

American Academy of Orthopaedic Surgeons
Clinical Guideline
on
Prevention of Pulmonary Embolism in Patients
Undergoing Total Hip or Knee Arthroplasty

Adopted by the American Academy of Orthopaedic Surgeons
Board of Directors
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DISCLAIMER

This clinical guideline was developed by an AAOS physician volunteer Work Group and is provided as an educational tool based on an assessment of the current scientific and clinical information and accepted approaches to treatment. It is not intended to be a fixed protocol as some patients may require more or less treatment. Patient care and treatment should always be based on a clinician's independent medical judgment given the individual clinical circumstances.

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Summary of Recommendations

The following recommendations are based on a systematic review of the literature and are evidence-base

Recommendation 3.3 Chemoprophylaxis of patients undergoing hip or knee replacement

Recommendation 3.3.1 Patients at standard risk of both PE and major bleeding should be considered for one of the chemoprophylactic agents evaluated in this guideline, including-in alphabetical order: **Aspirin, LMWH, synthetic pentasaccharides, and warfarin.** (Level III, Grade B (choice of prophylactic agent), Grade C (dosage and timing))

Note: The grade of recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature defining a clearly superior regime.

Recommendation 3.3.2 Patients at elevated (above standard) risk of PE and at standard risk of major bleeding should be considered for one of the chemoprophylactic agents evaluated in this guideline, including-in alphabetical order: **LMWH, synthetic pentasaccharides, and warfarin.** (Level III, Grade B (choice of prophylactic agent), Grade C (dosage and timing)).

Note: The grade of recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature on risk stratification of patient populations.

Recommendation 3.3.3 Patients at standard risk of PE and at elevated (above standard) risk of major bleeding should be considered for one of the chemoprophylactic agents evaluated in this guideline, including-in alphabetical order: **Aspirin, Warfarin, or none.** (Level III, Grade C)

Note: The grade of recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature on risk stratification of patient populations.

Recommendation 3.3.4 Patients at elevated (above standard) risk of both PE and major bleeding should be considered for one of the chemoprophylactic agents evaluated in this guideline, including-in alphabetical order: **Aspirin, Warfarin, or none.** (Level III, Grade C)

Note: The grade of recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature on risk stratification of patient populations. No studies currently include patients at elevated risk of major bleeding and/or PE in study groups.

The following additional recommendations are based on the results of the objective AAOS Consensus Process in which the work group members participated.

Recommendation 1.1 All patients should be assessed pre-operatively for elevated risk (greater than standard risk) of pulmonary embolism. (Level III, Grade B)

Recommendation 1.2 All patients should be assessed pre-operatively for elevated risk (greater than standard risk) of major bleeding. (Level III, Grade C)

Note: Grade of Recommendation reduced because of lack of consistent evidence on risk stratification of patient populations.

Recommendation 1.3 Patients with known contraindications to anticoagulation should be considered for vena cava filter replacement. (Level V, Grade C)

Recommendation 2.1 Patients should be considered for intra-operative and/or immediate postoperative mechanical prophylaxis. (Level III, Grade B)

Recommendation 2.2 In consultation with the anesthesiologist, patients should be considered for regional anesthesia. (Level IV, Grade C)

Recommendation 3.1 Post-operatively, patients should be considered for continued mechanical prophylaxis until discharge to home. (Level IV, Grade C)

Recommendation 3.2 Post-operatively, patients should be mobilized as soon as feasible to the full extent of medical safety and comfort. (Level V, Grade C)

Recommendation 3.4 Routine screening for DVT or PE post-operatively in asymptomatic patients is not recommended. (Level III, Grade B)

Recommendation 4.1 Patients should be encouraged to progressively increase mobility after discharge to home. (Level V, Grade C)

Recommendation 4.2 Patients should be educated about the common symptoms of deep venous thrombosis and pulmonary embolism. (Level V, Grade B)

Note: The level of evidence is level V, expert opinion, but the strength of recommendation is B rather than C because patient education is consistent with the minimal expected standard of care for today's medical practices.

Of the fourteen recommendations listed above, only recommendations 3.3.1, 3.3.2, 3.3.3 and 3.3.4 are based on the systematic review of the literature conducted between August 2006 and March 2007 by The Center for Clinical Evidence Synthesis at Tufts New England Medical Center. The other recommendations contained in this guideline are based on consensus development methods only.

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Overview

Goals and Rationale

This clinical guideline has been created to improve patient care by outlining the appropriate information gathering and decision making processes involved in managing the prevention of symptomatic pulmonary embolism (PE) in patients undergoing total hip or knee arthroplasty. This guideline has been created as an educational tool to guide orthopaedic surgeons and other clinicians who provide peri-operative care through a series of treatment decisions in an effort to improve the quality and efficiency of care.

This guideline should not be construed as including all proper methods of care or excluding methods of care reasonably directed to obtaining favorable results. The ultimate judgment regarding any specific procedure or treatment must be made in light of each patient's unique presentation and the needs and resources particular to the locality or institution.

Scope and Organization

Intended Users

The intended users of this guideline are orthopaedic surgeons who perform total hip or knee replacement and other clinicians who provide peri-operative care to patients who have undergone either of the procedures.

Patient Population

The patient population for whom this guideline has been prepared includes all patients who will undergo total hip or knee replacement for arthropathies that are not related to acute traumatic injury. It was the intention of the Work Group that the guideline be applicable to as widely diverse a population as possible. The literature that was extracted has variable applicability because of the eligibility criteria that were used in assembling the study populations. In many studies high risk patients are excluded because of their potential for confounding the analysis of efficacy. Therefore the task of formulating a risk stratification strategy fell largely to the level of expert opinion of the convened Work Group.

Burden of Disease

Incidence, Etiology, and Risk Factors

Orthopaedic surgery has been identified as a uniformly high-risk event for venous thromboembolism. The most recent ACCP guideline states, “Without prophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10 to 40% among medical or general surgical patients and 40 to 60% following major orthopedic surgery”(1). Total hip and knee replacement are examples of commonly performed orthopaedic procedures in which a significant incidence of deep venous thrombosis (DVT) has been recorded. Because DVT has been widely accepted as a proxy measure for the risk of PE it has naturally been assumed that any improvements in DVT prevention would be proportionately accompanied by added protection against PE.(2) Although current appropriately powered clinical trials have demonstrated statistically significant differences in DVT rates among selected agents, as this guideline will demonstrate by way of a systematic literature review, the concurrently reported PE rates for all prophylactic modalities are not statistically different (see Appendix III). One explanation for this may be that studies with DVT as an end point are underpowered to demonstrate real differences in PE rates that may exist. Liereported a 60-day PE-related mortality rate of 0.37% in 67,548 total hip replacement patients from the Norwegian Arthroplasty Registry (1987-1989), concluded that given the low PE rates, it would require the randomization of 30,000 patients to demonstrate a 50% reduction in mortality between two competing agents (3). Needless to stay, the cost of such a study would be prohibitive. Another explanation may be that other risk factors and pathophysiological processes may control the development of PE, apart from the sheer presence of a DVT. In any case, the presumed direct pathophysiological link between DVT and PE has not been proven by clinical observation, at least in the case of total hip and knee replacement. What then are the appropriate criteria for prescribing the safest and most effective thromboprophylactic regimens that will bring value to patients and to our financially stressed health care system?

PE following total hip or knee replacement is rare. In total hip replacement, the 90-day rate of non-fatal PE has been reported by Katz to be 0.93% in 58,521 Medicare patients who underwent primary total hip replacement with or without prophylaxis during 1995-1996 (4). Death following PE in total hip replacement is very rare, with a 90-day death rate reported by Howie in 44,785 patients in the Scottish Morbidity Record from 1992-2001 being 0.22%. Non-fatal and fatal PE following total knee replacement are even less common (5). SooHoo surveyed a California discharge database containing 222,684 patients who had undergone total knee replacement from 1991-2001. The 90-day non-fatal PE rate was reported as 0.41% (6). Howie reported a 0.15% rate of fatal PE in 27,000 total knee replacement patients in the Scottish Morbidity Record (5). In addition it has been shown that despite significant changes in venous thromboembolism prophylaxis and surgical techniques over the past 10 to 15 years, the rates of PE and PE-related mortality have been remarkably stable (3;5).

The occurrence of major bleeding complications following an elective total hip or knee replacement is potentially detrimental to patient outcomes, for example, resulting in chronic joint stiffness and infection. This systematic review found major bleeding episodes following total hip and knee replacement occurring with a frequency of 1% to 3%. Bleeding is a common cause of unplanned return to the operating room for evacuation of a hematoma, or, in the worst case,

removal of the implant because of infection. There is no contemporary study that adequately describes the incidence of major surgical bleeding in patients who have not received prophylaxis, but all reports of mechanical antithrombotic devices are noteworthy for an incidence of major bleeding of less than 1%. The literature is non-standardized with regard to identification and confirmation of major post-operative bleeding. There is significant variability in operationally defining a major bleed and the appropriate treatment options. The result has been a substantial likelihood of underestimating the bleeding risks. Moreover, studies that do report on bleeding-related complications do not have long-term follow-up that would link bleeding to the serious development of deep infection. Recent studies have demonstrated an important relationship between early post-operative wound hematoma and drainage and prosthetic joint infections (7;8). With the defined risk of surgical bleeding that may lead to more serious complications and compromised outcomes, and a historically low rate of life-threatening PE, the question may legitimately be asked, “Are the resources currently available to prevent serious thromboembolic complications of total hip and knee replacement being appropriately and cost-effectively utilized?”

Relevant Issues

The selection of an appropriate prophylactic regimen against PE in hip and knee replacement should be based on a balance between bleeding-related risks and medical adverse effects, on one hand, and the expected effectiveness in preventing symptomatic PEs, on the other. Using a regimen that has been shown to reduce the DVT rate does not necessarily imply that the risk-benefit ratio has been optimized. Therefore the optimal prophylactic regimen for a particular patient should reflect a clinical judgment regarding the relative risks of both major bleeding and symptomatic PE. An evidence-based stratification of the prophylactic regimens in terms of their risk of major bleeding would theoretically facilitate a more rational selection of prophylaxis based upon a more accurate risk-benefit profile. Eventually it may be possible to “customize” prophylaxis by better understanding of PE in various defined populations. The stratification of risk is currently difficult in light of the fact that all orthopaedic procedures are considered high risk for developing DVT. The more important task of risk stratification for PE and bleeding in total hip or knee replacement patients would require far more patients studied rigorously over a longer period of time than the current literature provides. Typically, randomized trials in this area exclude perceived “high risk” patients, who, by definition would need to be included in a study that is designed to scientifically prove the validity of a risk stratification methodology. Such studies should be conducted in a “real world” setting to achieve a more robust data set. In the absence of inclusive data it is very difficult to devise a sound clinical decision support process based purely on the results of randomized clinical trials. Alternatively, total joint registries offer the benefit of generalizability, realized by a more efficient and timely amalgamation of data taken from multiple surgeons and institutions. These data sets also deliver long-term follow-up that may link important risk factors with surgical outcomes.

Methods

Process Overview

A Work Group, with the assistance of an Evidence Review Team (ERT) from the Center for Clinical Evidence Synthesis at Tufts-New England Medical Center, completed a systematic

review of the relevant literature. Details of the systematic review process are provided below and in Appendix I; the results of the systematic review are presented in Appendix III. The Work Group included orthopaedic surgeons with clinical research experience. The members of the ERT were physician/clinical research methodologists with expertise in systematic review and guideline development. During the process of developing this document, the Work Group participated in numerous conference calls and a face-to-face meeting. Information from the systematic review was supplemented by additional literature suggested by the Work Group. The overall aim was to create guidelines and clinical performance measures through an evidence-based approach for the management of patients undergoing total hip or knee arthroplasty with the express purpose of preventing symptomatic PE. The primary key questions were addressed by a systematic review of the relevant literature. When available, high or moderately high quality evidence relevant to the primary key questions formed the basis for the development of evidence-based clinical practice guidelines. When only low quality or no evidence were available, guidelines were developed based on the consensus of expert opinion and the best available evidence.

The creation of the guidelines included many concurrent steps.

- Form the Work Group responsible for development of the guidelines
- Confer to discuss guideline development process, methods, and results
- Develop and refine primary key questions
- Define specific populations, interventions or predictors, comparator, and outcomes of interest, and other study eligibility criteria
- Create draft guideline statements and rationales
- Create and standardize quality and applicability assessment methods
- Create data extraction forms
- Develop literature search strategies and run searches
- Screen abstracts and retrieve full articles based on the predetermined eligibility criteria; screen and incorporate (if appropriate) additional literature suggested by the Work Group
- Extract data and perform critical appraisal of the literature
- Grade quality and applicability of each eligible study
- Tabulate data from articles into summary tables and perform analyses
- Perform meta-analyses (quantitative synthesis of data) when appropriate
- Grade the levels of evidence for each primary key question
- Write guideline recommendations and supporting rationale statements
- Grade the strength of the recommendations
- Write clinical performance measures

The Work Group participated in a series of conference calls for training in the guideline development process, topic discussion, and consensus development. During a meeting, the level of evidence for each recommendation was assigned and the strength of each of the recommendations was graded.

Creation of Panel

The AAOS Guidelines Oversight Committee and the Evidence Based Practice Committee Chairpersons appointed the Chair of the Work Group and members with clinical domain expertise in hip and knee replacement surgical procedures, who were then, assisted by the

physician/clinical research methodologists with expertise in guideline creation from the ERT, contracted by the AAOS. The Work Group, with assistance from the ERT, refined and formulated the final four systematic review research questions using a well-established system (9).

The ERT developed specific screening criteria and literature search strategies, performed the literature search, screened abstracts and full-text articles, created forms and extracted relevant data from articles, tabulated and confirmed results, conducted statistical analyses, assisted with grading the strength of the evidence, and offered suggestions for guideline development. Throughout the process, they led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, grading the quality of evidence and the strength of guideline recommendations, and the consensus development process for guideline creation. The ERT were the principal reviewers of the literature, and instructed and coordinated Work Group members in all steps of systematic review, critical literature appraisal, and guideline development. The Work Group reviewed in detail the results and conclusions of the ERT, and took the primary roles of writing the guidelines and rationale statements and grading the levels of evidence and the strength of the recommendations.

Consensus Development

Voting on guideline recommendations and performance measures was conducted using a modification of the nominal group technique defined by AAOS, in which each work group member ranked a recommendation or performance measure on a scale ranging from 1 (“extremely appropriate”) to 9 (“extremely inappropriate”). Consensus was obtained if 8 of the 9 Work Group members ranked the recommendation or measure as 7, 8, or 9. When 2 or more Work Group members did not rank a measure in this range, three rounds of discussion and voting were held to resolve disagreements. If disagreements were not resolved after these rounds, no recommendation or performance measure was adopted.

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Key Questions

The central guideline recommendations are based on the answers to four Key Questions. These questions were specified prior to conducting the literature searches and frame the scope of the guideline. Questions were constructed to specify the patients, interventions, comparisons, and outcomes of interest. The Key Questions addressed by these guidelines were:

- 1A. In patients having knee replacement surgery, what is the effect of prophylactic therapy (e.g., coumadin, low molecular weight heparin, aspirin, mechanical devices) compared with either no prophylaxis or placebo in preventing important clinical symptoms or events (e.g., shortness-of-breath, chest pain, arrhythmia, fatality, rehospitalization) secondary to pulmonary embolism?
- 1B. In patients having hip replacement surgery, what is the effect of prophylactic therapy (e.g., coumadin, low molecular weight heparin, aspirin, mechanical devices) compared with either no prophylaxis or placebo in preventing important clinical symptoms or events (e.g., shortness-of-breath, chest pain, arrhythmia, fatality, rehospitalization) secondary to pulmonary embolism?
- 2A. In studies of knee replacement surgery, how do these different prophylactic therapies compare among each other in preventing important clinical symptoms or events secondary to pulmonary embolism?
- 2B. In studies of hip replacement surgery, how do these different prophylactic therapies compare among each other in preventing important clinical symptoms or events secondary to pulmonary embolism?
3. What are risks of clinically important adverse events associated with these prophylactic therapies in patients having knee or hip replacement surgery?
- 4A. What is the risk of important clinical symptoms or events secondary to pulmonary embolism in patients who had knee replacement surgery, in whom no prophylactic therapies for the prevention of pulmonary embolism were prescribed?
- 4B. What is the risk of important clinical symptoms or events secondary to pulmonary embolism in patients who had hip replacement surgery, in whom no prophylactic therapies for the prevention of pulmonary embolism were prescribed?

