

TABLE E-1 Incidence of Postoperative VTE Events and Major Bleeding*				
Outcome	Total Hip Arthroplasty		Total Knee Arthroplasty	
	LMWH	ASA	LMWH	ASA
Symptomatic DVT	0.011	0.017	0.024	0.038
Symptomatic PE	0.0032	0.0051	0.0069	0.0109
Asymptomatic DVT	0.11	0.16	0.35	0.51
Bleeding at operative site	0.0292	0.0213	0.0292	0.0213
Bleeding at nonoperative site	0.0133	0.0097	0.0133	0.0097

*VTE = venous thromboembolism, LMWH = low-molecular-weight heparin, DVT = deep vein thrombosis, PE = pulmonary embolism, and ASA = aspirin (acetylsalicylic acid).

TABLE E-2 Estimated Prevalence of Prior Symptomatic Venous Thromboembolism at Each Starting Age			
Age (yr)	Prevalence in Women	Prevalence in Men	Overall Prevalence
55	0.016	0.015	0.018
60	0.023	0.021	0.025
65	0.032	0.029	0.035
70	0.044	0.040	0.048
75	0.057	0.053	0.063
80	0.071	0.065	0.078
85	0.084	0.077	0.092

TABLE E-3 Distributions for Probabilistic Sensitivity Analyses			
Parameter*	Distribution Type	Mean	Variation
Rates of symptomatic VTE	Normal	Base case	Standard deviation 18% of mean
Rate of asymptomatic DVT	Normal	Base case	Standard deviation 3% of mean
Rate of PPS following symptomatic VTE	Normal	Base case	Standard deviation 5% of mean
Rate of PPS following asymptomatic DVT	Uniform	Base case	50% to 150% of base case value
Risk of bleeding at operative site	Normal	Base Case	Standard deviation 7% of mean
Risk of bleeding at nonoperative site	Normal	Base Case	Standard deviation 10% of mean
Costs of VTE events	Triangular	Base Case	50% to 150% of base case value
Costs of bleeding events	Triangular	Base Case	50% to 150% of base case value
Costs of PPS	Triangular	Base Case	50% to 150% of base case value
Disutility of VTE events	Triangular	Base Case	50% to 150% of base case value
Disutility of PPS	Triangular	Base Case	50% to 150% of base case value
Disutility of bleeding events	Triangular	Base Case	50% to 150% of base case value
Relative risk of symptomatic VTE aspirin versus LMWH	Log-normal	0.457425	Standard deviation 0.128712
Relative risk of asymptomatic DVT aspirin versus LMWH	Log-normal	0.371564	Standard deviation 0.085782
Relative risk of bleeding aspirin versus LMWH	Log-normal	-0.316082	Standard deviation 0.058041

*VTE = venous thromboembolism, DVT = deep vein thrombosis, PE = pulmonary embolism, PPS = postphlebotic syndrome, LMWH = low-molecular-weight heparin.

TABLE E-4 Model Validation		
Outcome*	Literature Value (Source)	Model Prediction
Postoperative symptomatic DVT following THA	0.0078 (Januel et al. ²)	0.0082
Postoperative symptomatic PE following THA	0.0028 (Januel et al. ²)	0.0027
Postoperative symptomatic DVT following TKA	0.0164	0.165
Postoperative symptomatic PE following TKA	0.0054	0.0056
Major bleeding at operative site	0.0292 (Brown ¹)	0.0292
Major bleeding at nonoperative site	0.0133 (Brown ¹)	0.0122
Proportion of patients with symptomatic VTE who develop PPS	0.160 (Mohr et al. ³¹)	0.154

*DVT = deep vein thrombosis, THA = total hip arthroplasty, TKA = total knee arthroplasty, PE = pulmonary embolism, VTE = venous thromboembolism, and PPS = postphlebotic syndrome.

