

TABLE II Results of Lower-Dose Warfarin Protocols for Patients Treated with Joint Arthroplasty

Study	No. of Cases	Target	Pulmonary Embolism	Death
Vresilovic et al. ¹⁰²	852	Prothrombin time, 1.2-1.4 × control	6 (0.7%)	0
Paiement et al. ¹⁰³	268	Prothrombin time, 1.25-1.5 × control	2 (0.7%)	0
Lieberman et al. ¹⁰⁴	1099	Prothrombin time, 14-17 sec	12 (1.1%)	1 (0.09%)
Pellegrini et al. ⁷⁹	1972	International normalized ratio, 2.0	14 (0.7%)	3 (0.15%)
Pellegrini et al. ⁵	1321	International normalized ratio, 2.0	9 (0.7%)	2 (0.15%)
Keeney et al. ¹⁰⁵	705	International normalized ratio, 2-2.5	5 (0.7%)	0
Total	6217		48 (0.77%)	6 (0.1%)

of 2.5 (range, 2 to 3), low-molecular-weight heparin, or fondaparinux, for a minimum of ten days. The recommendations were the same for knee replacement but included pneumatic compression devices as a Grade-1B recommendation. There was a Grade-1A recommendation against the use of aspirin alone following elective hip or knee arthroplasty. A prolonged course of treatment, for four to five weeks, was recommended for patients at highest risk.

In addition to the rigorous, well-described methodology underlying the ACCP guidelines, an advantage of these recommendations is that they meet the criteria of virtually every oversight group, including hospitals, health maintenance organizations, and insurance companies, and therefore following them minimizes medicolegal exposure. The ACCP Grade-1A recommendations also meet requirements of state and federal programs, including the Surgical Care Improvement Project (SCIP) and the Center for Medicare and Medicaid Services Pay-for-Performance program (CMS P4P program) initiative. The SCIP has a goal of reducing surgical complications by 25% by 2010^{53,54}. Four areas have been targeted, one of which is minimizing venous thromboembolism. The P4P program was implemented by the Tax Relief and Health Care Act of 2006⁵⁵. In 2007, the Physician Quality Reporting Initiative (PQRI) identified numerous health-quality measures, including venous thromboembolism prophylaxis for all patients for whom it is indicated. Reporting that three performance measures were met for 80% of eligible patients qualified physicians for a 1.5% bonus while failure to report or comply in the future will in all likelihood result in a decreased reimbursement⁵⁶. While the ACCP recommendations for prophylaxis against deep venous thrombosis after hip and knee arthroplasty meet the requirements of the federal programs, following these recommendations is not necessary to satisfactorily meet the requirements of those programs. According to the manual for National Hospital Quality Measures, use

of low-molecular-weight heparin, factor-Xa inhibitor, or warfarin meets the requirement for both total hip replacement and total knee replacement⁵⁷. In addition, pneumatic compression devices meet the requirement for elective total knee arthroplasty. Of note is the fact that neither the dose nor the duration of pharmacologic prophylaxis is specified; this is especially relevant for warfarin, for which lower-dose protocols are often embraced by orthopaedic surgeons and shorter durations of prophylaxis have occasionally been used successfully as well. Aspirin alone is not recommended for prophylaxis against deep venous thrombosis.

Potential problems with following Grade-1A protocols have been noted in recent studies. Reviews of the available literature, particularly studies related to hip and knee arthroplasty, have resulted in differing conclusions. One major issue is whether the prevalence of deep venous thrombosis should be used as a surrogate marker for effectiveness since deep venous thrombosis does not correlate with symptomatic pulmonary embolism or death rates following hip and knee arthroplasty. Deep venous thrombosis is two to three times more common after knee replacement than it is after hip replacement, but the prevalence of pulmonary embolism following total knee arthroplasty is equivalent or reduced compared with that after total hip arthroplasty⁵⁸. Also of crucial importance is the observation, supported by a number of clinical studies, that the more effective reduction of deep venous thrombosis achieved with the aggressive use of chemoprophylactic agents leads to a higher risk of bleeding and subsequent morbidity. One recent study showed that converting to an

TABLE III Levels of Evidence

I	High-quality randomized trial
II	Cohort study (good control)
III	Case-control study
IV	Uncontrolled case series
V	Expert opinion

ACCP Grade-1A protocol actually substantially increased complications and decreased efficacy compared with the outcomes associated with a previously utilized protocol that did not meet any of the criteria set forth by the ACCP⁵⁹. Prior to 2004, 705 patients were treated with a short course (seven days) of low-dose Coumadin (warfarin), with a target international normalized ratio 2 to 2.5, and routine predischarge ultrasound screening. This course was shorter than the ten-day minimum recommended by the ACCP, the target international normalized ratio was lower than that recommended by the ACCP, and the use of routine screening was in disagreement with a Grade-1A ACCP negative recommendation. In spite of this, the efficacy of the pre-2004 protocol was high, with no deaths and only one symptomatic pulmonary embolism (0.1%). Patient acceptance of the protocol was high, with most of them receiving most or all of their prophylactic treatment while they were in the hospital, and the cost of the protocol to the patient was usually zero. On the basis of the ACCP recommendations, the protocol at the institution was changed in conjunction with an institutional review board-approved prospective study in which a ten-day course of low-molecular-weight heparin was

TABLE IV Strength of Recommendation

A	Good evidence: Level-I studies with consistent findings (adequate quality and applicability)
B	Fair evidence: Level-II or III studies with consistent findings (adequate quality and applicability)
C	Poor evidence: Level-IV or V studies with consistent findings
D	Insufficient or conflicting evidence not allowing a recommendation