Systematic Review

A full description of the methods used and results of the systematic review and meta-analyses can be found at www.aaos.org/research/guidelines/guide.asp. Briefly, a formal process was used to determine study eligibility criteria and to identify studies. For Key Questions 1 to 3, the ERT included prospective studies that evaluated at least 100 patients receiving either aspirin, fondaparinux, low molecular weight heparin (LMWH), mechanical devices, warfarin, or any combination of these prophylaxis regimens after either hip or knee arthroplasty performed after 1995. It was the opinion of the Work Group that surgical techniques and post-operative management had changed substantially since the care provided prior to 1996. The consensus was reached to exclude these patients from the review.

In addition, randomized trials comparing at least two of the interventions with at least 10 patients in each arm were included. Outcomes of interest principally included symptomatic, clinically

documented PE, PE-related death, all-cause death, major bleeding, bleeding-related death, and rehospitalization due to venous thromboembolism or bleeding. Eligible studies were summarized by the ERT for the Work Group, which reviewed summary tables and the primary articles as needed. Event rates were combined using a variety of statistical techniques to ensure the robustness of the results due to the behaviors of the statistical methods at very low event rates. For Key Question 4, eligible studies included prospective or retrospective studies with at least 1000 patients who received either total hip or knee replacement after 1995, but did not receive any prophylaxis. However, no such studies were found. Studies were rated for methodological quality (good, fair, or poor) applicability to the population of interest (wide, moderate, narrow).

Summarizing Reviews and Selected Original Articles

Work Group members summarized narrative reviews and citing original articles for topics that were outside the key questions addressed by the systematic review.

Rating the Quality of Evidence

The quality of evidence was rated using an evidence hierarchy for each of four different study types; therapeutic, prognostic, diagnostic, and economic or decision modeling. These hierarchies are shown in Appendix II. These hierarchies were predefined by AAOS and appear on the AAOS website at www2.aaos.org/aaos/archives/bulletin/feb03/fline1.htm.

Grading the Recommendations

Each guideline recommendation was graded using the following system:

- A: Good evidence (Level I Studies with consistent finding) for recommending intervention.
- B: Fair evidence (Level II or III Studies with consistent findings) for recommending intervention.
- C: Poor quality evidence (Level IV or V) for recommending intervention.

Revision Plans

Because of the high level of interest in this topic and the likelihood of rapidly emerging evidence, opinion, and practice, the guidelines will need to be revisited and revised in accordance with new, and we hope, higher quality evidence. It is anticipated that the guidelines will be revised in 2010.

Guideline Recommendations

Recommendation 1. Pre-operative Care

1.1 All patients should be assessed pre-operatively for elevated risk (greater than standard risk) of pulmonary embolism. The following patients are examples of those considered to be at elevated risk:

- Hypercoagulable states
- Previous documented pulmonary embolism

Level of Evidence: III

Grade of Recommendation: B

1.2 All patients should be assessed pre-operatively for elevated risk (greater than standard risk) of major bleeding. Patients with the following conditions are examples of those considered to be at elevated risk:

- History of a bleeding disorder
- History of recent gastrointestinal bleed
- History of recent hemorrhagic stroke

Level of Evidence: III

Grade of Recommendation: C

Note: This Grade of Recommendation was reduced from B to C because of the lack of consistent evidence in the literature on risk stratification of patient populations.

1.3 Patients with known contraindications to anticoagulation should be considered for vena cava filter placement.

Level of Evidence: V

Grade of Recommendation: C

Rationales

Recommendation 1.1

The risk of PE, however, differs among different patients; however, there is currently no satisfactory evidence-based risk stratification system. There have been studies suggesting that the risk of PE is elevated in patients with previous history of cancer, thromboembolism, hypercoagulable states such as polycythemia, spinal cord injury patients, and multi-trauma patients(10-12). It is also plausible that some patients may have genetic predisposition for development of PE(13;14). Currently no specific laboratory test can reliably identify patients at elevated risk of PE. Therefore, careful history taking and physical examination in combination with clinical judgment, which integrates knowledge of specific risk factors with the patient's clinical status is the cornerstone of PE risk management for patients undergoing hip or knee replacement.

The identification of patients at elevated risk for PE is important in the selection process of appropriate thromboprophylactic regimens (see Recommendation 3.3).

Recommendation 1.2

The selection of a thromboprophylactic regimen should aim for a balance between efficacy and safety. All chemoprophylaxis agents, by virtue of their action, are associated with bleeding. Some agents may result in a higher incidence of bleeding following total joint arthroplasty (15); although the differences in bleeding rates with the currently used agents are unclear (see Guideline 3.3) (16-19). Patients on aspirin or mechanical prophylaxis alone, on the other hand, may have lower bleeding rates (15;20-22). Not only might the bleeding potential of different prophylactic agents vary, there may also be varying bleeding tendencies among individuals that may affect the bleeding risk with surgery(23). The intention of this recommendation is to identify patients who may be at elevated risk of major bleeding after hip or knee replacement. The type of prophylactic agent, the duration of prophylaxis, and the intensity of anticoagulation needs to be modulated based on the perceived bleeding risk in an individual patient. Some factors that may place a patient at an elevated risk of bleeding include a previous history of uncontrolled bleeding, and a known coagulation factor deficiency, a recent history of gastrointestinal bleeding, and recent hemorrhagic stroke. This recommendation highlights the central importance of careful history taking, and physical examination for the purpose of risk stratification for bleeding. Although routine serological tests to screen patients for potential bleeding problems are not indicated, they may be useful in patients where there is a high level of suspicion of a predisposition for bleeding.

Recommendation 1.3

A vena cava filter may reduce the risk of PE in a non-anticoagulated patient(24). The assumed ability of a filter to stop emboli originating in the lower extremities underlies the expected clinical usefulness of filters in selected total hip and knee patients. The very low level of evidence and strength of recommendation reflect the poor evidence base behind this decision-making process. The need for a filter is most commonly encountered when there is elevated pre-operative risk of PE and a known contraindication for chemoprophylaxis, or if chemoprophylaxis becomes contraindicated in an elevated risk patient during the postoperative course. Similarly, if a patient with a known contraindication to chemoprophylaxis changes from standard to elevated PE risk in the postoperative period, a vena cava filter may be considered. Finally, in patients thought to be at elevated risk of major bleeding who develop symptomatic post-operative PE, a filter should be considered.

Recommendation 2: Intra-operative Care

2.1 Patients should be considered for intra-operative and/or immediate postoperative mechanical prophylaxis.

Level of Evidence: III

Grade of Recommendation: B

2.2 In consultation with the anesthesiologist, patients should be considered for regional anesthesia.

Level of Evidence: IV

Grade of Recommendation: C

Rationales

Recommendation 2.1

Thrombogenesis activation begins during total hip arthroplasty through a variety of mechanisms. These include venous stasis due to anesthesia, immobilization, intimal injury (due to kinking of the femoral vein with dislocation of the hip and femoral canal preparation) and activation of the clotting cascade (by a variety of mechanisms) (25;26). Mechanical venous compression ameliorates some of the factors involved in thrombogenesis and therefore should be considered intraoperatively, if practical, and there are no contraindications to use of the device (27;28). For total hip arthroplasty, mechanical prophylaxis can easily be used on the nonoperative limb, and there are sterile thigh-calf and calf-only pneumatic devices that can be used on the operative limb (27-29). In observational studies, the use of these devices (usually in combination with regional anesthesia and aspirin chemoprophylaxis) have been shown to result in a low rate of symptomatic PE (25;28). Alternatively, these pneumatic devices may be placed on the lower extremities in the recovery room after the procedure is completed (30). There are a variety of mechanical devices available, including thigh-calf, calf-only, and foot pumps (31). There are no prospective, randomized studies comparing the efficacy of these devices in the prevention of symptomatic PE.

The activation of thrombogenesis in total knee arthroplasty patients has been less well studied.. Intraoperative mechanical compression can be used on the nonoperative limb, but there is no effective sterile device for use on the operative limb, especially if a tourniquet is used. Most studies begin use of a mechanical device on the operative limb postoperatively in the recovery room (32-35).

Recommendation 2.2

Regional anesthesia (spinal, epidural or hypotensive epidural with cardiac monitoring) has been recommended over general endotracheal anesthesia for total hip and total knee arthroplasty patients (25;26;36;37). Regional anesthesia has been shown to decrease venous flow less and result in fewer pulmonary complications. However, there is only circumstantial evidence that regional anesthesia, as part of a multimodal prophylaxis protocol, reduces the prevalence of symptomatic and fatal PE (27;28;36).

The choice of anesthetic technique for these patients is based on multiple factors, including thromboembolism prophylaxis. There should be close consultation between the surgeon and the anesthesiologist for the anesthetic technique.

Recommendation 3: Post-operative/Inpatient Care

3.1 Post-operatively, patients should be considered for continued mechanical prophylaxis until discharge to home.

Level of Evidence: IV

Grade of Recommendation: C

3.2 Post-operatively, patients should be mobilized as soon as feasible to the full extent of medical safety and comfort.

Level of Evidence: V

Grade of Recommendation: C

3.3 Chemoprophylaxis of patients undergoing hip or knee replacement

3.3.1 **Patients at standard risk of both PE and major bleeding** should be considered for one of the chemoprophylactic agents evaluated in this guideline, including (*in alphabetical order*):

a. Aspirin, 325 mg 2x/day (reduce to 81 mg 1x/day if gastrointestinal symptoms develop), starting the day of surgery, for 6 weeks.

b. LMWH, dose per package insert, starting 12-24 hours post-operatively (or after an indwelling epidural catheter has been removed), for 7-12 days (N.B., the LMWHs have not been sufficiently evaluated for longer periods to allow recommendation beyond this period).

c. Synthetic pentasaccharides, dose per package insert, starting 12-24 hours post-operatively (or after an indwelling epidural catheter has been removed), for 7-12 days (N.B., the synthetic pentasaccharides have not been sufficiently evaluated for longer periods to allow recommendation beyond this period).

d. Warfarin, with an INR goal of ≤ 2.0 , starting either the night before or the night after surgery, for 2-6 weeks.

Level of Evidence: III

Grade of Recommendation: B (choice of prophylactic agent), C (dosage and timing)

Note: Note: The Grade of Recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature defining a clearly superior regime.

3.3.2 **Patients at elevated (above standard) risk of PE and at standard risk of major bleeding** should be considered for one of the following chemoprophylactic agents (*in alphabetical order*):

a. LMWH, dose per package insert, starting 12-24 hours post-operatively (or after an indwelling epidural catheter has been removed), for 7-12 days (N.B., the LMWHs have not been sufficiently evaluated for longer periods to allow recommendation beyond this period).

b. Synthetic pentasaccharides, dose per package insert, starting 12-24 hours post-operatively (or after an indwelling epidural catheter has been removed), for 7-12

days (N.B., the synthetic pentasaccharides have not been sufficiently evaluated for longer periods to allow recommendation beyond this period).

c. Warfarin, with an INR goal of ≤ 2.0 , starting either the night before or the night after surgery, for 2-6 weeks.

Level of Evidence: III

Grade of Recommendation: B (choice of prophylactic agent), C (dosage and timing)

Note: Note: The Grade of Recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature on risk stratification of patient populations. No studies currently include patients at elevated risk of major bleeding in study groups.

3.3.3 Patients at standard risk of PE and at elevated (above standard) risk of major bleeding should be considered for one of the following chemoprophylactic agents (*in alphabetical order*):

a. Aspirin, 325 mg 2x/day (reduce to 81 mg 1x/day if gastrointestinal symptoms develop), starting the day of surgery, for 6 weeks.

b. Warfarin, with an INR goal of ≤ 2.0 , starting either the night before or the night after surgery, for 2-6 weeks.

c. None

Level of Evidence: III

Grade of Recommendation: C

Note: This Grade of Recommendation was reduced from B to C because of the lack of consistent evidence in the literature on risk stratification of patient populations. No studies currently include patients at elevated risk of major bleeding in study groups.

3.3.4 Patients at elevated (above standard) risk of both PE and major bleeding should be considered for one of the following chemoprophylactic agents (*in alphabetical order*):

a. Aspirin, 325 mg 2x/day (reduce to 81 mg 1x/day if gastrointestinal symptoms develop), starting the day of surgery, for 6 weeks.

b. Warfarin, with an INR goal of ≤ 2.0 , starting either the night before or the night after surgery, for 2-6 weeks.

c. None

Level of Evidence: III

Grade of Recommendation: C

Note: This Grade of Recommendation was reduced from B to C because of the lack of consistent evidence in the literature on risk stratification of patient populations. No studies currently include patients at elevated risk of major bleeding and PE in study groups.

3.4 Routine screening for DVT or PE post-operatively in asymptomatic patients is not recommended.

Level of Evidence: III

Grade of Recommendation: B

Rationales

Recommendation 3.1

Unless contraindicated, mechanical compression should be utilized for both total hip(25;27-30;34) and knee arthroplasty (32-35). for patients in the recovery room and during the hospital stay . The optimal number of hours daily that mechanical compression should be used is unknown. A team approach involving surgeons, nurses, aides and therapists is required to optimize the amount of time the devices are on the patients' limbs. Many patients are transferred to "same site" rehabilitation floors or hospital services early postoperatively. It is recommended that mechanical prophylaxis continue at these locations if practical.

One prospective randomized study showed that rapid-inflation, asymmetric calf compression was superior to circumferential calf compression in total knee patients (32). For total hip patients, the postoperative devices studied included thigh-calf compression (27;28), rapid-inflation calf (30;34), other calf compression and foot pumps, usually part of a multimodal prophylaxis protocol. Patient preferences and comfort should be taken into account, when feasible. One study reported a high prevalence of patient intolerance and discontinuation of foot pumps postoperatively after total hip arthroplasty (21).

Recommendation 3.2

At a minimum, patients should be taught to actively dorsiflex and plantar flex the ankle and toes. This exercise should be performed in sets of 10 to 20 every half hour when the patient is awake. A plan for pain management that allows control for the patient to be out of bed and subsequently ambulate should be in place prior to surgery. All patients should be out of bed to a sitting chair several times a day for several hours at a time to encourage deep breathing and avoid recumbency. All efforts should be made to have the patient stand and ambulate within the restrictions placed by the operative surgeon. Practices should be in place to ensure that appropriate physical therapy, ambulatory assistance, and support are provided by the first postoperative day. Patients who are treated with epidural catheters postoperatively should also be out of bed to chair as soon as feasible. Standing and ambulation should begin for these patients when they are physically capable of it. During hospitalization, when patients are not ambulating mechanical prophylaxis should remain in place at all times, even when the patient is out of bed.

Recommendation 3.3

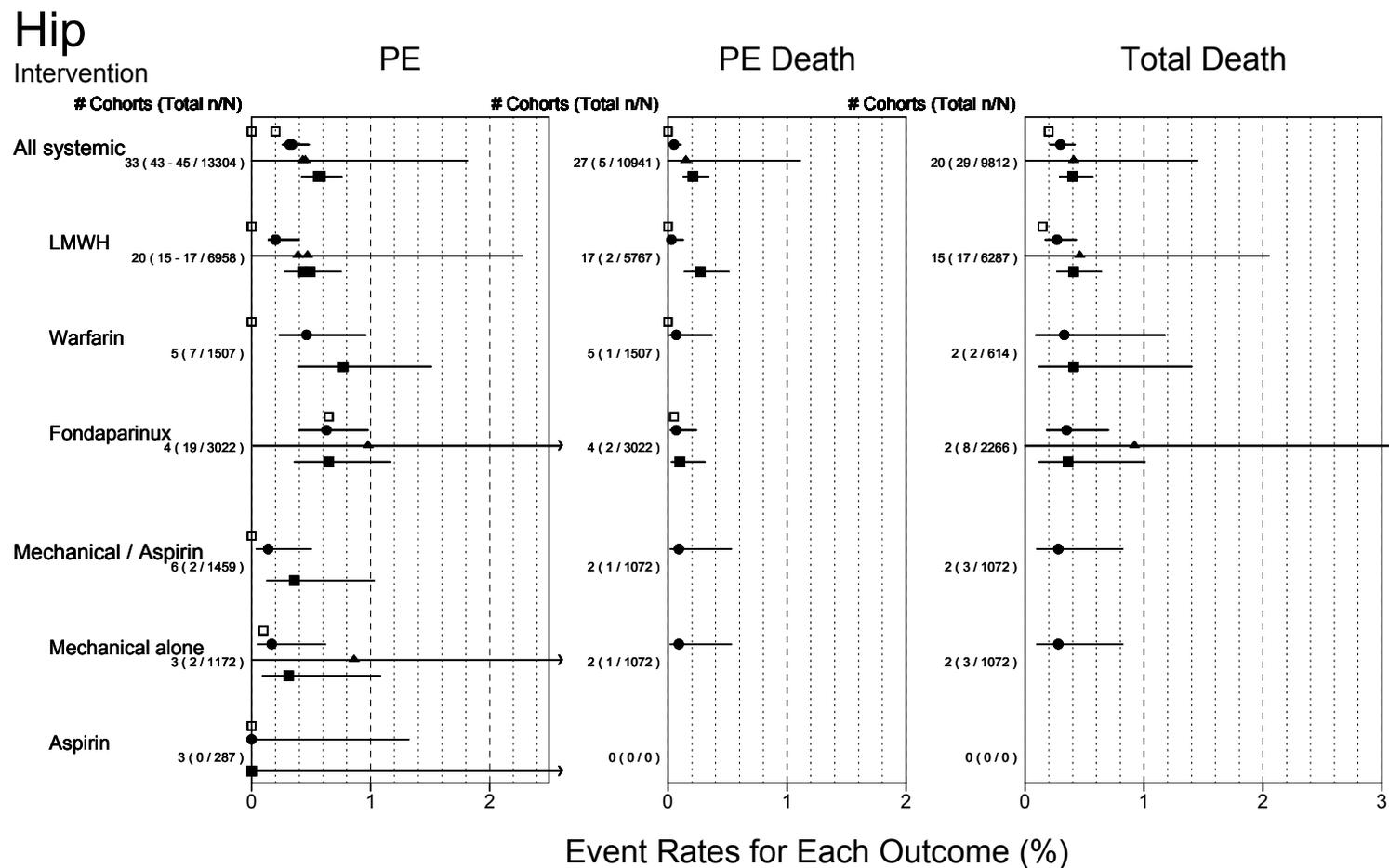
The studies that were systematically reviewed for this guideline primarily addressed Recommendation 3.3. A full description of the results of the systematic review can be found at www.aaos.org/research/guidelines/guide.asp. Briefly, 42 studies met eligibility criteria, of which 23 included patients who had knee arthroplasty and 25 included patients who had hip arthroplasty. Across the studies, outcomes were reported for 11,665 patients who received knee arthroplasty and for 16,304 patients who received hip arthroplasty. None of the studies was deemed to be of Good quality regarding the outcomes of interest; 23 studies were graded Fair

quality; and 19 were graded Poor quality. Two studies had Wide applicability for pulmonary embolism-related outcomes, 21 had Moderate applicability and 18 had Narrow applicability for pulmonary embolism outcomes. The studies were highly heterogeneous regarding specific intervention, dose or intensity of intervention, start time and duration of intervention, follow-up time, co-treatments used, eligibility criteria, inclusion of patients receiving revision or bilateral surgery, surgical and anesthetic techniques.