TABLE E-5 Results of Primary versus Expanded Models (Costs per QALY Gained with LMWH Versus Aspirin)*				
Age (yr)	Total Hip Arthroplasty		Total Knee Arthroplasty	
	Primary Model	Expanded Model	Primary Model	Expanded Model
55	\$315,410	\$301,258	\$35,997	\$34,984
60	\$441,881	\$420,254	\$50,693	\$49,432
65	\$691,641	\$652,320	\$73,527	\$71,878
70	\$1,387,029	\$1,278,902	\$112,085	\$109,785
75	\$4,859,376	\$4,071,635	\$174,915	\$171,621
80	Aspirin dominant	Aspirin dominant	\$278,256	\$273,611
85	Aspirin dominant	Aspirin dominant	\$447,992	\$442,152

*QALY = quality-adjusted life-year, and LMWH = low-molecular-weight heparin.

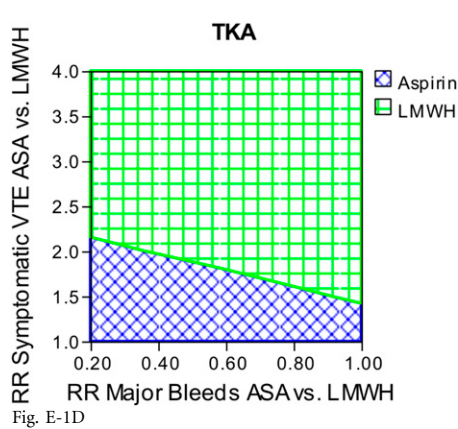
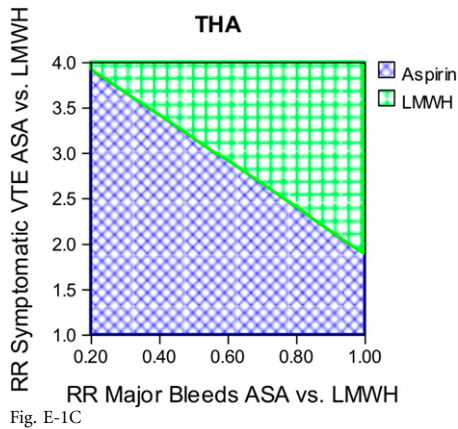
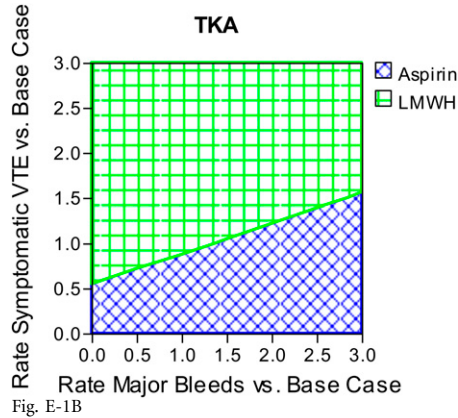
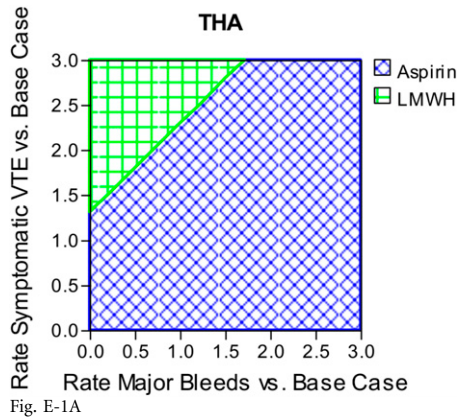