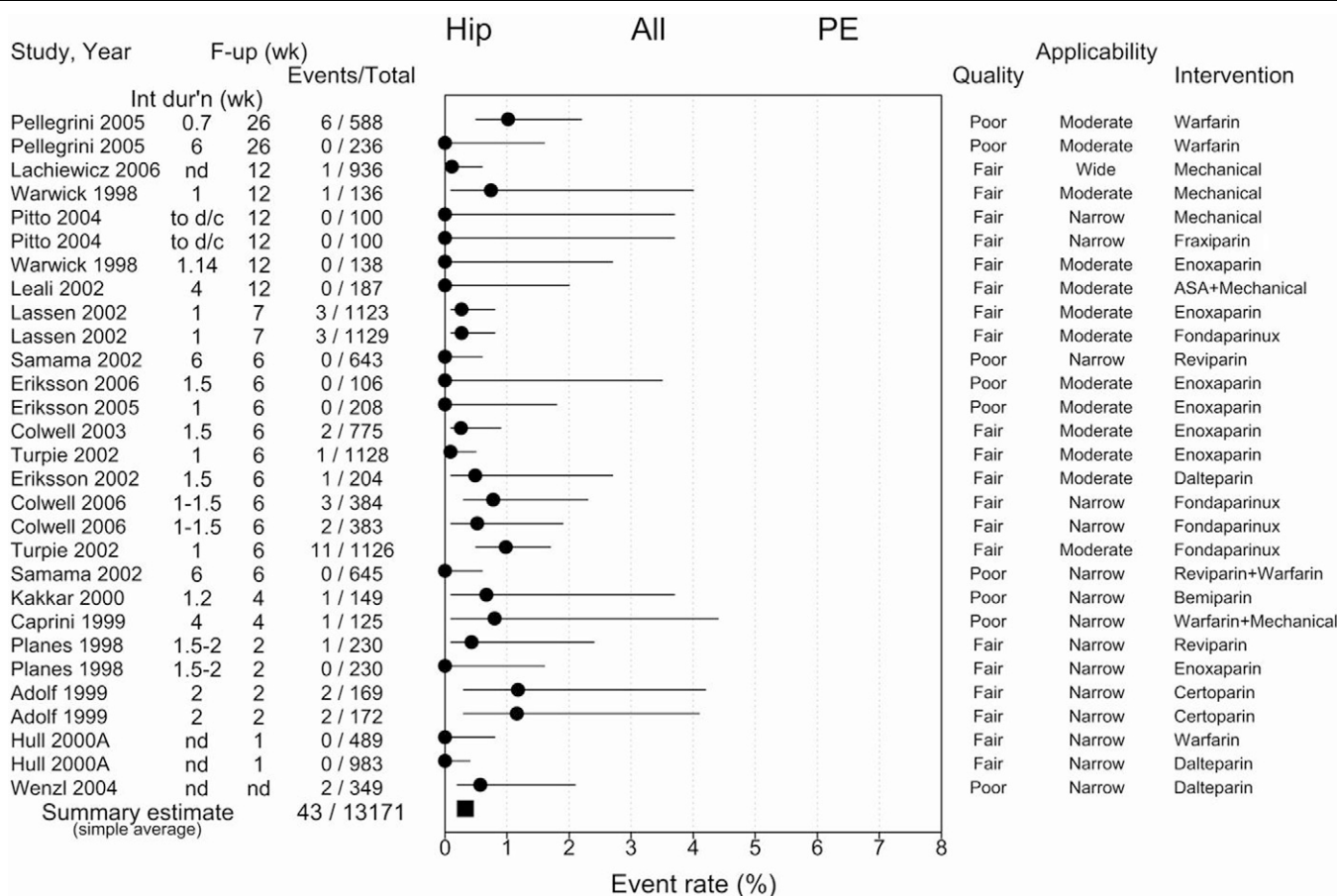


Fig. 1

Event rates of pulmonary embolism (PE) after total hip arthroplasty in the reviewed studies. Int dur'n = duration of intervention, F-up = duration of follow-up, d/c = discharge, ASA = aspirin, and nd = no data.

used for all eligible patients⁵⁰. Data on wound drainage, symptomatic deep venous thrombosis and pulmonary embolism, hospital readmission, injection site problems, heparin-induced thrombocytopenia, and patient satisfaction and compliance were collected prospectively. Complete data were collected on 290 consecutive patients treated with total joint replacement. The original study design called for more than 2000 patients, but the study was terminated prematurely because of a concern about patient safety. The results were compared with those from the previous study⁵⁹. Major complications occurred in 9%; symptomatic deep venous thrombosis, in 7%; pulmonary embolism, in 1.6%; hematoma and a reoperation, in 2.3%; local wound problems, in 6.2%; and heparin-induced thrombocytopenia, in 0.8%.

The rate of major complications was significantly higher and the efficacy was significantly lower than those with the non-ACCP protocol utilized immediately prior to the institution of this study (Table I). In addition, the rate of minor complications, including prolonged hospitalization, was 7%.

Complications associated with the use of more aggressive protocols for prophylaxis against deep venous thrombosis have recently been reported at other centers. Patel et al. reported prolonged wound drainage and subsequent associated complications following primary hip and knee replacement⁶⁰. The proportion of patients who still had wound drainage on the fifth postoperative day was significantly higher in their group that received low-molecular-weight heparin than it was in their groups treated with the other studied

modalities ($p = 0.003$); each day of prolonged wound drainage increased the risk of wound infection by 42% following a total hip arthroplasty and by 29% following a total knee arthroplasty. Parvizi et al. studied the effect of "excessive anticoagulation" on the subsequent prevalence of periprosthetic infection⁶¹. For the patients in whom infection developed following hip or knee replacement, the factors that were strongly associated with that complication were wound hematoma, wound drainage, or an international normalized ratio of >1.5 at the time of discharge. Saleh et al. noted that implementation of a protocol based on ACCP Grade-1A recommendations led to a substantial increase in the prevalence of complications as compared with the rate associated with a previously utilized low-dose-Coumadin protocol⁶².