There were major limitations to the body of evidence for estimating and comparing PE, death, and major bleeding rates. These included large clinical heterogeneity in the interventions, other related procedures and cointerventions, doses, study populations, follow-up times, and in the case of major bleeding, definitions. In addition, none of the studies was designed to investigate PE as a primary outcome. Reporting of PE-related events was frequently incomplete and vague. Commonly, it was not clear how many patients were evaluated for each outcome. The numbers of patients within each study were inadequate to properly estimate the event rates of interest for these guidelines. Because the event rates were frequently either zero or close to zero, combining data across studies could not provide robust estimates of event rates across studies. All evaluations were based on indirect comparisons across different arms (cohorts) of different studies.

The available evidence shows no statistically significant differences among the interventions in rates of pulmonary embolism, pulmonary embolism-related death, total death, major bleeding, bleeding-related death, or rehospitalization (**Figures 1-4**). However, given the rarity of these events, the total number of patients in the studies remains too small to adequately evaluate possible differences among the interventions. This lack of adequate evidence holds true for the broader comparison of systemic interventions (fondaparinux, LMWH, and warfarin) and mechanical devices or aspirin alone. Except to note that major bleeding was very rare among patients receiving aspirin or mechanical devices alone (1 case in 697, or 0.14%, exact 95% CI 0.03-0.8%) compared to those who received systemic interventions (random effects model summary estimate 1.8%, 95% CI 1.4-2.5%). Because of the limitations and the overall relatively small number of patients evaluated (given the rarity of pulmonary embolism after arthroplasty), at best rough estimates of event rates can be surmised from the evaluated evidence.

Figure 1. Summary pulmonary embolism, pulmonary embolism death, and total death rates for patients after hip arthroplasty receiving different prophylaxis regimens.



- = median rate among studies (only determined if ≥ 3 cohorts of patients)
- = simple average (total n/total N) and “exact” estimate of confidence interval of that average
- ▲-- = random effects estimate and confidence interval using Bayesian methodology
- = random effects estimate and confidence interval using logit of proportions methodology

Dotted vertical lines represent 0.2% increments.

Where there are ranges of total n's (events), one or more studies were unclear as to the total number of events (eg, whether PE's were confirmed or not, whether deaths were due to confirmed PE or not). Multiple medians or averages represent the range of estimates.

All systemic = LMWH + warfarin + fondaparinux studies combined (in addition to studies that combined these interventions).

LMWH = LMWH alone and combination LMWH & mechanical; Warfarin = warfarin alone and combination warfarin & mechanical.

Mechanical / Aspirin = Either mechanical alone, aspirin alone, or mechanical and aspirin

Aspirin= aspirin and combination aspirin and mechanical

These approaches do not adequately account for the heterogeneity of interventions, follow-up duration, quality, applicability, etc.

These analyses do not include studies that excluded events that occurred in-hospital.

Figure 2. Summary pulmonary embolism, pulmonary embolism death, and total death rates for patients after knee arthroplasty receiving different prophylaxis regimens.

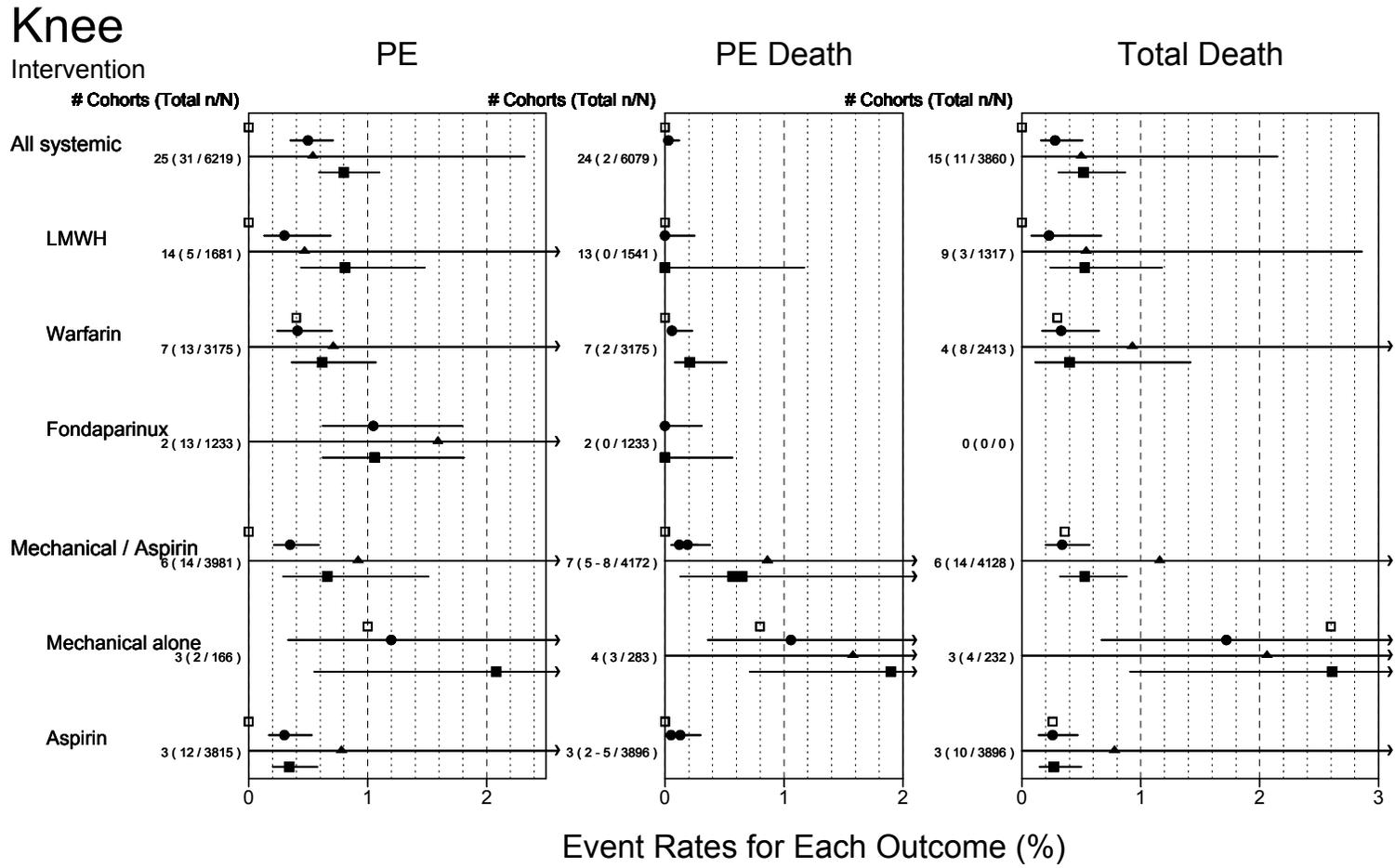


Figure 3. Major bleeding and death from bleeding rates for patients after hip arthroplasty receiving different prophylaxis regimens.

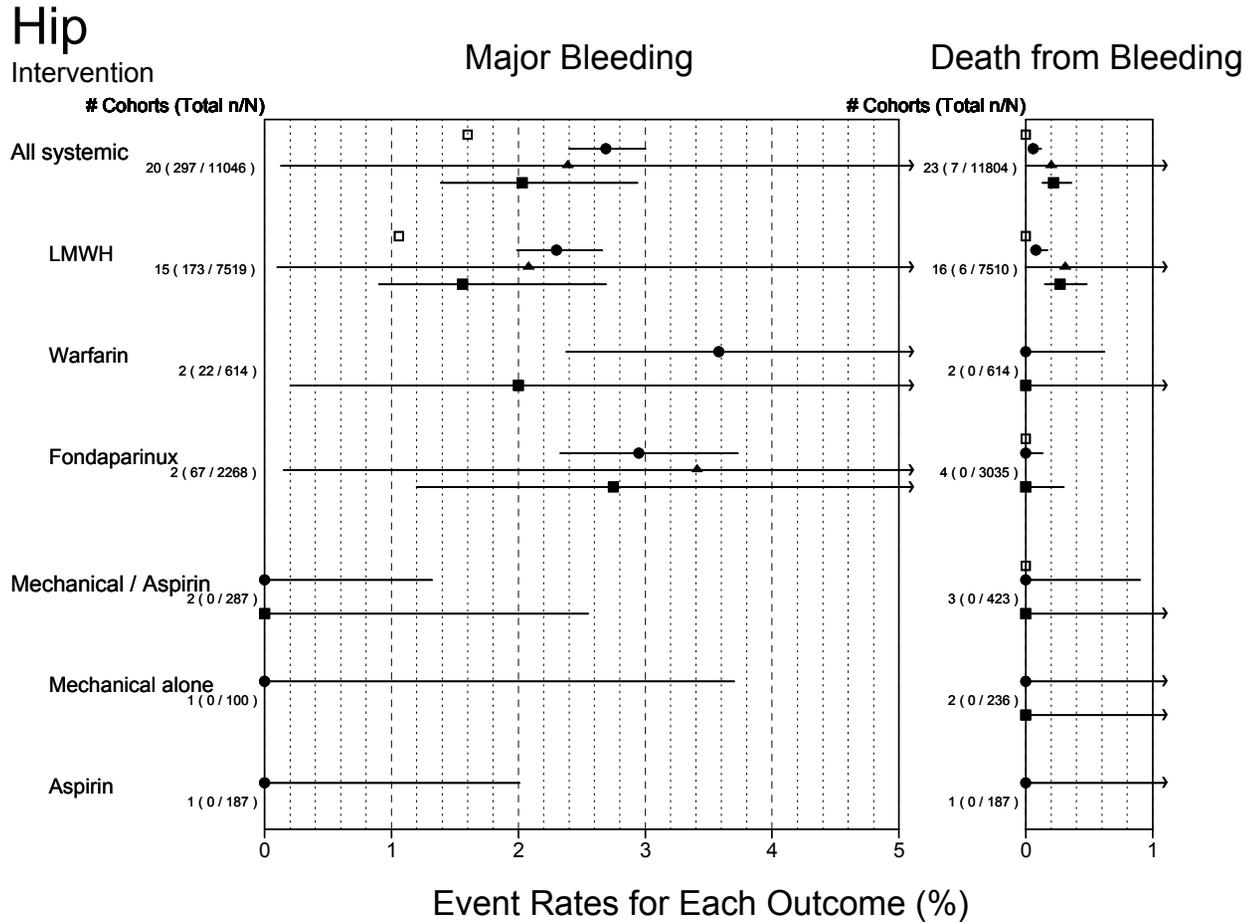
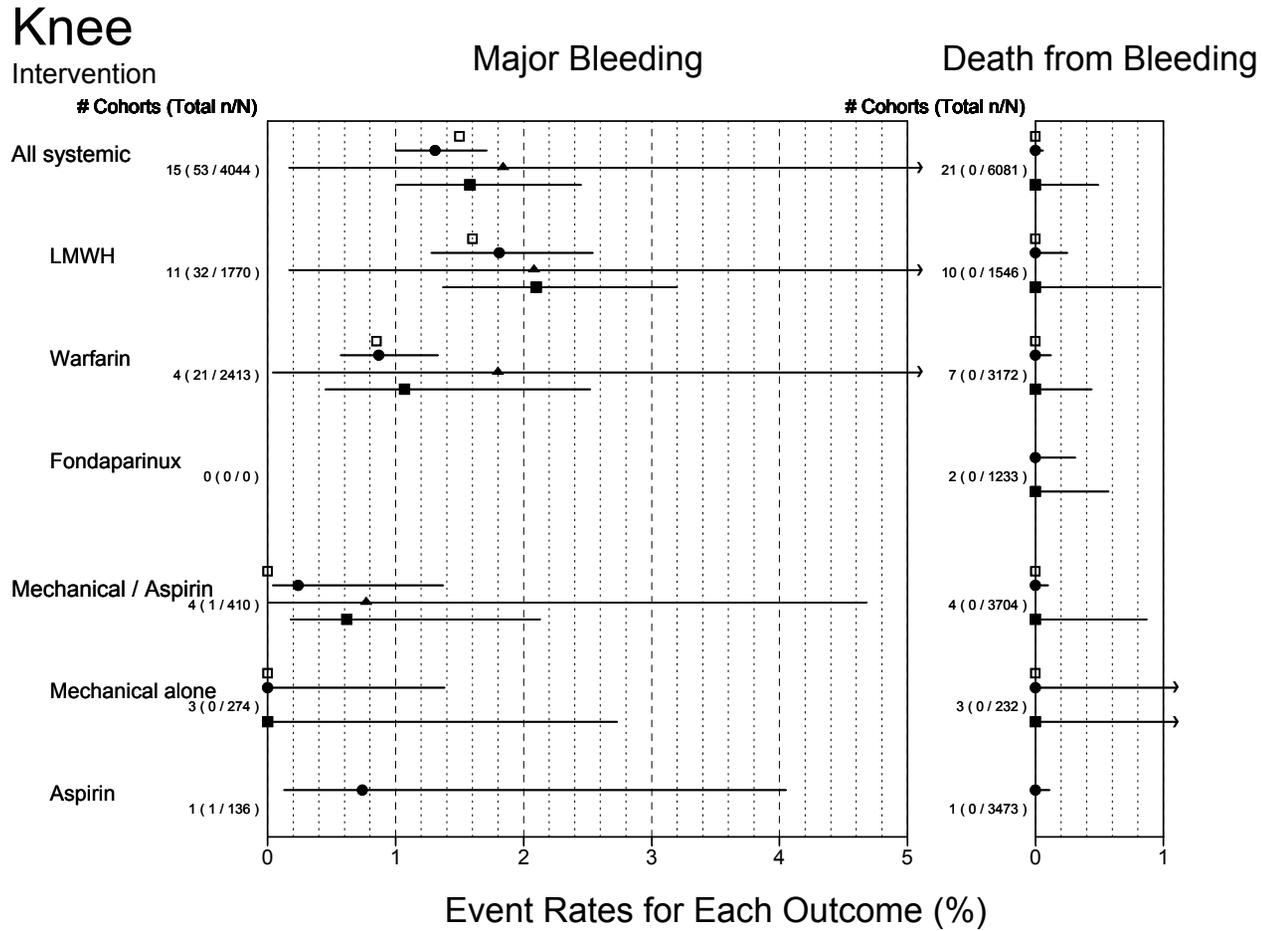


Figure 4. Major bleeding and death from bleeding rates for patients after hip arthroplasty receiving different prophylaxis regimens.