Fig. E-1A Two-way sensitivity analysis (a sixty-five-year old patient with no history of venous thromboembolism [VTE] events): the preferred agent according to the rates of VTE events and major bleeding episodes compared with the base case, following total hip arthroplasty (THA). LMWH = low-molecular-weight heparin. **Fig. E-1B** Two-way sensitivity analysis (a sixty-five-year old patient with no history of venous thromboembolism [VTE] events): the preferred agent according to the rates of VTE events and major bleeding episodes compared with the base case, following total knee arthroplasty (TKA). LMWH = low-molecular-weight heparin. **Fig. E-1C** Two-way sensitivity analysis (a sixty-five-year old patient with no history of venous thromboembolism [VTE] events): the preferred agent according to the relative risks (RR) of VTE events and major bleeding episodes on aspirin (ASA; acetylsalicylic acid) compared with low-molecular-weight heparin (LMWH), following total hip arthroplasty (THA). **Fig. E-1D** Two-way sensitivity analysis (a sixty-five-year old patient with no history of venous thromboembolism [VTE] events): the preferred agent according to the relative risks (RR) of VTE events and major bleeding episodes on aspirin (ASA; acetylsalicylic acid) compared with low-molecular-weight heparin (LMWH), following total knee arthroplasty (TKA).

Technical Supplement: Cost-Effectiveness of LMWH Versus Aspirin for Prophylaxis Against Venous Thromboembolism After Total Joint Arthroplasty

Introduction

This supplement provides in substantial detail the structure of the cost-effectiveness model we have used to address the research questions regarding the cost-effectiveness of various forms of anticoagulation following total hip or knee arthroplasty. The model has been constructed primarily to compare low-molecular-weight heparin (LMWH) and aspirin (161 mg per day) for fourteen days following total hip or knee replacement surgery, with half of the days (mean, 7.5 days) part of the in-hospital stay during which the total joint replacement is performed¹. However, this model can be adapted to address the cost-effectiveness of other anticoagulant therapies, longer periods of postoperative anticoagulation, and the cost-effectiveness of different venous thromboembolism (VTE) strategies for patients undergoing surgical fixation of a hip fracture.

Model Structure

We constructed a Markov cohort model with a lifetime horizon, since some possible outcomes related to joint replacement or surgical repair of hip fracture (most notably postphlebotic syndrome) can have lifelong consequences. Many of the complications of these surgical procedures are short-term, self-limited events that do not have long-term effects on costs or quality of life. Other longer-term complications are not immediately apparent after surgery but emerge over the following few years (such as postphlebotic syndrome following asymptomatic VTE events). To capture the costs and loss of quality of life from one-time immediate postoperative events, from events that emerge gradually over time following surgery, and from chronic postoperative states, our model was constructed with the following features:

- An initial state for the first month after surgery.
- Transition costs and loss of quality of life for those experiencing one-time complications from surgery (minor bleeding, major operative site bleeding, major nonoperative site bleeding, deep vein thrombosis [DVT], pulmonary embolism [PE], and thrombocytopenia related to the use of LMWH).
- Transition to the healthy state for those who experience one-time events of non-intracranial bleeding or thrombocytopenia associated with use of LMWH.
- Transition out of the healthy state for those proportions in the health state postoperatively who develop postphlebotic syndrome attributable to asymptomatic VTE events.
- Transition to other chronic health states for events associated with ongoing costs or chronic loss of quality of life: post-intracranial hemorrhage, post-VTE events without postphlebotic syndrome, and post-VTE with postphlebotic syndrome.

For our primary analyses, we did not consider outcomes such as chronic thromboembolic pulmonary hypertension (CTPH) and periprosthetic joint infection associated with postoperative intra-articular hemorrhage. We did sensitivity analyses with an expanded model including these states that are described at the end of this document.

Patients in the initial surgical state can have an uneventful recovery to the healthy state, can develop symptomatic DVT, symptomatic PE, major operative site bleeding, major nonoperative site bleeding that is either intracranial or extracranial, minor postoperative bleeding, or thrombocytopenia. Those who develop a symptomatic PE postoperatively can die from the event, and there is a small risk of death from background all-cause mortality from the initial surgical state as well. Those who have a postoperative intracranial hemorrhage can die from that event or transition to the post-intracranial hemorrhage state.