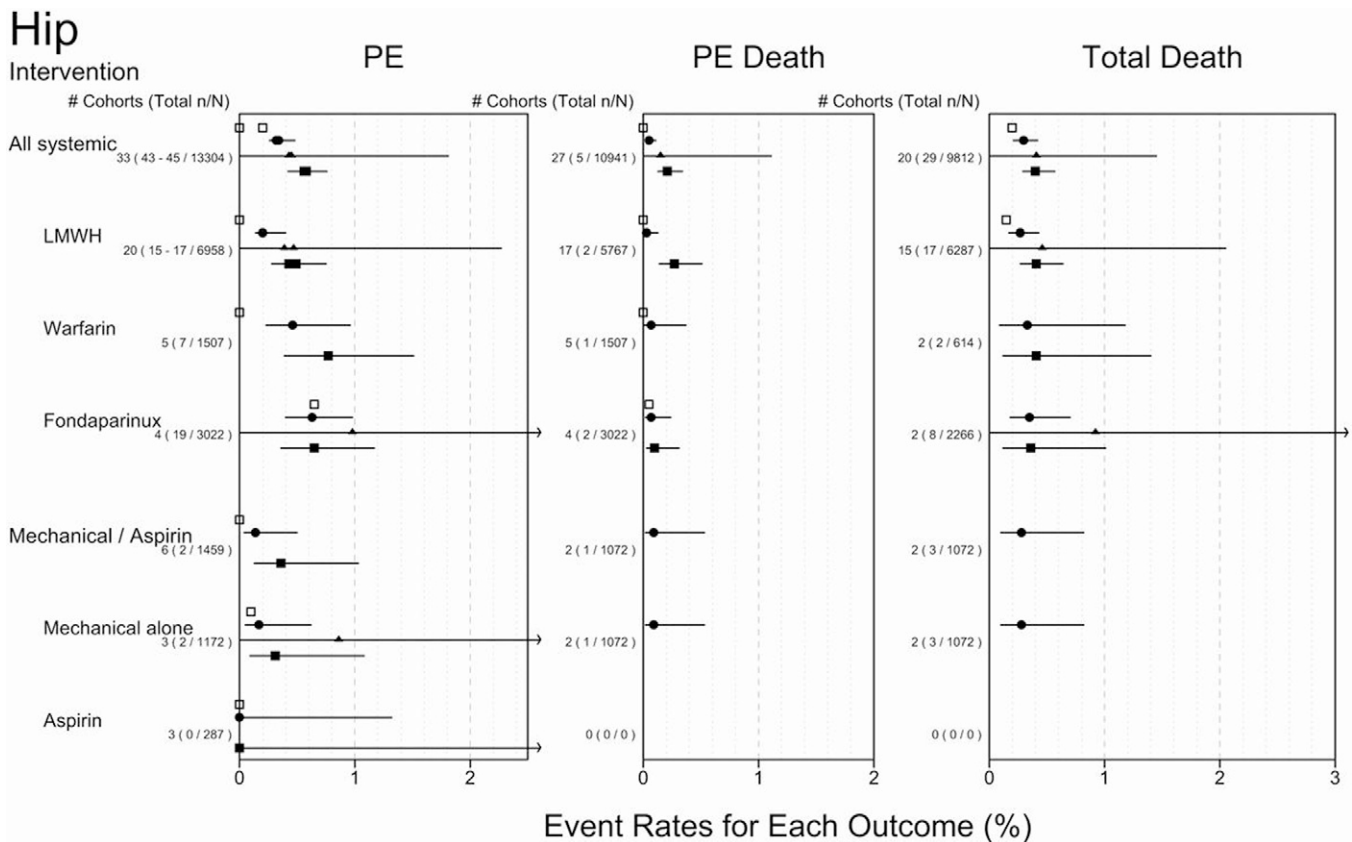


Fig. 2

Pooled event rates of pulmonary embolism (PE), fatal pulmonary embolism (PE Death), and all deaths after total hip arthroplasty in the reviewed studies. LMWH = low-molecular-weight heparin.

A number of orthopaedic studies of less aggressive pharmacologic prophylaxis for patients treated with hip or knee replacement have demonstrated excellent results when the end points were death and symptomatic pulmonary embolism. The largest body of data relates to the use of lower-dose warfarin protocols with a target international normalized ratio of ≤ 2.0 . Extremely low prevalences of symptomatic pulmonary embolism and death have been noted in a number of studies from leading total joint replacement centers over the past fifteen years (Table II). Bern et al. reported on more than 1000 patients treated with total hip arthroplasty and an ultra-low-dose warfarin protocol consisting of 1 mg/day for seven days prior to surgery, a variable dose with a target international normalized ratio of 1.5 to 2 while the patient was in the hospital, and 1 mg/day for four to six weeks following discharge⁶³. There were

only two cases of symptomatic deep venous thrombosis and one nonfatal pulmonary embolism, with a follow-up rate of >99%.

The other deep venous thrombosis prophylaxis regimen that has received some support in the orthopaedic literature is the use of aspirin. Although there is an ACCP Grade-1A recommendation against the use of aspirin alone, Lotke and Lonner reported a prevalence of pulmonary embolism of only 0.06% after more than 3000 total knee arthroplasties with aspirin prophylaxis⁶⁴. More recently, Callaghan et al. reported no deaths after 427 total knee arthroplasties, 73% of which were low-risk procedures, in patients treated with aspirin, foot pumps, and screening ultrasound⁶⁵. In a study of a large total joint arthroplasty database of patients treated with various prophylactic modalities, including aspirin (4719), warfarin (51,923), and low-molecular-

weight heparin or fondaparinux (37,198), Bozic et al. reported no difference in mortality rates but substantially less bleeding in the aspirin group⁶⁶.