Recommendation 3.3.1

Patients with standard risk of PE and standard risk of major bleeding represent the majority of total joint replacement patients. As noted in the introduction to this guideline orthopaedic surgery carries with it a higher level of risk for thromboembolic complications than for general surgical or medical patients. Therefore the term “standard” should be understood as a relative term specifically for hip and knee replacement. Since the incidence rates of symptomatic PE are low, it is not possible to make definitive recommendations on the occurrence of PE alone. In order to determine differences in current chemoprophylactic regimens, we would need at least 25,000 and 150,000 patients, respectively (calculated using a relative risk of 0.5 for the efficacy of prophylaxis). These low incidence rates of PE and fatal PE mean that we must look more closely at the opposite side of the risk equation and fully assess the adverse effects (primarily bleeding) that result from our recommendations.

The bleeding risk from chemoprophylactic agents may rise with increased effectiveness in reducing DVT (15). The incidence of major bleeding is less than 1% in patients without chemoprophylaxis and may be as high as about 3 to 5% in patients given chemoprophylactic agents (38). Precise estimates of the true risk of bleeding are difficult to obtain since the definitions of major bleeds vary among different studies. In general, the definitions of a major bleed include; life threatening, intraocular, or intracerebral bleeds, or a bleed requiring more than a specified number of transfusions. Furthermore, most of the prospective data from drug comparison studies utilize selected populations, which exclude patients with prior gastrointestinal bleeds and noncompliant or frail patients. Also patients may not have been included within the major bleed definitions if they had bleeding events that did not immediately affect surgical outcomes. In general, clinical outcomes in patients with a defined major bleed or in the spectrum of patients with lesser bleeding have not been well studied.

The present recommendations reflect the Work Group’s concerns about increased bleeding associated with the use of chemoprophylactic agents without a demonstrated reduction in PE. The duration for the administration of chemoprophylactic agents has not been clearly established. The older literature notes that most postoperative PEs occurred within the first 6 week (5;39-42). Therefore, many regimens were established to conform to that experience. Some reports on the heparin like drugs, that shows it is not necessary to prolong the administration beyond the first 8 to 12 days (43). The Work Group’s recommendations reflect these practices.

Combinations of agents may also be considered, such as a short course of a LMWH followed by aspirin. However, there is no definitive evidence that demonstrates a reduction in PE using any of these regimens.

Recommendation 3.2, which recommends that patients should be mobilized rapidly after surgery unless contraindicated, should be viewed as universally applicable, regardless of choice of chemical chemoprophylaxis. Mechanical devices have no inherent bleeding risk; however, their effectiveness in reducing the incidence of PE has not been definitively demonstrated. Therefore, they remain an adjunct in the armamentarium for prophylaxis unless there is a contraindication for chemoprophylaxis, in which case they become the primary means of prevention.

Recommendation 3.3.2

Warfarin (INR \leq 2.0), LMWH, or a synthetic pentasaccharide are recommended as chemoprophylaxis for patients known or suspected to be at increased risk of PE after total hip or knee arthroplasty. In this clinical setting, the customary risk-benefit balance between therapeutic anticoagulation and bleeding risk is tipped in favor of the most effective prophylaxis while acknowledging a potentially higher bleeding risk as a tradeoff for optimal efficacy in prevention of PE.

The data presented in Figures 1 and 2 do not demonstrate differentiation of effectiveness among any of the chemoprophylactic agents in the prevention of PE. This is in clear contrast to the results of DVT oriented studies, where there is evidence to support distinctions. For example, the efficacy in prevention of DVT has been shown, in declining order, for the synthetic pentasaccharide (fondaparinux), LMWH (enoxaparin, dalteparin) (16;44-46), and low intensity warfarin (INR 2.0) (47).

Although the incidence of major bleeding after hip arthroplasty appears to be higher than knee arthroplasty (Figures 3 and 4) the clinical tolerance for major bleeding may be less after knee arthroplasty owing to the more superficial nature of the knee and the tenuous character of its soft tissue envelope. Therefore, a higher level of concern for post-operative bleeding in total knee replacement is prevalent among most surgeons in light of a theoretically higher potential for a bleed to compromise the clinical outcome.

In addition to the use of chemoprophylactic agents it is prudent to employ other adjunctive measures as outlined in Recommendations 2.1, 2.2, and 3.1.

Recommendation 3.3.3

Patients that are at standard risk of PE but at an elevated risk of major bleeding are relatively uncommon. Examples of this include thrombocytopenia, bone marrow suppression, known hemophilia or other defined coagulation defects, recent radiation, or chemotherapy. The management of these patients should be individualized (perhaps in association with a hematologist). The first priority is to correct the clotting defect, if possible, prior to surgery, using transfusions of clotting factors, platelets, or frozen plasma. The use of a chemoprophylactic agent in a patient with a known diminished ability to clot must be considered judiciously, as there is currently no evidence base to assist in this decision.

In addition to the use of chemoprophylactic agents it is prudent to employ other adjunctive measures as outlined in Recommendations 2.1, 2.2, and 3.1.

Recommendation 3.3.4

In the setting of elevated risk of both PE and major bleeding (above standard risk), the selection of the most appropriate prophylactic regimen is dependent on the clinical judgment of the surgeon and medical consultants. The final judgment is the result of integrating the knowledge of the severity of existent risk factors for PE and bleeding with the patient's current status.

Although the recommendations 3.3.3 and 3.3.4 regarding chemoprophylaxis contain identical agents, the range of options (from warfarin to no chemoprophylaxis) is wide. Particularly for patients at elevated risk of both PE and major bleeding, it is very important that the physician has as accurate an assessment as possible of the actual likelihood of a life-threatening PE. Aspirin, with its attendant very low risk of bleeding and warfarin, which can be dosed to lower INRs in

high-risk bleeding situations are the agents recommended if chemoprophylaxis is deemed necessary.

In addition to the use of chemoprophylactic agents it is prudent to employ other adjunctive measures as outlined in Recommendations 2.1, 2.2, and 3.1.

Recommendation 3.4

Specific recommendation is made against routine surveillance for venous thromboembolism after total hip or knee arthroplasty. There is neither a sufficiently sensitive noninvasive screening tool nor a clearly established period of risk for venous thromboembolism as to make routine screening reliably predictive or cost-effective in preventing PE.

The premise that routine screening is an effective strategy to prevent PE is predicated upon the hypothesis that secondary prophylaxis, namely prevention of propagation and embolization of existing thrombi, is a valid approach to reducing the incidence of PE. One study of over 3,000 patients with 6 month follow-up of readmission for symptomatic proximal DVT or PE demonstrated a readmission rate in patients discharged without continued anticoagulation on the basis of negative screening contrast venography nearly 8 times greater than patients who received 6 weeks of warfarin based on a positive screening venogram or empiric continuation of prophylaxis (48;49).

Other imaging modalities have been suggested for routine screening. Duplex ultrasound is highly operator dependent, test performance is variable from institution to institution, and the test is not sensitive to thrombus identification distal to level of the adductor canal and in the pelvis.

Magnetic resonance venography has been shown to be sensitive in imaging asymptomatic pelvic thrombi but remains costly and cumbersome to repeat on a regular basis.

Routine screening by genetic predisposition or identification of a single serum clotting factor has yet to demonstrate a strong correlation with venous thromboembolic disease after total hip or knee arthroplasty.

Recommendation 4: Discharge to Home

4.1 Patients should be encouraged to progressively increase mobility after discharge to home.

Level of Evidence: V

Grade of Recommendation: C

4.2 Patients should be educated about the common symptoms of deep venous thrombosis and pulmonary embolism.

Level of Evidence: V

Grade of Recommendation: B

Note: The level of evidence is level V, expert opinion, but the strength of recommendation was increased from C to B because patient education is consistent with the minimal expected standard of care for today's medical practices.

Rationales

Recommendations 4.1 and 4.2

During post-operative hospitalization, the team caring for the patient, should collaborate with physical therapy, occupational therapy and discharge planning to extend hospital program to home environment. The team should stress appropriate range of motion, appropriate conditioning programs, and encouraging the patients to avoid prolonged immobility.

All patients should be educated regarding common symptoms of DVT and PE. DVT symptoms are usually localized to site and include: pain, swelling, tenderness and redness or discoloration of skin. PE symptoms include: shortness of breath, rapid pulse, sweating, feeling of apprehension, chest pains worsening with deep breath, coughing up blood, decreased blood pressure and light headedness.

These recommendations are an extension of the AAOS concept of patient-centered care encouraging patient education as part of the surgical process. The presumption is that patient participation and education will enhance awareness, improve outcomes and potentially diminish the risk associated with the procedure specifically the potential for PE-related morbidity and mortality.

Future Research

Appropriately powered studies to detect the superiority of any preventive strategy for PE would be far more costly than for DVT. Consequently DVT, which occurs much more frequently, and seems to occur with a wider variability among treatment groups is a more attractive proxy measure. But the reduction of DVT does not appear to have a significant effect on the PE rate, and this calls into question the long assumed epidemiologic if not pathophysiologic link between the two processes. Additional research, which better describes this relationship, would be helpful.

Post-operative bleeding in and around the surgical wound is an example of a complication, which may be directly caused by prophylaxis. In contrast to an asymptomatic DVT a post-operative bleed may lead to even more serious problems that significantly impact the surgical outcome. In this sense the expected benefit of prevention of one type of surgical complication may be overshadowed by the increased risk of another. The incidence of major post-operative

bleeding should be addressed in a more uniform and standardized fashion to facilitate a more reliable comparison of different studies, and pooling of the results. The functional outcomes in patients with major bleeds should be followed in studies that are concerned primarily with thrombo-embolic events in order to fairly estimate the costs of treatment complications in comparison with those of fatal and non-fatal PE.

The issue of PE risk stratification in the pre-operative assessment of total hip and knee replacement patients is very important. By developing an evidence-based risk adjustment system it will be possible to utilize a more cost-effective individualized prophylactic strategy. Future research should be directed at the assessment of the incidence of PE following hip or knee replacement in large unselected populations where the potential risk factors are reliably documented. Large databases such as Medicare and those administered by states may provide some assistance, but currently do not include enough specific risk stratification and outcome variables. Hip and knee replacement registries present real opportunities to enhance the quality and applicability of the data. The AAOS has demonstrated a commitment to oversee the development of a national total joint registry which would facilitate an efficient and timely approach to preventing PE and post-operative bleeding complications. Successful implementation of this strategy would undoubtedly improve the quality of care for our patients and deliver value to the health care system.

Conclusion

There were major limitations to the body of evidence, including large clinical heterogeneity in the interventions, other related procedures and cointerventions, doses, study populations, follow-up times, and in the case of major bleeding, definitions. In addition, none of the studies was designed to investigate PE as a primary outcome. Reporting of PE-related events was frequently incomplete and vague. Commonly, it was not clear how many patients were evaluated for each outcome. Overall, the numbers of patients within each study were inadequate to properly estimate the event rates of interest. Because the event rates were frequently either zero or close to zero, combining data across studies had limitations. We investigated 4 different methods of combining rates, but relied primarily on the simple pooled average (sum of events over sum of patients) as this method appeared to provide the most logical estimates, though narrow confidence intervals. Even if these limitations could have been better overcome, the evidence would still be very limited due to the near lack of direct comparisons within studies. Thus, all evaluations were based on indirect comparisons across different arms (cohorts) of different studies, a less reliable analysis than direct comparisons (e.g., randomized trials).

It is also important to note that the number of studies and patients evaluated were restricted by several decisions made regarding the eligibility criteria, including restriction to prospective studies (greatly reducing the number of patients evaluated, but avoiding the numerous biases and lack of pre-defined interventions of retrospective studies), study size restrictions (which greatly reduced the number of studies, but did not greatly reduce the number of subjects or events), and restriction to patients operated on since 1996. A large number of studies were not included because of this last restriction. However, the consensus among the Work Group was that surgical techniques and post-operative care have changed sufficiently since 1996. They agreed that estimates of PE and bleeding rates from older studies would not be accurate for contemporary patients. It was acknowledged though, that the specific choice of 1996 was somewhat arbitrary.

The available evidence shows no differences among the interventions in rates of PE, PE-related death, total death, major bleeding, bleeding-related death, or rehospitalization. This lack of adequate evidence holds true for the broader comparison of systemic interventions (fondaparinux, LMWH, and warfarin) and mechanical devices or aspirin alone. Except to note that major bleeding was very rare among patients receiving aspirin or mechanical devices alone (1 case in 697, or 0.14%, exact 95% CI 0.03-0.8%) compared to those who received systemic interventions (random effects model summary estimate 1.8%, 95% CI 1.4-2.5%). Because of the limitations and the overall relatively small number of patients evaluated (given the rarity of PE after arthroplasty), only approximate estimates of event rates can be surmised from the evaluated evidence.

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Appendices

Appendix I: Systematic Review and Meta-Analysis Methods

Key Questions

The guideline recommendations are based on the answers to four Key Questions. These questions were specified prior to conducting the literature searches and frame the scope of the guideline. Questions were constructed to specify the patients, interventions, comparisons, and outcomes of interest. The Key Questions addressed by these guidelines were:

- 1A. In patients having knee replacement surgery, what is the effect of prophylactic therapy (e.g., coumadin, low molecular weight heparin, aspirin, mechanical devices) compared with either no prophylaxis or placebo in preventing important clinical symptoms or events (e.g., shortness-of-breath, chest pain, arrhythmia, fatality, rehospitalization) secondary to pulmonary embolism?
- 1B. In patients having hip replacement surgery, what is the effect of prophylactic therapy (e.g., coumadin, low molecular weight heparin, aspirin, mechanical devices) compared with either no prophylaxis or placebo in preventing important clinical symptoms or events (e.g., shortness-of-breath, chest pain, arrhythmia, fatality, rehospitalization) secondary to pulmonary embolism?
- 2A. In studies of knee replacement surgery, how do these different prophylactic therapies compare among each other in preventing important clinical symptoms or events secondary to pulmonary embolism?
- 2B. In studies of hip replacement surgery, how do these different prophylactic therapies compare among each other in preventing important clinical symptoms or events secondary to pulmonary embolism?
3. What are risks of clinically important adverse events associated with these prophylactic therapies in patients having knee or hip replacement surgery?
- 4A. What is the risk of important clinical symptoms or events secondary to pulmonary embolism in patients who had knee replacement surgery, in whom no prophylactic therapies for the prevention of pulmonary embolism were prescribed?
- 4B. What is the risk of important clinical symptoms or events secondary to pulmonary embolism in patients who had hip replacement surgery, in whom no prophylactic therapies for the prevention of pulmonary embolism were prescribed?

Literature Searches

We searched Medline from 1970 through August 2006 to identify all citations relevant for the guideline and the associated performance measures. Search terms included arthroplasty, replacement, knee prosthesis, hip prosthesis, and specific terms for anticoagulants, and mechanical intervention. The search strategies are provided (see Appendix Table 1). Additional articles, including later publications, were suggested by the Work Group members. These articles were screened in accordance with the same criteria as those found by the Medline search.

Appendix Table 1. MEDLINE search, August 28, 2006

#	Search History	Results
1	exp Arthroplasty, Replacement, Knee/ or exp Arthroplasty, Replacement, Hip/	10112
2	exp Hip Prosthesis/	13279

3	exp Knee Prosthesis/	5698
4	exp Arthroplasty, Replacement, Knee/ or Knee Joint/	28927
5	((knee or hip) and (surger\$ or arthroscop\$ or arthroplas\$ or replacement)).mp.	38579
6	or/1-5	61439
7	exp pulmonary embolism/	22498
8	thrombophlebitis.mp.	19895
9	(pulmonary adj (thrombo\$ or embolism)).mp.	26783
10	clot\$.mp.	39588
11	coumadin.mp.	600
12	exp Warfarin/	9257
13	warfarin.mp.	12264
14	exp Heparin, Low-Molecular-Weight/	6318
15	dalteparin.mp.	722
16	enoxaparin.mp.	1823
17	nadroparin.mp.	386
18	exp Aspirin/	28675
19	aspirin.mp.	37601
20	exp Platelet Aggregation Inhibitors/	72235
21	clopidogrel.mp.	2177
22	90055-48-4.rn.	1584
23	50-78-2.rn.	28675
24	compression boot\$.mp.	36
25	foot pump\$.mp.	53
26	exp Anticoagulants/	130057
27	or/7-26	270779
28	6 and 27	2567
29	limit 28 to humans	2497
30	limit 29 to english language	2087
31	limit 30 to yr="1970 - 2006"	2072

Article Eligibility Criteria

During citation screening, only full journal articles that reported original data were included. Editorials, letters, abstracts, unpublished reports and articles published in non-peer reviewed journals were not included. Selected review articles and key meta-analyses were retained from the searches for background material. Members of the ERT screened the abstracts identified via the Medline search for relevance. Eligibility criteria were developed for each Key Question. For each key question, clear and explicit criteria were agreed on for the population, intervention, comparator, and outcomes of interest. Additional study eligibility criteria were applied based on study design, minimal sample size, minimal follow-up duration, and the calendar year in which the patient had the surgery. In general, eligibility criteria were determined based on clinical value, relevance to the guidelines and clinical practice (applicability), determination whether a set of studies would affect guidelines or the strength of evidence, and practical issues such as available time and resources. Full articles of relevant abstracts were retrieved and were rescreened using the pre-defined eligibility criteria (Appendix Table 2). Work Group members reviewed the final list of potentially relevant citations and also suggested additional articles that were not identified by the electronic database searches. These additional articles were also screened using the same set of eligibility criteria.