Those in the healthy state after the first half-cycle of six weeks include a minority who had an asymptomatic postoperative VTE event. Some of these individuals will develop postphlebotic syndrome over the subsequent five years and will then transition to the post-VTE with postphlebotic syndrome state. Importantly, asymptomatic VTE otherwise is not considered to be associated with costs or disutility, and therefore is not considered in the model. Those in the healthy state can otherwise stay healthy or die from background causes.

Those in the post-VTE state without postphlebotic syndrome are at higher risk of developing a recurrent VTE event and/or postphlebotic syndrome than those who have had an asymptomatic VTE event. Hence, individuals in this state can stay healthy, can develop a recurrent VTE event and stay in the same state, can develop postphlebotic syndrome and transition to the post-VTE with postphlebotic syndrome state, or die from either recurrent PE or background causes.

Those in the post-VTE state with postphlebotic syndrome have some chronic loss of quality of life from postphlebotic syndrome, and hence a separate state is needed to capture this. These individuals can stay healthy, develop recurrent VTE event, or die from either recurrent PE or background causes. Survivors of intracranial hemorrhage have seriously compromised quality of life, and hence a separate state is needed to capture that disutility. Individuals can stay in that state or die of background causes.

The model has a cycle length of one month. While some transition probabilities change according to the number of years after the start of the model, no transition probabilities are altered according to any tracker variables. Hence, this model can be run as a Markov cohort process, and does not require Monte-Carlo microsimulations for the base case, secondary, univariate, or bivariate sensitivity analyses. This was considered to be very important to allow us to do threshold univariate and bivariate sensitivity analyses.

Rates of Clinical Events

Rates of Symptomatic DVT, PE, and Major Bleeding on LMWH Following Total Joint Arthroplasty

Januel et al. recently published a comprehensive meta-analysis of randomized controlled trials and observational studies of those undergoing total or partial knee or hip arthroplasty in order to estimate the absolute incidence of symptomatic VTE following both procedures, while being treated prophylactically with LMWH, direct Xa or IIa factor inhibitors, or indirect Xa or IIa factor inhibitors². Following total hip arthroplasty, the authors estimated the symptomatic VTE cumulative incidence to be 0.53%, and the cumulative incidence specifically of symptomatic PE to be 0.14%. Similarly, following total knee arthroplasty, the authors estimated the total symptomatic VTE cumulative incidence to be 1.09%, and the cumulative incidence specifically of symptomatic PE to be 0.27%, while being treated with LMWH, direct Xa or IIa factor inhibitors, or indirect Xa or IIa factor inhibitors. However, a substantial proportion of VTE events after total joint arthroplasty occur after discharge³. In a systematic review of all randomized controlled trials of anticoagulation strategies following total hip or knee arthroplasty or surgical treatment of hip fracture, the mean length of stay among 6050 patients receiving total hip arthroplasty and 2306 patients receiving total knee arthroplasty was 7.57 days⁴⁻¹⁵. We modeled fourteen days of treatment with either LMWH or low-dose aspirin, and hence estimated the cumulative incidence of symptomatic VTE events to be twice the estimates of Januel et al.: 1.06% following total hip arthroplasty (0.28% for PE and 0.78% for symptomatic DVT) and 2.18% (0.54% for PE and 1.64% for symptomatic DVT) following total knee arthroplasty. Consistent with these estimates, other studies have noted relative risks of VTE following total knee arthroplasty versus total hip arthroplasty of 1.4 to 2.4¹⁶⁻¹⁸.