Many arthroplasty surgeons disagree with some of the major conclusions and recommendations of the ACCP guidelines. The two major issues are the use of venographically proven deep venous thrombosis as the end point of prophylaxis against venous thromboembolic disease and the measure of efficacy of prophylactic regimens. These criteria generally favor aggressive pharmacologic prophylaxis and correlate poorly with the prevalences of death and symptomatic pulmonary embolism following hip and knee arthroplasties. Largely because of this issue, the AAOS formed a task force to recommend clinical guidelines specifically for prophylaxis against deep venous thrombosis in patients treated with lower-extremity total joint re-

Hip

Intervention

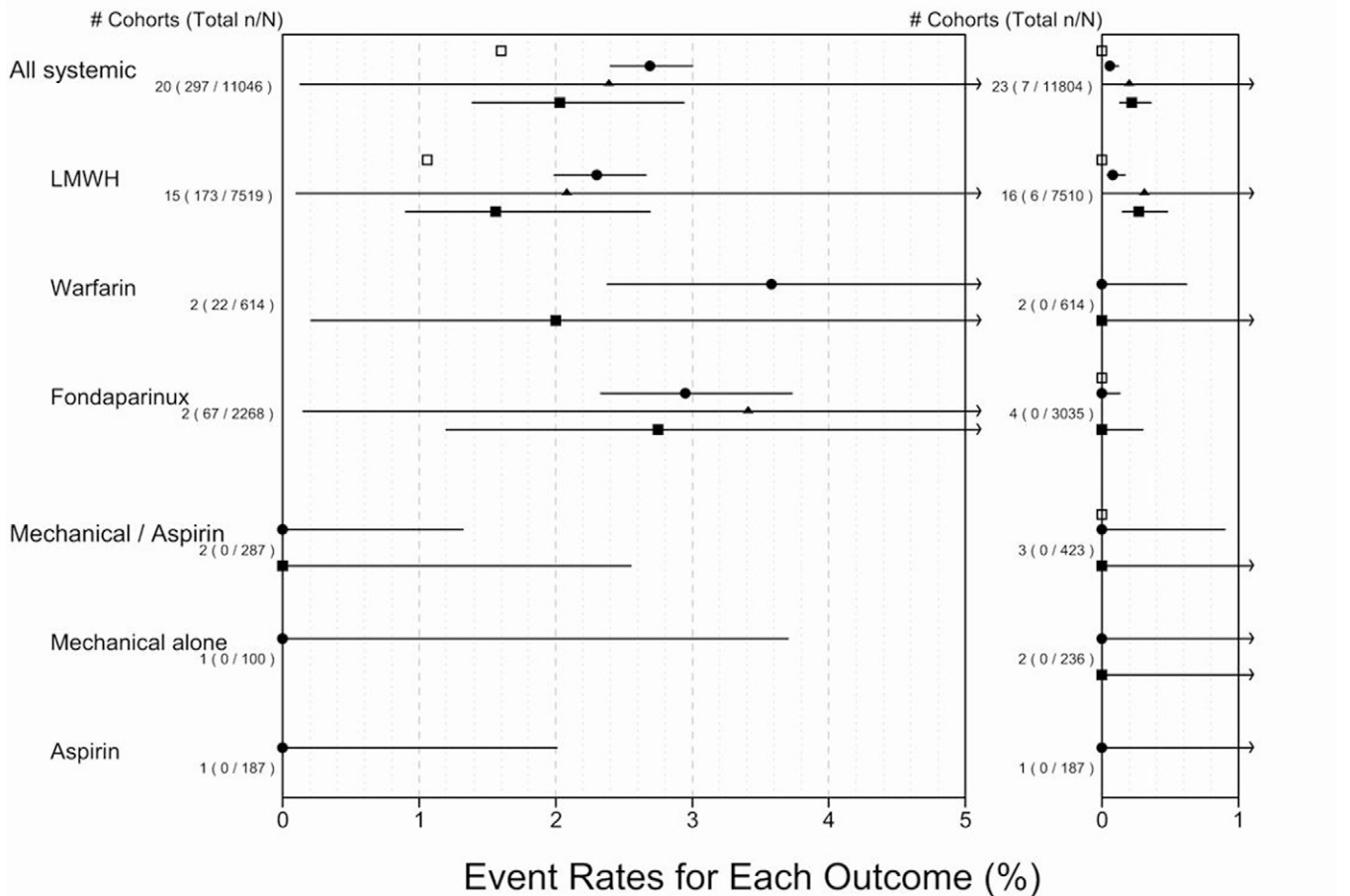


Fig. 3

Pooled event rates of major bleeding and death from bleeding after total hip arthroplasty in the reviewed studies. LMWH = low-molecular-weight heparin.

placement. This task force chose prevention of symptomatic pulmonary embolism, rather than reduction in the prevalence of deep venous thrombosis, as the end point⁶⁷. Use of this different end point led to different recommendations regarding appropriate regimens for prophylaxis against deep venous thrombosis. Probably the greatest difference of opinion, however, is over the prevalence of complications related to the use of aggressive pharmacologic prophylaxis. Many orthopaedic surgeons have observed a higher prevalence of prolonged wound drainage with the use of the more aggressive anticoagulation protocols. Pharmacologic prophylactic protocols resulting in a high risk of wound drainage have also been associated with hematoma formation,

prolonged hospitalization, and other complications that can compromise the clinical result. The number of total joint procedures is expected to increase dramatically in the immediate future⁶⁸, with the increase in knee arthroplasties predicted to be much greater than that in hip arthroplasties and the highest rate of increase expected among younger patients, who tend to be healthier and at lower risk for deep venous thrombosis. The use of aggressive pharmacologic protocols on a routine basis, therefore, may put an increasingly higher number of patients with a low risk for deep venous thrombosis at risk for complications from the prophylaxis; therefore, it is less likely to be cost-effective. The clinical success of less aggressive protocols and the increasing number of

young, healthy patients who are undergoing hip and knee replacements seem to indicate that selective use of these aggressive pharmacologic protocols, with an emphasis on identifying patients who are at risk and more judicious utilization of aggressive prophylaxis against deep venous thrombosis, is prudent.