Appendix Table 2. Study eligibility criteria.

Study design

- Questions 1, 2, & 3
 - Prospective cohort, randomized controlled trial, nested case-control studies (data collected prospectively)
 - Randomized controlled trials: $N \geq 10$ (in each arm)
 - Other designs: $N \geq 100$ (receiving total hip replacement (≥ 100) or total knee replacement (≥ 100) and an intervention)
- Question 4
 - Any study design (prospective or retrospective)
 - $N \geq 1000$
 - No active intervention
- All Questions
 - Longitudinal (no minimum duration)
 - Comparative or non-comparative (pre-post studies)
 - English language publications
 - Peer reviewed primary studies (exclude abstracts, case reports, reviews, conference presentations, expert opinion)
 - Dates:
 - Start with publication date 2000-2006
 - At least 2/3 of patients (or time period) within time period of interest
 - Order studies by year of intervention
 - If study does not report year(s) of intervention, then use one year prior to manuscript submission or two years before publication date
 - Consult regularly with Work Group about how far back to go for each intervention (and question 4 / no intervention)

Population

- Patients who are undergoing hip or knee replacement surgery for any reason (exclude patients who have PE at baseline, except for case-control and similar studies) (will need to decide on how best to deal with mixed populations, receiving multiple types of surgery)
- No restriction on age, race, country or other demographic features
- Include high risk population (e.g., hemophiliacs, prior recent surgery, diabetes, immunocompromised, malignancy, heart failure)

Intervention

- Warfarin and related drugs
- Low molecular weight heparin and related drugs (including fondaparinux and other heparin-derived drugs)
- Aspirin, clopidogrel, and other anti-platelet drugs
- Mechanical devices
- Any duration of intervention, timing of intervention, or combination of interventions

Outcomes

- Critical events
 - Mortality (all cause and PE-related)
 - Embolectomy or need for other PE treatments
 - PE-related acute respiratory distress syndrome or other respiratory events
 - PE-related cardiac events
 - Rehospitalization (any cause)
 - classify by cause, with emphasis on PE-related or adverse event-related
 - consult with Work Group as necessary re: specific causes of rehospitalization
 - Major infection (not including superficial infections)
- Symptomatic events
 - Shortness of breath
 - Chest pain
 - Arrhythmia
- Adverse events (short- and long-term)
 - Clinically important bleeding
 - Requiring surgical or other intervention
 - Requiring rehospitalization
 - Hemorrhagic stroke
 - Other major bleeding

Do not evaluate:

- Asymptomatic PE, eg diagnosed only by V/Q scan
 - PE with minor symptoms only
- Deep Vein Thrombosis related outcomes
- Other non-pulmonary embolisms
- Intermediate outcomes (unless no evidence for clinical outcomes)
 - Measures of blood O_2 and CO_2 levels
 - d-dimers and other measures of coagulation

Data Extraction

The ERT designed data extraction forms to capture information on various aspects of the primary studies. Data fields for each study included: study setting, funding source, eligibility criteria, study design characteristics, patient demographics, co-morbidities, number of subjects, description of surgical and anesthetic techniques, description of relevant risk factors or interventions, description of outcomes, statistical methods, results, study quality, applicability (see below), and free text fields for comments and assessment of biases. Work Group members were apprised of the entire data extraction process. They also reviewed the data extraction form. Data from each article were extracted by one member of the ERT. A second member verified each set of data extraction and discrepancies were resolved through discussions. Work Group members reviewed the results of the data extraction.

Outcomes of interest included symptomatic, clinically documented PE including treatment for PE, clinically documented PE-related death, all-cause death, other PE-related clinical events, rehospitalization due to venous thromboembolism or bleeding, major infection (not including superficial infections), major bleeding (as defined by authors, but generally including life threatening, intraocular, intracerebral, a bleed requiring more than a specified number of transfusions, extending the length of hospital stay, or resulting in a return to the operating room), and bleeding-related death.

Summary Tables

Summary tables describe the studies according to four dimensions: study size and important characteristics, results, methodological quality, and applicability. The ERT generated summary tables using data from extraction forms and/or the articles. Work Group members reviewed the summary tables.

Grading of Individual Studies

Methodological Quality Assessment

Methodological quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Many methods have been devised to measure study quality. There remains controversy regarding how different aspects of study design and quality may impact study results (1;2). The ERT used a three-category grading system (A, B, C) to denote the methodological quality of each study. This system has been used for a range of systematic reviews and clinical practice guidelines (3;4). It defines a generic grading system that is applicable to different study designs. The quality rating was based primarily on the study design and the quality of reporting pertained specifically to PE, major bleeding, and death.

A Good quality: Likely to have the least bias and results are considered valid.

Clear protocol, clear description of the population, setting, and interventions; appropriate measurement of and reporting of rates of PE or death due to PE; appropriate statistical and analytic methods; no obvious reporting errors; less than 20% dropout; clear explanation of dropouts; and no obvious bias.

B Fair quality: Susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in good quality studies because they have some deficiencies, but none are likely to cause major biases. The studies may be missing information, making it difficult to assess limitations and potential problems.

C Poor quality: Significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information, or discrepancies in reporting.

Studies that reported results for a specific outcome that were poorly defined were downgraded to poor for that specific outcome (e.g., if it was unclear whether all the PEs reported were confirmed).

Applicability Assessment

Applicability addresses the relevance of a given study to a population of interest. Every study applies certain eligibility criteria when selecting study subjects. Most of these criteria are explicitly stated (e.g., disease status, age, comorbidities). Some of them may be implicit or due to unintentional biases, such as those related to location (e.g., multicenter vs. single center; urban vs. rural setting), intervention (e.g., an outmoded dose), factors resulting in study withdrawals, or issues related to compliance with stated criteria, and others. The applicability of a study is dictated by the key questions, the populations, and the interventions that are of interest only to these specific guidelines (as opposed to those of interest to the original investigators).

The Work Group determined that short duration studies (follow-up duration of less than 6 weeks) were of limited applicability for estimating rates of PE and total death after arthroplasty. It was also the opinion of the Work Group that surgical techniques and post-operative management had changed significantly over time. Because of these changes, the care of patients enrolled prior to 1996 was sufficiently different than current practice. The consensus was reached to exclude these patients from the review.

To address these issues, we categorized studies within a target population into 3 categories of applicability that are defined as follows:

Wide: Sample is representative of the target population. It should be sufficiently large to cover a range of patient ages, other demographic features, and reasons for arthroplasty. Minimal exclusions based on age, comorbidities, or underlying risk of bleeding or venous thromboembolism. In addition, the intervention should be applicable to currently used interventions, including dose and duration of intervention. Complete reporting of baseline characteristics. Follow-up duration for at least 6 weeks with respect to the PE-related outcomes and total death.

Moderate: Sample is representative of a relevant sub-group of the target population, but not the entire population. Limitations include such factors as exclusion of patients based on medical or surgical history, or narrow age range. Adequate reporting of baseline characteristics. Follow-up duration for at least 6 weeks with respect to the PE-related outcomes and total death.

Narrow: Sample is representative of a narrow subgroup of subjects only, and is of limited applicability to other subgroups. Multiple deficiencies regarding applicability or poor reporting of eligibility criteria and/or baseline characteristics. Follow-up duration may have been less than 6 weeks.

Studies with less than 6 weeks follow-up may have been graded Narrow for PE, PE-related death, and total death, but Moderate or Wide for bleeding-related outcomes.

Statistical Methods

The primary units of analyses were rates of clinical outcomes. For the few relevant randomized trials with two interventions of interest or an intervention and a no intervention control, the odds ratios for the clinical outcomes were also analyzed. Rates of clinical outcomes of interest were

calculated for each study based on the number of reported events and the best estimate of the denominator (the number of evaluated patients). For each event rate, a 95% confidence interval of the rate was calculated using an exact confidence interval approach (5).

Several of the studies reported only event rates after hospitalization. These studies randomized patients at discharge and specifically evaluated post-hospitalization interventions. Since these studies excluded patients who had thromboembolic events – including PE – during hospitalization, they were not included in our calculations of rates of events after arthroplasty. However, these studies were fully evaluated and reviewed by the Work Group members.

Because the event rates for most outcomes of interest were very small (less than 1%) and none of the studies included sufficient numbers of patients to provide estimates of the outcomes of interest, the estimated event rates were not normally distributed in the studies. In this situation, there are not adequate (i.e., reliable) methods of meta-analyzing rates. However, to provide the best estimates of event rates for different interventions, four different statistical approaches were used to pool the data.

Medians. For each analysis in which there were at least 3 cohorts of patients, the median value across cohorts was documented. The size of the cohorts and the confidence intervals of the study rates were not considered.

Simple Pooling. For each analysis, the total number of events was divided by the total number of patients across studies. This is equivalent to a fixed effects meta-analysis weighted by sample size (or a simple average). The confidence interval for the pooled estimate was calculated using the exact confidence interval approach.

Random Effects Model Meta-Analysis of Logit of Event Rate. The logit [$\ln(\text{rate}/(1-\text{rate}))$] for each study was calculated. When the event rate was zero, 0.5 was added to all 4 cells of the 2x2 table (6). The logit values were then meta-analyzed using standard DerSimonian and Laird random effects model meta-analysis (7). However, a large number of studies had zero event rates and because of the relatively small sample sizes, adding 0.5 to cells frequently caused anomalous results. Use of smaller “fudge factors” (Woolf’s corrections) sometimes resulted in exceedingly large confidence intervals. Thus, when summary estimates of rates were outside the range of estimates among the constituent studies, these estimates were discarded.

Bayesian meta-analysis of proportions. The event rates in each study were modeled as binomial distributions. Prior probability information was elicited as relatively non-informative beta distributions. Details on the parameterization of the Bayesian models and the specifications of the priors per analysis, are available upon request. As specified, the prior distributions are incompatible with a zero event prevalence; therefore we did not perform these analyses when all numerators were zero across studies.

Individual study estimates and all four sets of summary estimates were graphed to highlight the relative rates across interventions and across outcomes. Because of the low event rates of outcomes of interest and the small sample sizes of the randomized trials (frequently resulting in 0 events in both arms), and because only one or two randomized trials were comparable in interventions, controls, and surgeries, the odds ratio of events were not calculated.

For all analyses, studies that reported only outpatient events that failed to adequately describe events during hospitalization were excluded. The Work Group, however, did review these studies.

Appendix II: Rating Quality of the Body of Evidence

We considered the quality of the available evidence when grading the strength of guideline recommendations. Quality was determined using a “Levels of Evidence” approach in which five levels of evidence were designed for each of four study designs; therapeutic, prognostic, diagnostic and economic or decision modeling. The higher the level of evidence, the greater the ability to draw causal inferences from the results of a study and, hence, the greater the quality of that study.

Each guideline recommendation was graded using the following system:

- A: Good evidence (Level I Studies with consistent finding) for or against recommending intervention.
- B: Fair evidence (Level II or III Studies with consistent findings) for or against recommending intervention.
- C: Poor quality evidence (Level IV or V) for or against recommending intervention.

Level I evidence is from high quality randomized clinical trials (e.g., a randomized trial comparing revision rates in patients treated with cemented and uncemented total hip arthroplasty).

Level II evidence is from cohort studies (e.g., revision rates in patients treated with uncemented total hip arthroplasty compared with a control group of patients treated with cemented total hip arthroplasty at the same time and institution).

Level III evidence is from case-control studies (e.g., the rates of cemented and uncemented total hip arthroplasty in patients with a particular outcome called "cases"; i.e. revised total hip arthroplasty, are compared to those who did not have outcome, called "controls"; i.e. non-revised total hip arthroplasty).

Level IV evidence is from an uncontrolled case series (e.g., a case series of patients treated with uncemented total hip arthroplasty).

Level V evidence is from expert opinion. The table is relatively simple with four types of studies and five levels. The actual criteria for assignment is a little more complicated, and for interested readers, are contained in the cells of the table.

Appendix III: Systematic Review Results

Literature search

The literature search resulted in 2712 citations. Ten additional articles were suggested by the Work Group for evaluation. Among these, 42 studies met criteria. All 5 eligible studies recommended by the Work Group were published after the original literature search.

There were 23 studies of the effect of prophylaxis after knee arthroplasty, 16 studies of adverse events from prophylaxis after knee arthroplasty, 25 studies of the effect of prophylaxis after hip surgery, and 19 studies of adverse events from prophylaxis after hip arthroplasty. Sixteen studies directly compared 2 interventions. Across the studies, outcomes were reported for 11,665 patients who received knee arthroplasty and for 16,304 patients who received hip arthroplasty.

Among the 152 articles that were retrieved but ultimately rejected, the primary reasons for rejection were patient recruitment prior to 1996 (121 articles, it was the opinion of the Work Group that surgical techniques and post-operative management had changed substantially since the care provided prior to 1996; thus these studies were excluded), retrospective analysis (7), no intervention of interest (6), and no outcomes of interest reported (4). Among the 4 potentially relevant studies of incidence rates of pulmonary embolism (PE) without prophylaxis since 1996, none classified patients based on their prophylaxis intervention (or lack of prophylaxis).

Study quality and applicability

None of the studies was deemed to be of Good quality regarding the outcomes of interest; 23 studies were graded Fair quality; and 19 were graded Poor quality. One of the Fair quality studies was rated Poor quality for PE-related death due to unclear reporting for this outcome. Since all reviewed studies were designed to evaluate deep vein thrombosis, numerous studies were downgraded because of incomplete reporting or follow-up for PE, despite excellent design and reporting for deep vein thrombosis. It was commonly difficult to confidently ascertain the total number of patients who were evaluated for both PE and bleeding outcomes.

Only two studies had Wide applicability for PE-related outcomes. These studies did not exclude patients commonly considered for chemoprophylaxis, including those with histories of deep vein thrombosis or bleeding. Among the remaining studies, 21 had Moderate applicability and 18 had Narrow applicability for PE outcomes. Several of these studies were of Narrow applicability due to relatively short follow-up duration (less than 6 weeks). Since follow-up duration was not considered for the applicability of bleeding outcomes (and several studies did not report bleeding outcomes), 20 studies had Moderate applicability and 13 Narrow applicability for bleeding outcomes.

In addition to the range of quality and applicability across studies, the studies were highly heterogeneous regarding specific intervention, dose or intensity of intervention, start time and duration of intervention, follow-up time, co-treatments used, eligibility criteria, inclusion of patients receiving revision or bilateral surgery, surgical and anesthetic techniques. Among the studies, only 3 reported no commercial funding.

Analytic methods

For all analyzed outcomes, 4 different meta-analysis techniques were used: median value, pooled estimate, random effects model estimate, and Bayesian estimate (**Figures 1-4**). This was done because of the inherent difficulties in both estimating event rates and determining a combined estimate of the event rates in the setting of small numbers of events (frequently zero) in individual studies. However, each of the methods has deficiencies. Compared to simple pooling, median event rates tended to be lower, particularly since for several outcomes event rates were zero in a majority of studies. Both random effects model meta-analyses and the Bayesian analyses tended to produce larger estimates of event rates than simple pooling, though the 2 methods often produced different estimates. All 4 methods of combining studies are presented in the summary figures, but the following description and conclusions are based primarily on the simple pooled estimates where exact confidence intervals are estimated as if all patients were enrolled in a single study. It should be noted that this method does not account for the variance within studies or the heterogeneity across studies and thus produces substantially narrower confidence intervals compared to more traditional methods of meta-analysis.

Pulmonary embolism

Hip arthroplasty

There were 25 studies that met criteria and reported PE rates with various interventions after hip arthroplasty (8-32). One study evaluated aspirin (27), 2 aspirin and a mechanical device (22;27), 3 a mechanical device alone (19;24;31), 3 fondaparinux (with 4 cohorts) (11;21;30), 18 low molecular weight heparin (LMWH) with or without a mechanical device (with 23 cohorts) (8;10;12-18;20;21;24;25;28-32), 5 warfarin with or without a mechanical device (with 8 cohorts) (9;16;17;23;26), and 1 a course of LMWH followed by warfarin (28).