In the systematic review by Brown, the proportion of all patients whose surgical procedure could be identified to be a total knee arthroplasty was 29.3%¹. A positive ultrasound or venogram for asymptomatic DVT was 3.3 times more likely in those undergoing total knee arthroplasty compared with total hip arthroplasty. The overall proportion of patients with a positive test for DVT on LMWH was 17.9%. Therefore, we estimated the incidence of asymptomatic DVT on LMWH to be 11% following total hip arthroplasty (THA) and 35% following total knee arthroplasty (TKA) (Table E-1) by the following formulae:

$$\text{Incidence of asymptomatic DVT (THA)} = 0.179 / (1 + [3.3 - 1] * 0.293) = 0.11$$

$$\text{Incidence of asymptomatic DVT (TKA)} = 3.3 * 0.179 / (1 + [3.3 - 1] * 0.293) = 0.35$$

Brown also estimated the proportions of individuals experiencing operative site and nonoperative site major bleeding following total joint arthroplasty, which were, respectively, 2.92% and 1.33% during hospitalization¹.

Rates of VTE Events and Major Bleeding on Aspirin Compared with LMWH

Unfortunately, to our knowledge, there have been no randomized controlled trials nor any high-quality observational studies comparing the incidence of DVT and PE following total joint arthroplasty on aspirin compared with LMWH. There are published data comparing the incidence of thromboembolic events on LMWH with a placebo and other data comparing aspirin and placebo following total joint arthroplasty. Therefore, in order to calculate relative risks of VTE (and bleeding) events on aspirin compared with LMWH, the relative risks of these events on aspirin versus placebo were divided by the relative risks of these events on LMWH versus placebo.

Our main source for the risks of symptomatic DVT (with or without PE), symptomatic PE, asymptomatic DVT, and major bleeding events on LMWH compared with placebo is the large set of meta-analyses performed by the Royal College of Surgeons¹⁹. The relative risks of symptomatic PE and proximal DVT on LMWH compared with placebo were estimated to be, respectively, 0.36 and 0.38, on the basis of thirteen separate studies.

The meta-analysis by the Royal College of Surgeons also compared aspirin with placebo, but did not segregate the outcomes into the three categories of VTE events noted above. Because the disutility, costs, and risk of subsequent postphlebotic syndrome are different among asymptomatic versus symptomatic types of VTE events, we believed it is important to estimate relative risks for these three types of events on aspirin versus LMWH. Data on the relative risks of these specific end points on aspirin prophylaxis compared with placebo are available from the PEP (Pulmonary Embolism Prevention) trial, a randomized controlled trial of aspirin (161 mg daily) versus placebo following surgical repair of hip fracture, elective total hip arthroplasty, or elective total knee arthroplasty²⁰. The relative risk of symptomatic PE and/or DVT on aspirin versus placebo through the first two weeks of the PEP trial was 0.67²⁰. Hence, the relative risks of DVT (symptomatic and asymptomatic) and symptomatic PE and of DVT on aspirin versus LMWH are calculated to be, respectively, 1.76 and 1.86.

The risk of major bleeding on aspirin versus placebo alone in the PEP trial was 1.06, and was not significantly different from 1.0. However, the Royal College of Surgeons estimated the risks of major bleeding following total joint arthroplasty on aspirin versus placebo and LMWH versus placebo to be, respectively, 1.29 and 1.77¹⁹. For our primary analyses, we assumed the risk of major bleeding on aspirin versus placebo to be 1.29, and therefore the risk of major bleeding on aspirin versus LMWH to be 0.729 (1.29 divided by 1.77).

Proportion of Nonoperative Site Bleeding Episodes That Are Intracranial

Because intracranial hemorrhage and fatal bleeding after total joint arthroplasty are relatively rare events, the observational studies and randomized controlled trials of anticoagulation following total joint arthroplasty cannot provide a satisfactory estimate of these events. Moreover, there are no published estimates of the proportion of major bleeding episodes that are intracranial with use of LMWH in other clinical circumstances. Hence, we are basing our estimates on the meta-analysis of Linkins et al., who evaluated the incidence of major hemorrhage, intracranial hemorrhage, and fatal hemorrhage on full-dose oral anticoagulation²¹. Among 2422 patients receiving anticoagulation therapy, fifty-four individuals had a major bleeding episode (a rate of 2.06 per 100 patient-years) within the first three months of therapy, and four (7.4%) of them had intracranial hemorrhage.