AAOS Clinical Guidelines

Orthopaedic surgeons have been affected by the ACCP guidelines for the prevention of deep venous thrombosis in patients treated with total hip or knee arthroplasty. Deep venous thrombosis (generally asymptomatic, detected by venography or ultrasonography) was the primary outcome measure in the development of these guidelines⁵⁰. Be-

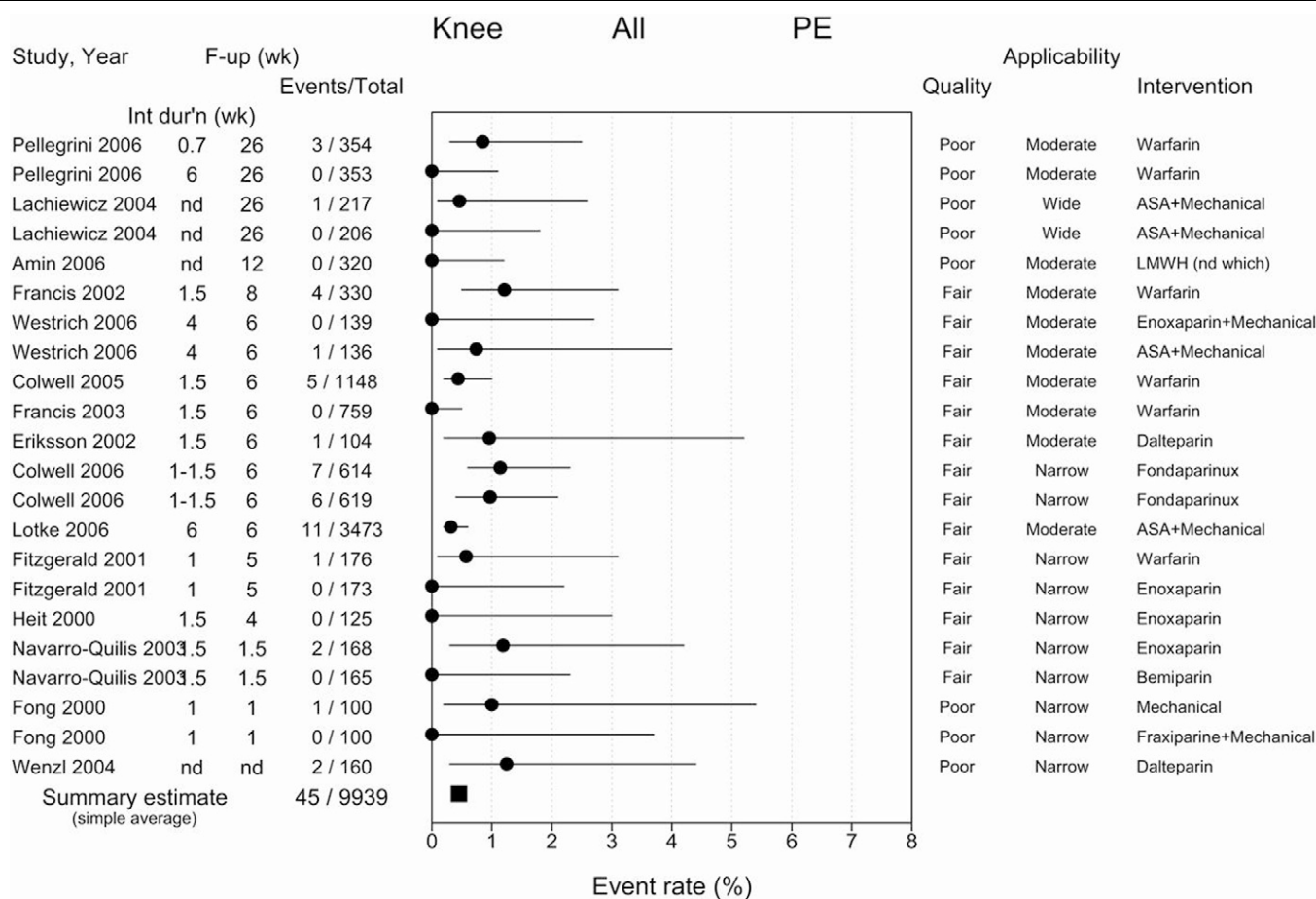


Fig. 4

Event rates of pulmonary embolism (PE) after total knee arthroplasty in the reviewed studies. Int dur'n = duration of intervention, F-up = duration of follow-up, ASA = aspirin, and nd = no data.

cause of the differences among patients found in randomized pharmaceutical studies and in the general arthroplasty population, many orthopaedists believe that these guidelines have limited relevance to “real-world” decision-making⁵⁸. These guidelines emphasize prophylaxis with strong pharmacologic agents and seem to underrate the risks of bleeding and ignore other adverse outcomes, such as infection and joint stiffness, related to these agents⁵⁸.

Symptomatic pulmonary embolism is relatively rare after total hip and knee arthroplasty. In the Scottish Registry, the ninety-day rate of fatal pulmonary embolism was 0.22% after 44,785 total hip arthroplasties and 0.15% after 27,000 total knee arthroplasties⁶⁹. In the United States, a study of Medicare data showed a ninety-day rate of nonfatal pulmonary embolism of

0.93% after 58,521 total hip arthroplasties⁷⁰. A review of 222,684 total knee arthroplasties in California revealed a ninety-day rate of symptomatic pulmonary embolism of 0.41%⁷¹. Despite the introduction of the ACCP guidelines, there appears to have been no change in the rate of symptomatic or fatal pulmonary embolism over the past ten to fifteen years^{69,72}. One study of 290 patients who were treated with total hip or knee arthroplasty and given a ten-day course of low-molecular-weight heparin (Lovenox) according to the ACCP Grade-1A recommendation demonstrated a 9% rate of major bleeding or wound complications, including a 4.7% rate of readmission⁵⁹. Symptomatic deep venous thrombosis still occurred in 3.8% of the patients, nonfatal symptomatic pulmonary embolism still occurred in 1.3%, and heparin-induced thrombo-

cytopenia still occurred in 1.3%. These results led the authors to recommend against the use of the ACCP Grade-1A guideline of administering low-molecular-weight heparin for ten days⁵⁹.