Across all studies and all interventions (Figure 1), between 45 and 47 symptomatic PEs were documented in 14,763 patients, or 0.3% (exact 95% confidence interval [CI] 0.2-0.4%); one study was unclear regarding the number of symptomatic PEs. The rate of PEs ranged from 0% to 1.2% in individual studies (**Appendix Figure 5**). Across interventions, the event rate estimates were all less than 1%. Notably, the 95% confidence intervals for the estimates for individual interventions were generally fairly wide (Figure 1).

Given the lack of precision in the estimates, as manifested by the wide and overlapping confidence intervals, the rates of PE after hip arthroplasty were statistically similar across the different interventions. Interestingly, the summary estimates of PE rates were higher in patients who received systemic prophylaxis than those who were treated with aspirin or mechanical devices alone, though this finding may be due to chance alone and may be related to the relatively small number of patients evaluated with aspirin or mechanical devices alone.

In addition, there was no evidence across studies of different rates of PE related to dose, intensity, or timing of intervention, duration of follow-up, study quality or applicability.

Knee arthroplasty

There were 21 studies that met criteria and reported PE rates with various interventions after knee arthroplasty (11-13;15;29;32-47). Three studies (with 4 cohorts) evaluated aspirin and a mechanical device (36;37;39), 3 a mechanical device alone (35;43;44), 1 fondaparinux (with 2 study arms) (11), 11 LMWH (11-13;15;29;32;34;40;42;43;45), 4 a LMWH with a mechanical device (29;35;39;44), 5 warfarin (with 7 cohorts) (34;38;41;46;47), and 1 a LMWH or a mechanical device both followed by outpatient warfarin (33).

Across all studies and all interventions (Figure 2), 45 symptomatic PEs were documented in 10,200 patients, or 0.4% (exact 95% CI 0.3-0.6%). The rate of PEs ranged from 0% to 1.2% in individual studies, not including a study with only 15 patients (**Appendix Figure 6**). Across interventions, the event rate estimates were generally 1% or less. The rates of PE after knee arthroplasty were similar across different interventions.

In addition, there was no evidence across studies of different rates of PE related to dose, intensity, or timing of intervention, duration of follow-up, study quality or applicability.

Pulmonary embolism-related death

Hip arthroplasty

There were 19 studies that provided sufficient data to estimate rates of death due to confirmed PE with various interventions after hip arthroplasty (8;9;11-14;16-21;23;25;26;28-31). None evaluated aspirin, 2 evaluated a mechanical device alone (19;31). 3 evaluated fondaparinux (with 4 cohorts) (11;21;30), 14 evaluated LMWH with or without a mechanical device (with 18 cohorts) (8;12-14;16-18;20;21;25;28-31), 5 warfarin with or without a mechanical device (with 8 cohorts) (9;16;17;23;26), and 1 a course of LMWH followed by warfarin (28).

Across all studies and interventions, 6 of 12,013 (0.05%, exact 95% CI 0.02-0.11%) patients died with a confirmed PE (Figure 1). Overall, approximately 13% of the symptomatic, confirmed PEs resulted in death. No PE deaths occurred in 27 of 33 cohorts of patients (**Appendix Figure 7**). The summary estimates of PE deaths for specific interventions were all similar, generally 0.1% or less. The very small number of events precludes an accurate estimate of the PE death rate.

Knee arthroplasty

There were 19 studies that provided sufficient data to estimate rates of death due to confirmed PE with various interventions after knee arthroplasty (11-13;29;33-38;40-48). Two (with 3 cohorts) evaluated aspirin and a mechanical device (36;37), 4 a mechanical device (35;43;44;48), 1 (with 2 cohorts) fondaparinux (11), 9 (with 10 cohorts) LMWH (12;13;29;34;40;42;43;45;48), 3 LMWH with a mechanical device (29;35;44), 5 (with 6 cohorts) warfarin (34;38;41;46;47), and 1 a LMWH or a mechanical device both followed by outpatient warfarin (33).

Across all studies and interventions, 7 of 10,251 (0.07%, exact 95% CI 0.03-0.14%) patients died with a confirmed PE (Figure 2). Overall, approximately 14% of the symptomatic, confirmed PEs resulted in death. No PE deaths occurred in 26 of 31 cohorts of patients (**Appendix Figure 8**). The summary estimates of PE deaths for specific interventions were mostly similar, generally 0.1% or less. However, 3 PE deaths occurred in the small studies of mechanical devices used alone (283 patients in 4 cohorts). The very small number of events precludes an accurate estimate of the PE death rate.

Other events

Hip and knee arthroplasty

Total death rates were reported in 17 studies after hip arthroplasty (**Appendix Figure 9**) (8-10;13-21;25;26;28;30;31) and 15 after knee arthroplasty (**Appendix Figure 10**) (13;15;33-37;40-43;45-48). Rehospitalization for all cause or specifically for thromboembolic events was reported by only 3 studies after hip arthroplasty (18;23;31) and 3 after knee arthroplasty (37;38;48).

The pattern of total death rates across interventions was similar to PE death rates (Figures 1 & 2), with little discernable difference across interventions (except for high rates among the very small number of patients treated with mechanical devices alone after knee arthroplasty). The overall death rate was 0.3% (95% CI 0.2-0.4%, hip and knee arthroplasty combined). The very small number of studies that reported rehospitalization rates precludes a meaningful comparison of interventions. Overall, approximately 0.8% of patients were rehospitalized (45 of 5608 patients) for a thromboembolic event, with a range across studies of 0% to 3.4%.

Major bleeding

Studies used a variety of definitions of major, or clinically significant, bleeding, adding a level of complexity to evaluating bleeding rates across studies. The definitions included such items as a drop in hemoglobin level of 2 g/dL, need for blood transfusion, orthostasis or other clinical symptoms, gastrointestinal bleeding, intracerebral, intraspinal, or retroperitoneal bleeding, or loss of a range of blood volumes. Frequently, the definition of major bleeding was not given. Some studies also only reported specific incidents of bleeding episodes, though too rarely to provide adequate estimates of rates. It is likely that the different definitions used accounts for a large part of the heterogeneity of bleeding rates across studies.

Hip arthroplasty

Major bleeding was reported in 18 studies of prophylaxis after hip arthroplasty (**Appendix Figure 11**) (8-10;13-21;25;26;28;30;31). One study evaluated combination aspirin and a mechanical device (22), 1 study evaluated a mechanical device alone (24), 2 fondaparinux (21;30), 15 (with 18 cohorts) LMWH (8;12-14;16-18;20;21;25;28-31), 4 (with 5 cohorts) warfarin with or without a mechanical device (9;16;17;26), and 1 a course of LMWH followed by warfarin (28).

No major bleeding occurred in the 287 patients who received only aspirin or a mechanical device (exact 95% CI 0-1.3%). The summary estimates of major bleeding rates were similar for the different systemic interventions (Figure 3), with a total of 297 events in 11,046 patients (random effects model summary estimate 2.0%, 95% CI 1.4-2.9%); the numbers of events per study were deemed to be sufficiently great to allow more reliable meta-analysis.

Knee arthroplasty

Major bleeding was reported in 14 studies of prophylaxis after knee arthroplasty (**Appendix Figure 12**) (12;13;15;33-35;39;41;42;45-49). One study evaluated combination aspirin and a mechanical device (39), 3 a mechanical device alone (33;35;48), none fondaparinux, 11 (with 13 cohorts) LMWH with or without a mechanical device (12;13;15;33-35;39;42;45;48;49), and 4 warfarin (34;41;46;47).

Major bleeding occurred in 1 of 410 patients who a mechanical device with or without aspirin (0.2%, exact 95% CI 0.04-1.4%). The summary estimates of the major bleeding rates were broadly similar for the different systemic interventions, with a total of 53 of 4,044 patients (random effects model summary estimate 1.6%, 95% CI 1.0-2.5%).

Death due to bleeding

Hip and knee arthroplasty

Bleeding death rates were reported in 20 studies after hip arthroplasty (**Appendix Figure 13**) (8-18;21;22;24-26;28;30;31;49) and 17 after knee arthroplasty (**Appendix Figure 14**) (11-13;15;33-35;37;38;41-43;45-49).

Death from bleeding was reported only among patients who received either LMWH or LMWH followed by warfarin after hip arthroplasty. However, since the largest numbers of patients and studies were in this category, there is inadequate evidence to suggest that death from bleeding is more common in hip patients receiving LMWH. Overall, 7 of 22,012 (0.03%, exact 95% CI 0.02-0.07%) patients died of major bleeding after arthroplasty.

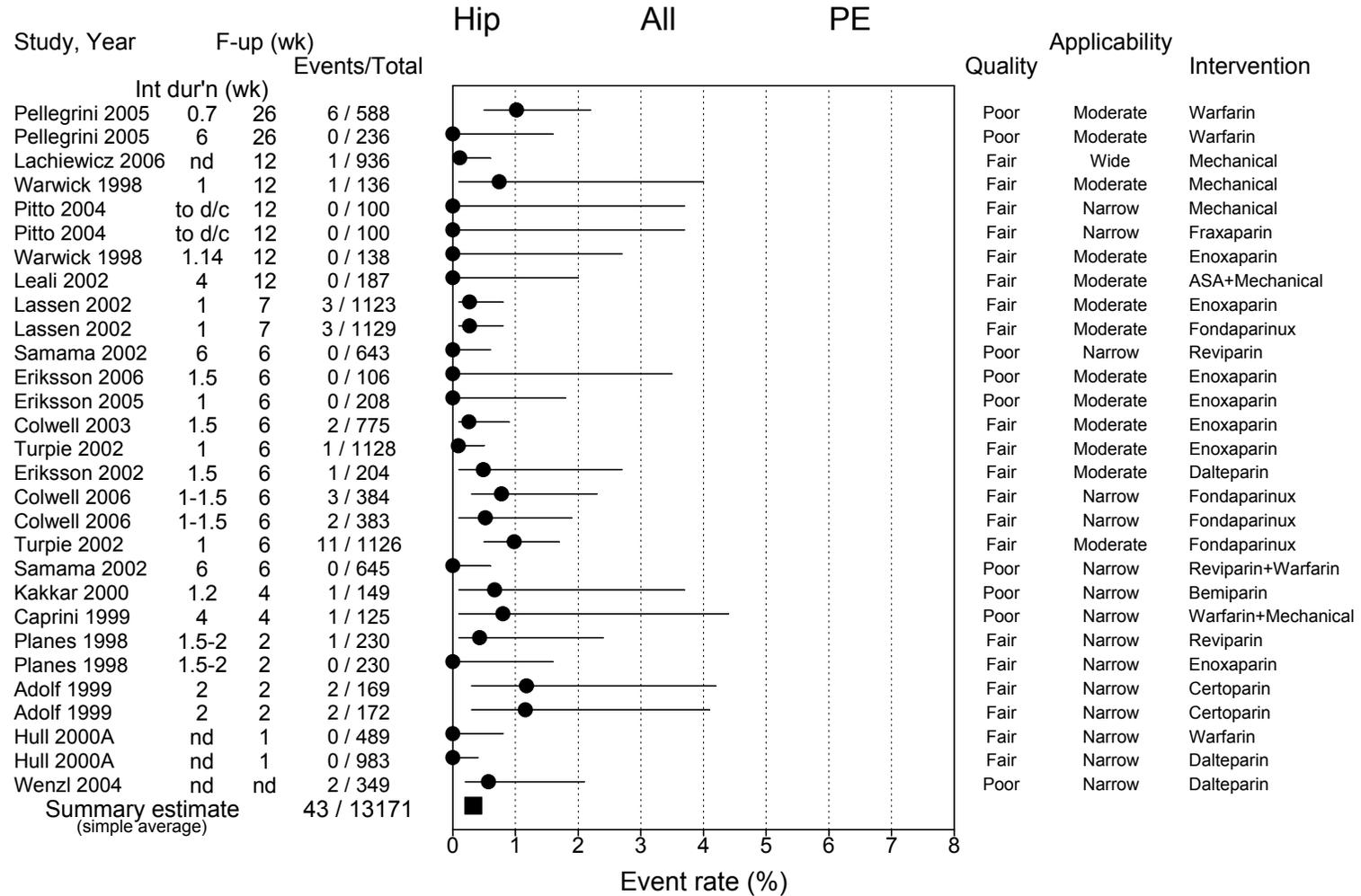
Conclusion

There were major limitations to the body of evidence, including large clinical heterogeneity in the interventions, other related procedures and cointerventions, doses, study populations, follow-up times, and in the case of major bleeding, definitions. In addition, none of the studies was designed to investigate PE as a primary outcome. Reporting of PE-related events was frequently incomplete and vague. Commonly, it was not clear how many patients were evaluated for each outcome. Overall, the numbers of patients within each study were inadequate to properly estimate the event rates of interest. Because the event rates were frequently either zero or close to zero, combining data across studies had limitations. We investigated 4 different methods of combining rates, but relied primarily on the simple pooled average (sum of events over sum of patients) as this method appeared to provide the most logical estimates, though narrow confidence intervals. Even if these limitations could have been better overcome, the evidence would still be very limited due to the near lack of direct comparisons within studies. Thus, all evaluations were based on indirect comparisons across different arms (cohorts) of different studies, a less reliable analysis than direct comparisons (e.g., randomized trials).

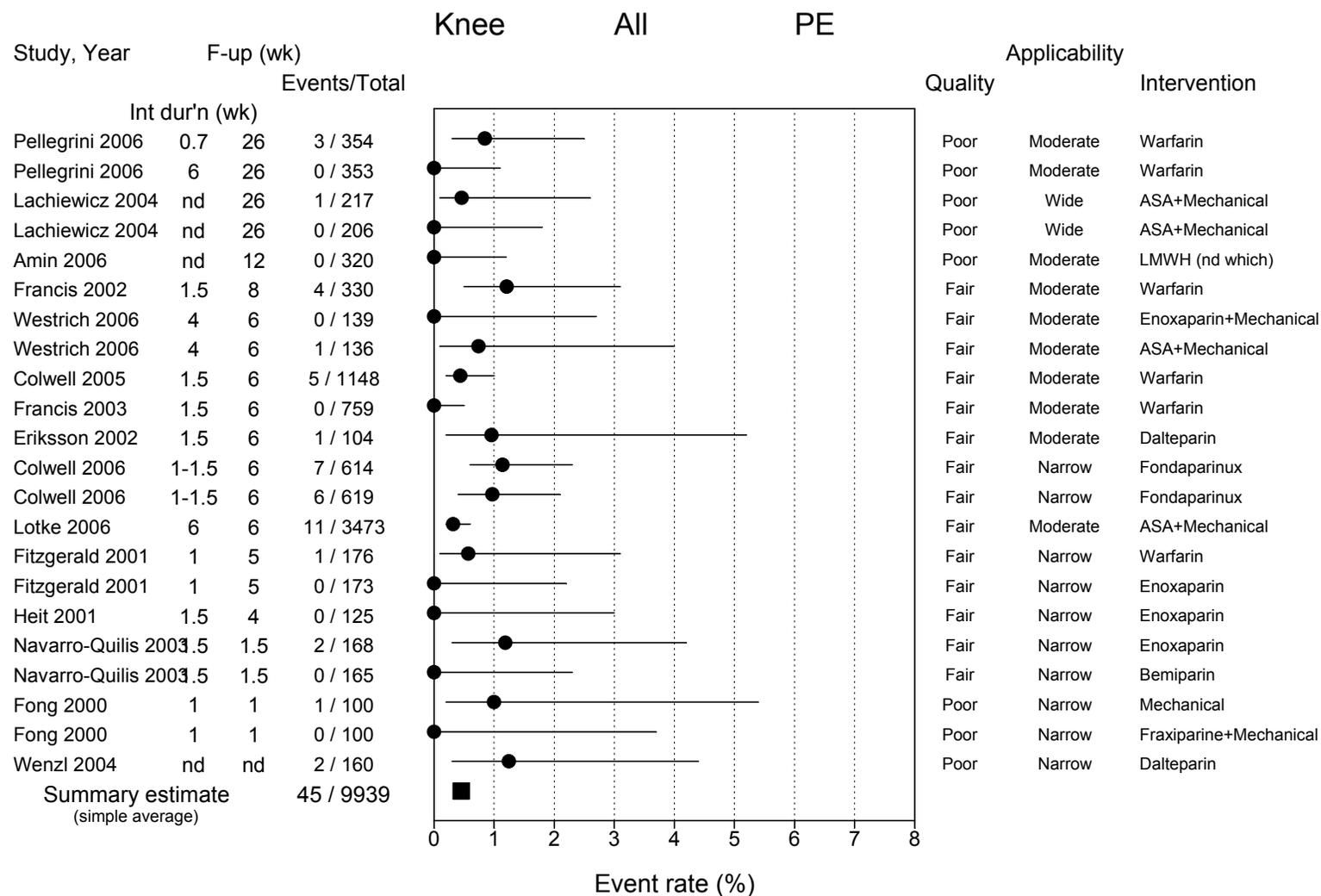
It is also important to note that the number of studies and patients evaluated were restricted by several decisions made regarding the eligibility criteria, including restriction to prospective studies (greatly reducing the number of patients evaluated, but avoiding the numerous biases and lack of pre-defined interventions of retrospective studies), study size restrictions (which greatly reduced the number of studies, but did not greatly reduce the number of subjects or events), and restriction to patients operated on since 1996. A large number of studies were not included because of this last restriction. However, the consensus among the Work Group was that surgical techniques and post-operative care have changed sufficiently since 1996. They agreed that estimates of PE and bleeding rates from older studies would not be accurate for contemporary patients. It was acknowledged though, that the specific choice of 1996 was somewhat arbitrary.