The AAOS formed a working group in early 2006 to develop a new consensus guideline for prophylaxis against symptomatic pulmonary embolism after total hip and knee arthroplasty. The key goals were to determine the event rates of symptomatic and fatal pulmonary embolism associated with several interventions (aspirin, low-molecular-weight heparin, synthetic pentasaccharides, and warfarin), the adverse-event rates (bleeding or death) associated with these interventions, and the natural history without prophylaxis (in a study of a minimum of 1000 patients). The working group was composed of eight members from the

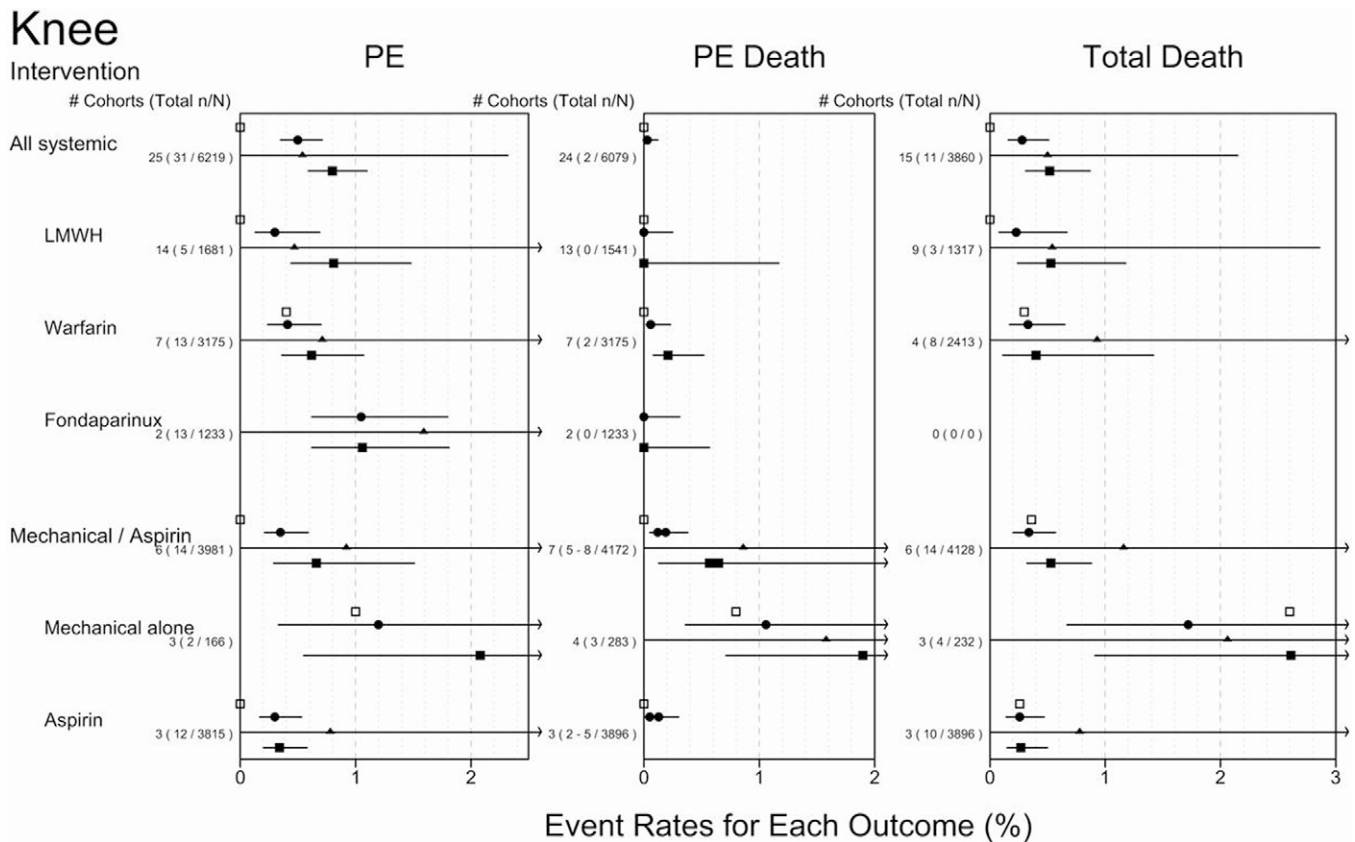


Fig. 5

Pooled event rates of pulmonary embolism (PE), fatal pulmonary embolism (PE Death), and all deaths after total knee arthroplasty in the reviewed studies. LMWH = low-molecular-weight heparin.

AAOS (Norman A. Johanson, MD [Chairman]; Paul F. Lachiewicz, MD; Jay R. Lieberman, MD; Paul A. Lotke, MD; Javad Parvizi, MD; Vincent Pellegrini, MD; Theodore A. Stringer, MD; and Paul Tornetta III, MD), and this group consulted an evidence-review team from the Center for Clinical Evidence Synthesis at Tufts-New England Medical Center (May Adra, PharmD; Ethan Balk, MD, MPH; Stanley Ip, MD; Gowri Raman, MD; and Joseph Lau, MD). The working-group consensus decision was to critically review the literature that met the following criteria: a prospective study of total hip or knee arthroplasties performed since 1996 only, a cohort study with at least 100 patients per group, or a randomized controlled trial with at least ten patients per treatment. The evidence-review team found no recent study on the natural history (without prophylaxis) that included at least 1000 patients. The literature review

included 2713 citations from MEDLINE and Cochrane search engines and ten other recent citations that the working group was aware of but had not been retrieved by the MEDLINE and Cochrane search engines. Of these 2723 citations, only forty-two articles met the working-group criteria. There were twenty-six articles with cohorts totaling 16,304 total hip arthroplasties and sixteen articles with cohorts totaling 11,665 total knee arthroplasties. As was the case in the development of the previous AAOS knee osteoarthritis guidelines, the individual studies were graded according to levels of evidence (Table III). The strength of each guideline recommendation was graded on the basis of the quality of the collection of studies from which the recommendation was derived (Table IV).