The available evidence shows no differences among the interventions in rates of PE, PE-related death, total death, major bleeding, bleeding-related death, or rehospitalization. This lack of adequate evidence holds true for the broader comparison of systemic interventions (fondaparinux, LMWH, and warfarin) and mechanical devices or aspirin alone. Except to note that major bleeding was very rare among patients receiving aspirin or mechanical devices alone (1 case in 697, or 0.14%, exact 95% CI 0.03-0.8%) compared to those who received systemic interventions (random effects model summary estimate 1.8%, 95% CI 1.4-2.5%). Because of the limitations and the overall relatively small number of patients evaluated (given the rarity of PE after arthroplasty), only approximate estimates of event rates can be surmised from the evaluated evidence.

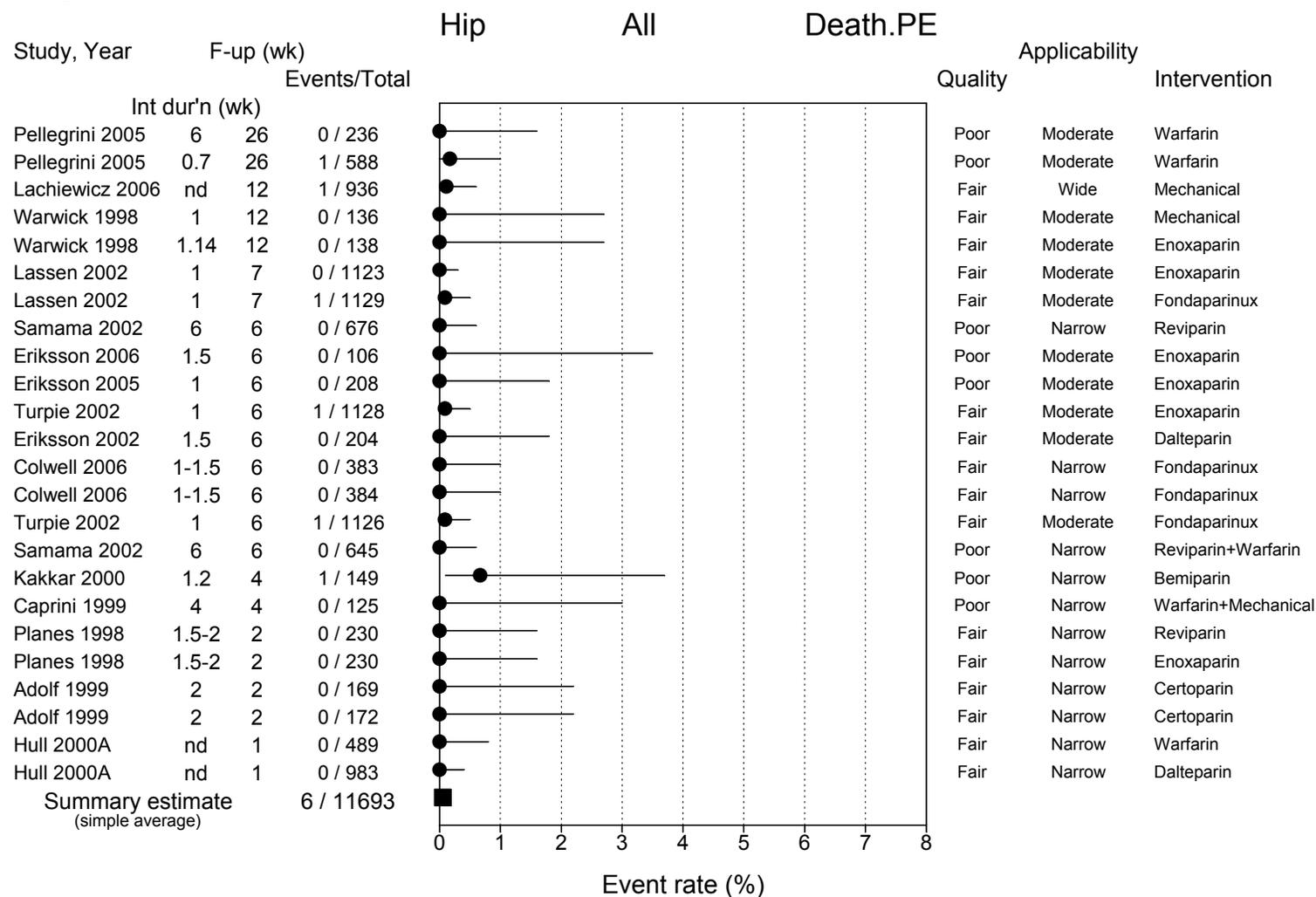
Appendix Figure 5. Rates of pulmonary embolism in cohorts of patients receiving mechanical or chemoprophylaxis after hip arthroplasty.



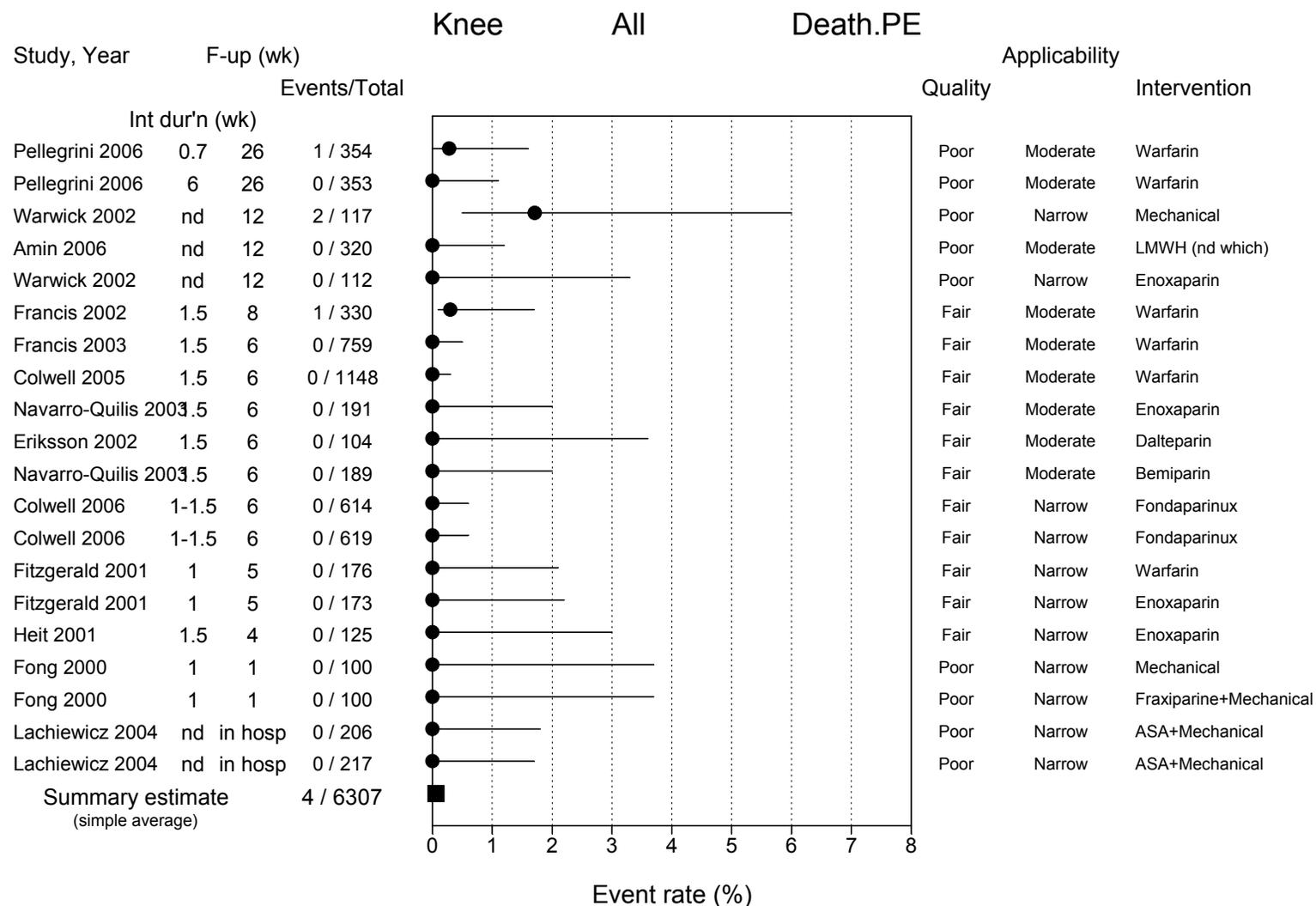
Appendix Figure 6. Rates of pulmonary embolism in cohorts of patients receiving mechanical or chemoprophylaxis after knee arthroplasty.



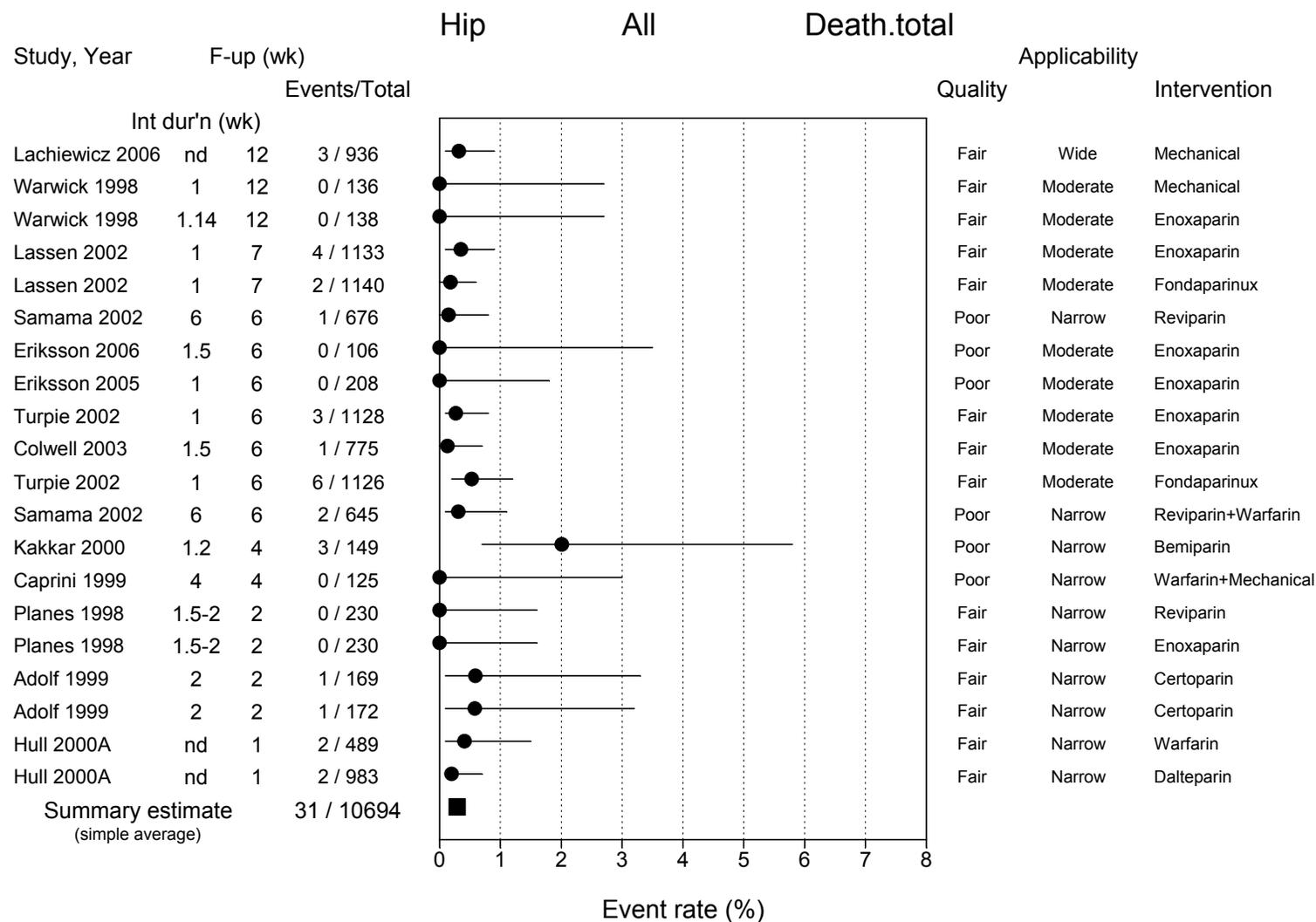
Appendix Figure 7. Rates of death from pulmonary embolism in cohorts of patients receiving mechanical or chemoprophylaxis after hip arthroplasty.



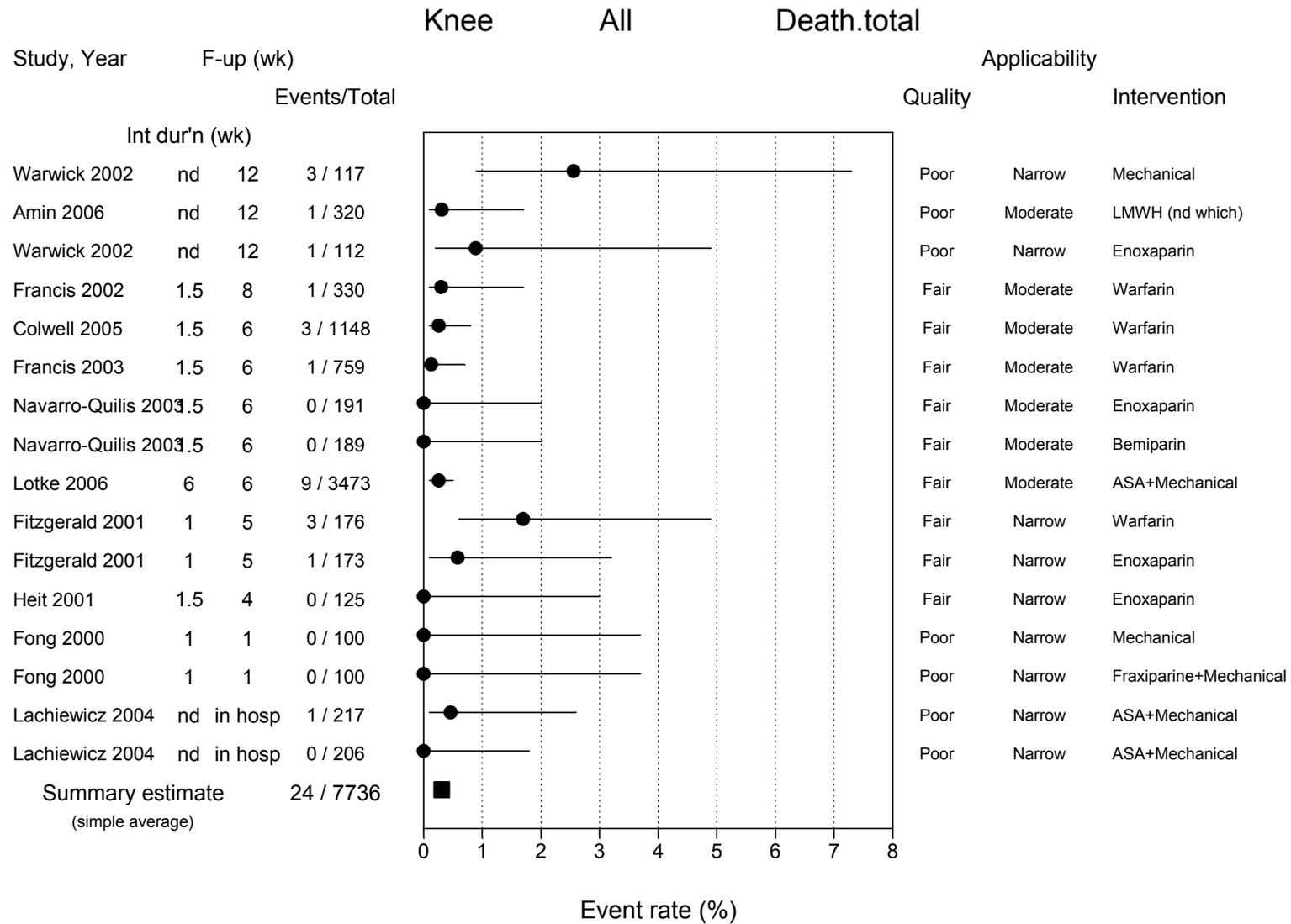
Appendix Figure 8. Rates of death from pulmonary embolism in cohorts of patients receiving mechanical or chemoprophylaxis after knee arthroplasty.