Since the event rates in most studies were <1% and were not normally distributed, a formal meta-

analysis was precluded. Statistical methods included simple pooling (total events/total patients) with calculations of standard deviations, analyses of medians among three or more cohorts, random-effects-model meta-analysis of logit transformed data⁷³, and Bayesian meta-analysis of proportions.

The Tufts evidence-review team reported that one of the reviewed studies was of good quality, twenty-four were of fair quality, and seventeen were of poor quality. The findings of only two studies, in which patients with a history of thromboembolism or bleeding were not excluded, had a wide application. The outcomes, with regard to pulmonary embolism, of twenty-two studies had moderate application. The outcomes of eighteen studies had only narrow application because of a short follow-up. The reviewed studies were heterogeneous in terms of follow-up time, doses, intensity and timing of

Knee

Intervention

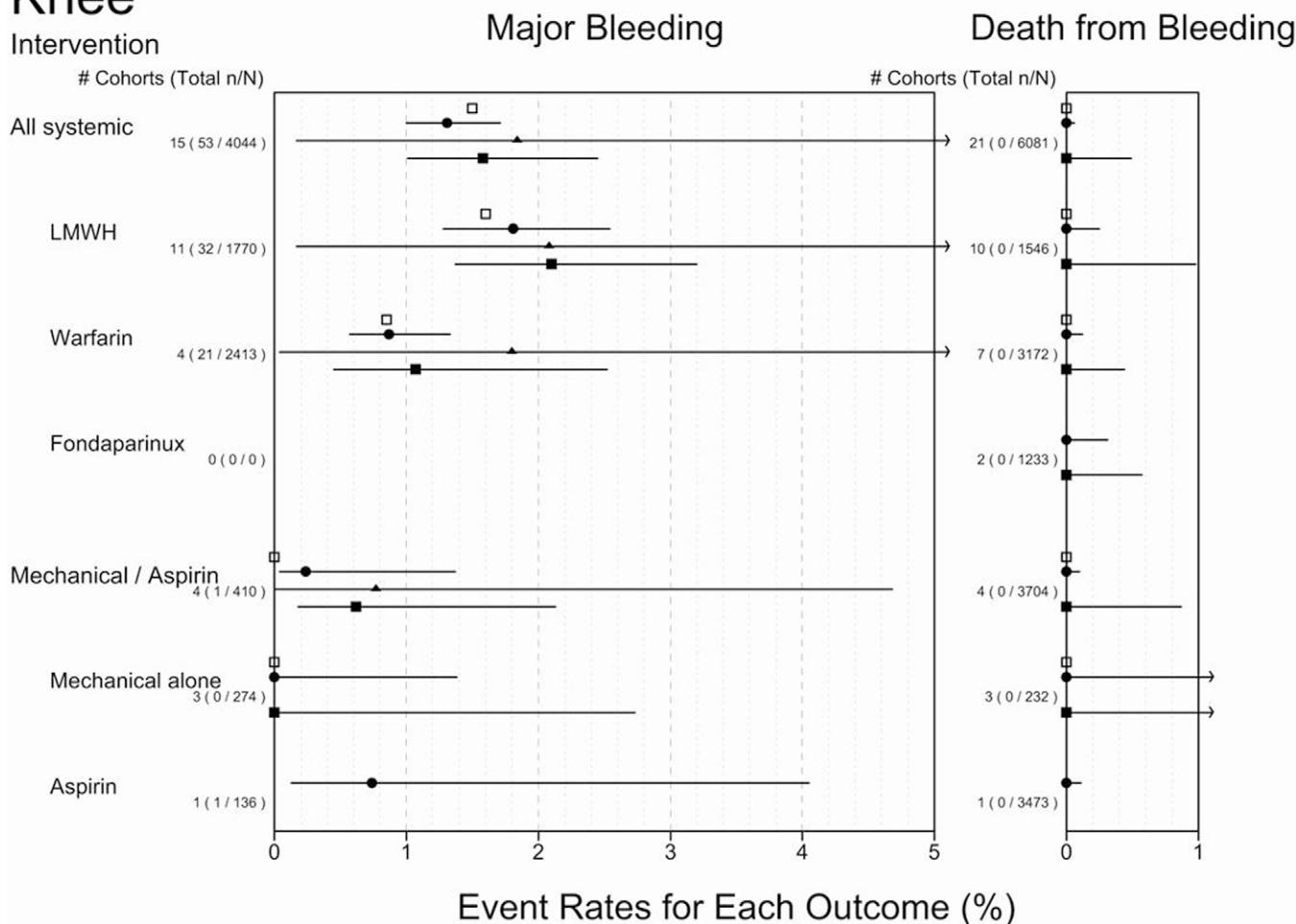


Fig. 6

Pooled event rates of major bleeding and death from bleeding after total knee arthroplasty in the reviewed studies. LMWH = low-molecular-weight heparin.

interventions, cotreatments, eligibility criteria, and surgical and anesthetic techniques. In addition, the authors of only three studies reported no support from commercial funding.