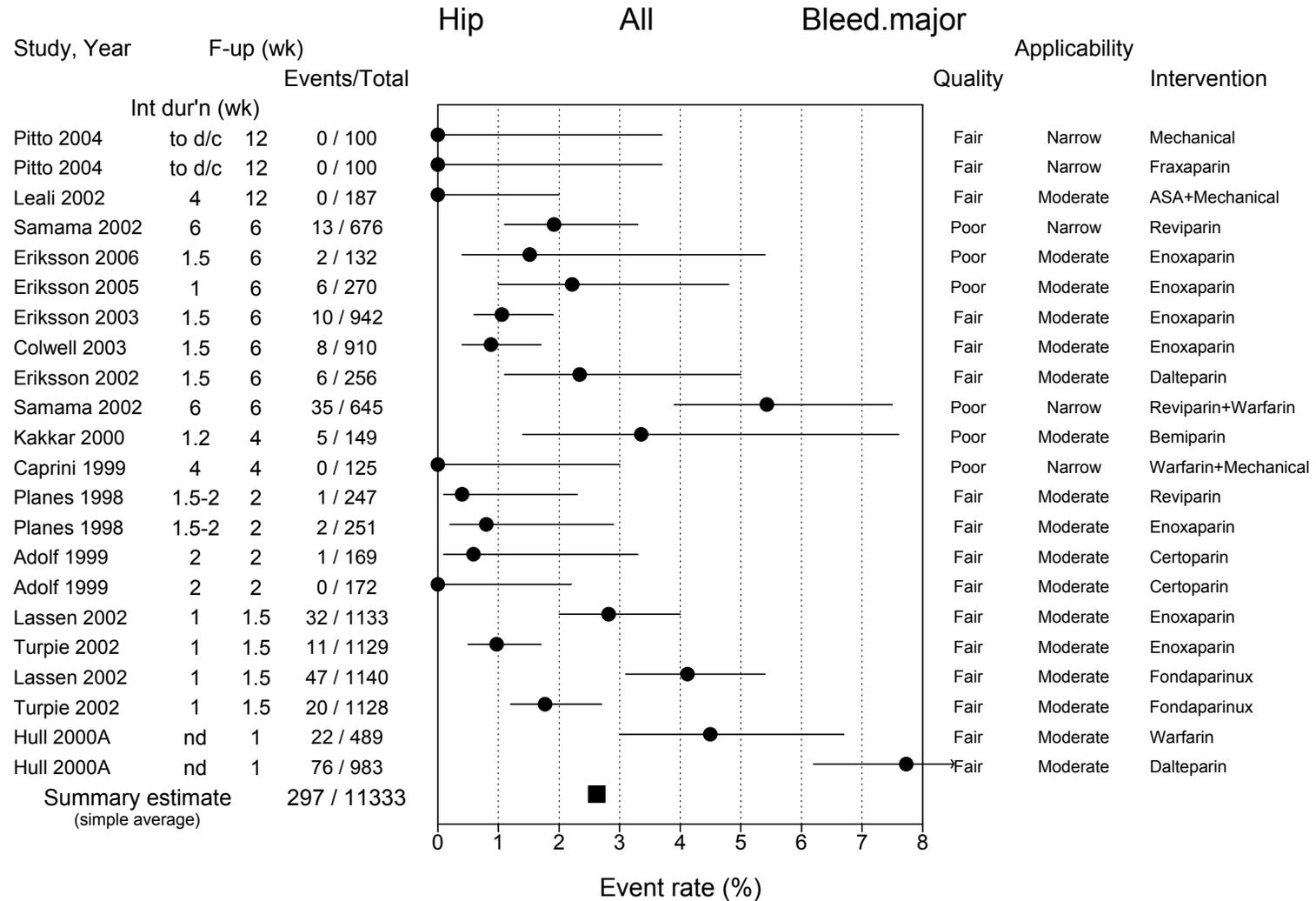
Appendix Figure 9. Rates of death (all cause) in cohorts of patients receiving mechanical or chemoprophylaxis after hip arthroplasty.



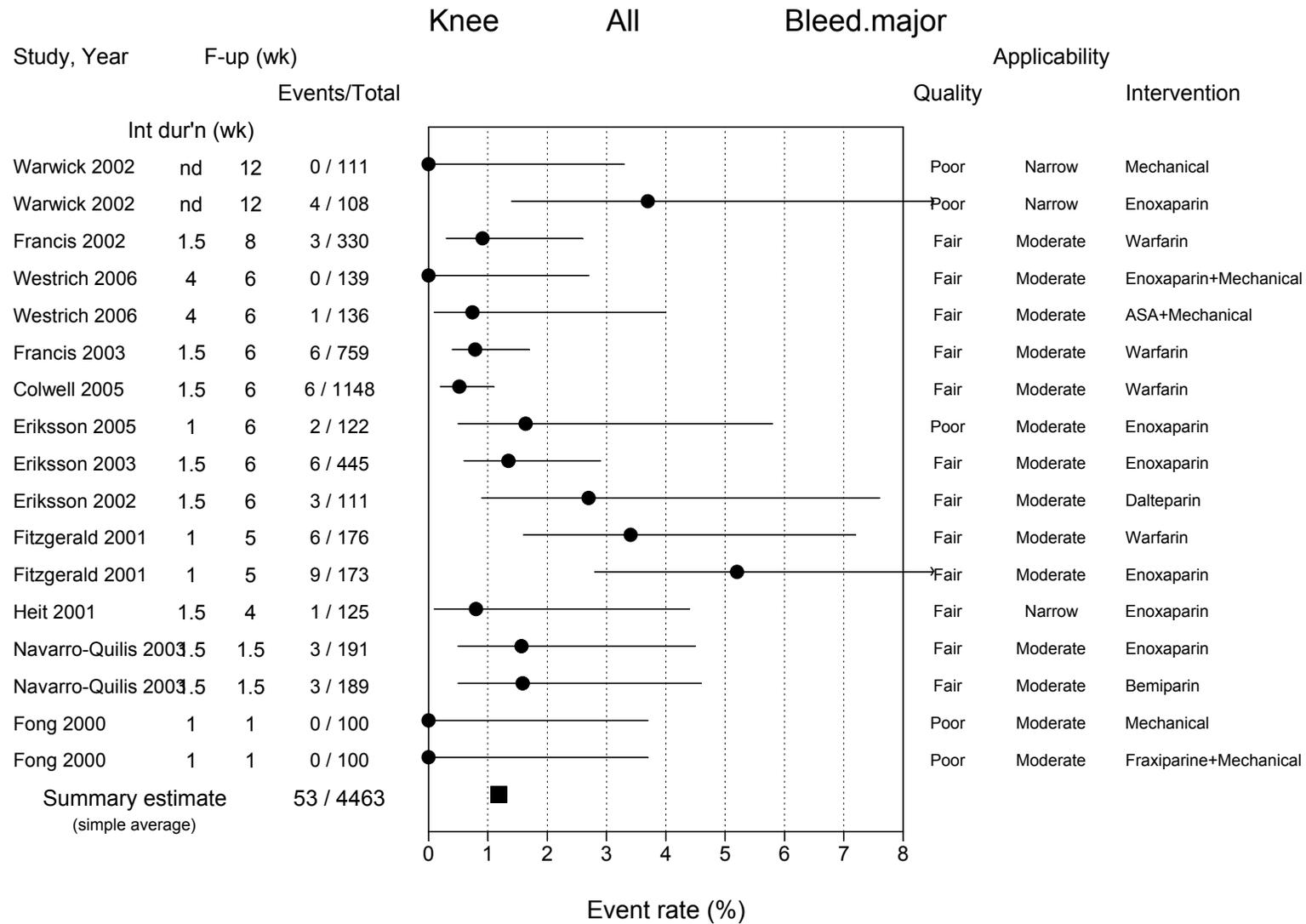
Appendix Figure 10. Rates of death (all cause) in cohorts of patients receiving mechanical or chemoprophylaxis after knee arthroplasty.



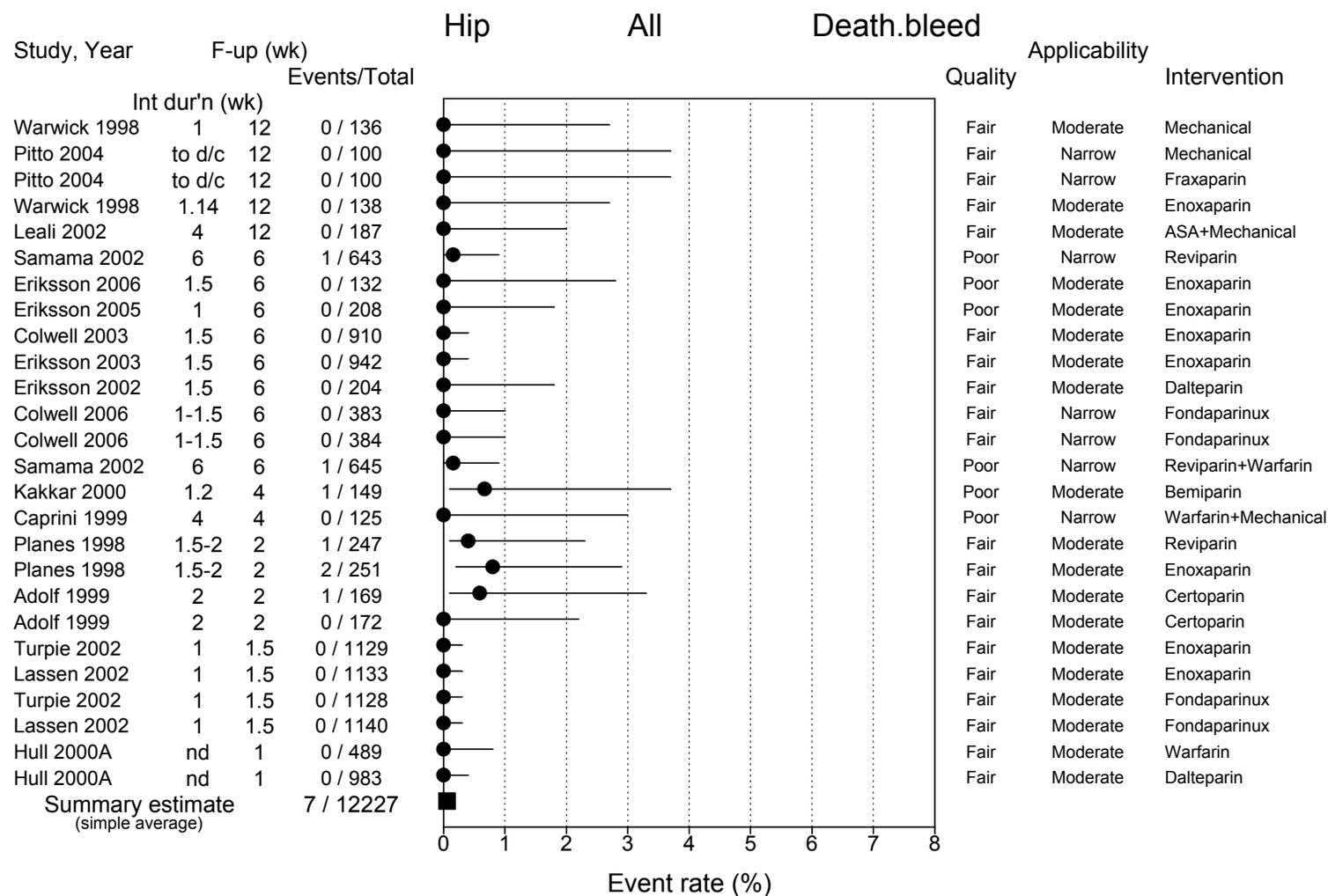
Appendix Figure 11. Rates of major bleeding in cohorts of patients receiving mechanical or chemoprophylaxis after hip arthroplasty.



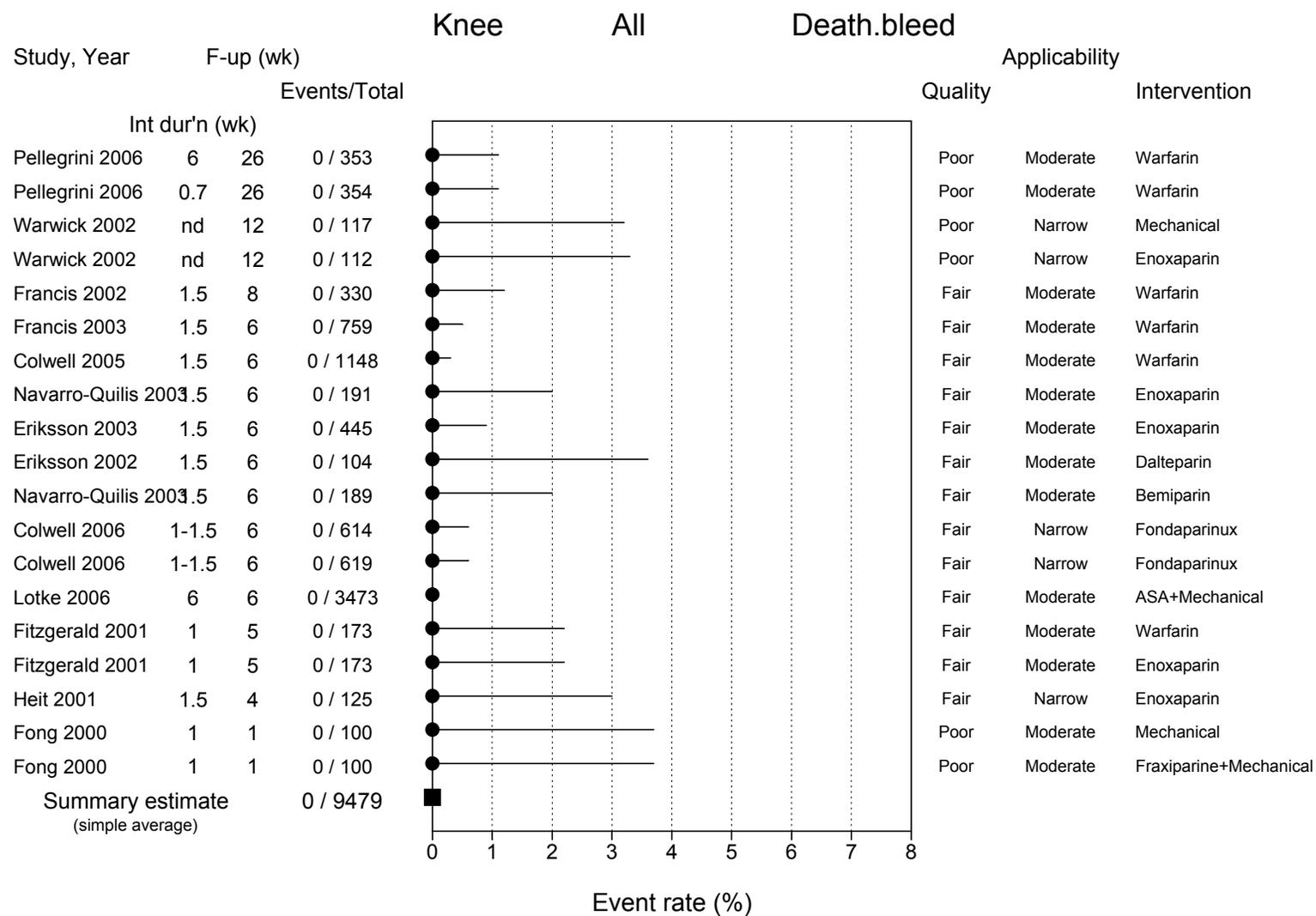
Appendix Figure 12. Rates of major bleeding in cohorts of patients receiving mechanical or chemoprophylaxis after knee arthroplasty.



Appendix Figure 13. Rates of death from major bleeding in cohorts of patients receiving mechanical or chemoprophylaxis after hip arthroplasty.



Appendix Figure 14. Rates of death from major bleeding in cohorts of patients receiving mechanical or chemoprophylaxis after knee arthroplasty.



Appendix IV: Evidence Tables

Appendix V: Summary Tables

Appendix VI: Conflicts of Interest

Dr. P. Lotke disclosed that he received an institutional research grant from DePuy/Johnson and Johnson from 1998-2003. No other members of the panel declared any conflict of interest.

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