The results of the literature review are presented as separate forest plots for hip and knee arthroplasty. These include plots for pulmonary embolism after total hip arthroplasty (Fig. 1); pulmonary embolism, fatal pulmonary embolism, and all deaths after total hip arthroplasty (Fig. 2); major bleeding and death from bleeding after total hip arthroplasty (Fig. 3); pulmonary embolism after total knee arthroplasty (Fig. 4); pulmonary embolism, fatal pulmonary embolism, and all deaths after total knee arthroplasty (Fig. 5); and major bleeding and death from

bleeding after total knee arthroplasty (Fig. 6). Several conclusions were derived from the literature review. The rate of asymptomatic pulmonary embolism was approximately one per 300 arthroplasties with prophylactic treatment. The rate of fatal pulmonary embolism was approximately one per 1700 arthroplasties, and there was no difference among prophylactic treatments. The rate of death from bleeding was approximately one per 3000 arthroplasties. Major bleeding complications were more common in patients treated with systemic pharmacologic prophylaxis (random effects model summary estimate, 1.8%; 95% confidence interval, 1.4% to 2.5%) than in those treated with mechanical prophylaxis and aspirin (random effects model

summary estimate, 0.14%; 95% confidence interval, 0.03% to 0.8%). There were numerous limitations of the literature review and the analysis process. There was a large amount of clinical heterogeneity. Pulmonary embolism was not the primary outcome in any study, and the reporting of pulmonary embolism was vague in many studies. As the sample sizes in most of the studies were inadequate for estimation of event rates, pooled averages were used to estimate the event rates. The working group restricted the literature review to studies in which the arthroplasties had been performed since 1996, so many older studies were excluded from analysis. The consensus among the working group was that surgical techniques and postoperative care have changed greatly since

TABLE V General Recommendations Derived with the Consensus Process

Recommendation	Level of Evidence/ Strength of Recommendation*
Assess all patients preoperatively to determine whether risk of pulmonary embolism is standard or high	III/B
Assess all patients preoperatively to determine whether risk of bleeding complications is standard or high	III/C
Consider use of vena cava filter in patients who have contraindications to anticoagulation	V/C
Consider intraoperative and/or immediate postoperative mechanical compression	III/B
Consider regional anesthesia for the procedure (in consultation with anesthesiologist)	IV/C
Consider continued use of mechanical prophylaxis postoperatively	IV/C
Rapid patient mobilization	V/C
Routine screening for thromboembolism is not recommended	III/B
Educate patient about symptoms of thromboembolism after discharge	V/B

*See Tables III and IV.

postoperative medication, based on the literature review and analysis, stratify the choices on the basis of the risks of pulmonary embolism and major bleeding complications (Table VI).

Overview

This critical literature review and analysis demonstrated no differences, in terms of the total pulmonary embolism rate, rate of fatal pulmonary embolism, total death rate, or rate of death from bleeding, among the different thromboembolism prophylaxis interventions. The prevalence of major bleeding associated with the combined intervention of mechanical prophylaxis and aspirin was very low compared with the prevalences associated with the other interventions. Orthopaedic surgeons should carefully evaluate and document preoperatively each patient's specific risks for pulmonary embolism and major bleeding. Patients with previous symptomatic pulmonary embolism, heritable thrombophilia, or a hypercoagulable state, and those who will not be capable of rapid mobilization, are usually mentioned as examples of those who are at elevated risk for pulmonary embolism. When performing a total hip or knee arthroplasty procedure that could entail excessive bleeding (e.g., a revision arthroplasty or a complicated primary arthroplasty) or treating a patient who is at higher risk for bleeding in other locations (e.g., one with a history of a bleeding disorder, recent gastrointestinal

1996. There were very wide confidence intervals for all of the interventions.

The AAOS guideline recommendations derived from the working-group consensus process included preoperative evaluation of all patients by the orthopaedic surgeon to assess the risk of pulmonary embolism and the risk of bleeding complications. It was

also recommended that the patient and surgeon consider, in consultation with the anesthesiologist, the use of regional anesthesia^{41,45,74-77} and that the surgeon consider using mechanical prophylaxis intraoperatively or immediately postoperatively with continuation until discharge (Table V)^{14,30,41,64,74,78}. The AAOS guideline recommendations regarding

TABLE VI Recommendations for Medication Derived from Literature Review and Analysis Process

Risk	Agents*	Level of Evidence/ Strength of Recommendation†
Standard risk of pulmonary embolism and major bleeding	Aspirin, low-molecular-weight heparin, pentasaccharide, warfarin (international normalized ratio ≤ 2)	III/B (C for dosing and timing)
Elevated risk of pulmonary embolism; standard risk of bleeding	Low-molecular-weight heparin, pentasaccharide, warfarin (international normalized ratio ≤ 2)	III/B (C for dosing and timing)
Standard risk of pulmonary embolism; elevated risk of bleeding	Aspirin, warfarin (international normalized ratio ≤ 2), no prophylaxis	III/C
Elevated risk of pulmonary embolism and bleeding	Aspirin, warfarin (international normalized ratio ≤ 2), no prophylaxis	III/C

*The agents in each row are given in alphabetical order.†See Tables III and IV.

bleeding, or recent hemorrhagic stroke), the orthopaedic surgeon should carefully consider the overall risk-benefit ratio before proceeding with any specific pharmacologic intervention. The AAOS working group encourages the future performance of prospective, randomized multicenter studies comparing the various interventions that we mentioned, as well as new agents, with use of symptomatic pulmonary embolism and major bleeding that may affect the patient's outcome as clinical end points.

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Surgery, for her assistance in the preparation of this manuscript.

Steven B. Haas, MD, MPH
Geoffrey Westrich, MD
The Hospital for Special Surgery,
535 East 70th Street, New York,
NY 10021

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

Paul F. Lachiewicz, MD
University of North Carolina,
3151 Bioinformatics Building,
Campus Box 7055,
130 Mason Farm Road,
Chapel Hill, NC 27514

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