Our calculated proportion of all patients undergoing total joint arthroplasty who have a fatal hemorrhage at a nonoperative site while on LMWH = $0.0133 \times 0.093 = 0.00124$, and the rate of those who have an intracranial hemorrhage is $0.0133 \times 4/54 = 0.00098$. The latter figure is modestly below the rate reported in Linkins et al. (1.48 per 100 patient-years or 0.00123 per patient-month). We assumed no mortality related to major bleeding at the operative site.

We assumed no association of bleeding risk with age while on anticoagulation in this study. In a large cohort of 13,559 individuals with atrial fibrillation either treated with warfarin therapy or not treated with warfarin, Singer et al. found that, among this cohort, age was not associated with an increased risk of intracranial hemorrhage while taking warfarin²².

Risks of Mortality

Mortality rates for men and women were taken from U.S. vital statistics for 2004²³. The proportion of those with an acute PE who die from that event was assumed to be 15% (10% within the first hour of presentation and an additional 5% after that)²⁴.

Estimates of in-hospital mortality rates following intracranial hemorrhage have ranged from 25.5% to 45.7%²⁵⁻²⁷; we assumed the case fatality rate for intracranial hemorrhage to be 25.5%, derived from the one study of U.S. Medicare beneficiaries²⁷. The case fatality rate during the first three months among those who had a major hemorrhage that was not intracranial during the first three months of warfarin therapy was 6% among 10,757 individuals treated with warfarin²¹.

Proportion of Operative Site Bleeding Episodes That Require Surgical Intervention

According to Vera-Llonch et al., in a study of 16,970 patients undergoing total hip or total knee arthroplasty (in a private insurance claims database), 433 (2.55%) had major in-hospital bleeding; of these, 126 (29.1%) required reoperation²⁸. However, according to Brown, 68.7% of all major bleeding episodes are at the operative site. Hence, of all operative site bleeding episodes, we estimated that 42.4% (0.291 of 0.687) require reoperation.

Risks of Recurrent DVT or PE Following an Initial Postoperative VTE Event

The risk of recurrent VTE events as a function of time following an initial VTE event was estimated from population-based Rochester Epidemiology Project data²⁹. A look-up table was constructed as a function of time since the initial VTE event such that the cumulative incidence of a recurrent VTE would be 13%, 23%, and 30%, respectively, at one, five, and ten years after the initial VTE event. If a recurrent VTE event occurred, the individual would be at high risk yet again for recurrence, following the same decrement of risk with follow-up time after the last recurrence. After ten years without a recurrence, the rate of VTE events would be the same as the rate of an initial VTE event in the general population. Of all symptomatic recurrent VTE events in the Rochester Epidemiology Project population, 41% were isolated DVT and 59% were PE with or without DVT. We assumed those same proportions in our model.

The rate of initial DVT or PE with or without DVT as a function of age was also derived from Rochester Epidemiology Project data³⁰. In this instance, we were able to fit the Rochester data to polynomial equations with R² values of >0.91:

$$Rate_{DVT} = 0.0014644 - 0.0000804 * age + 1.29 * (10^{\wedge} - 6) * (age^{\wedge}2) - 1.27 * (10^{\wedge} - 9) * (age^{\wedge}3)$$

$$Rate_{PE+DVT} = 0.0000366 * age - 1.83 * (10^{\wedge} - 6) * (age^{\wedge}2) + 2.43 * (10^{\wedge} - 8) * (age^{\wedge}3)$$

Risks of Postphlebotic Syndrome Following Symptomatic and Asymptomatic VTE Events

Rates of postphlebotic syndrome were also derived from the population-based Rochester Epidemiology Project³¹. A look-up table for rates as a function of time since an initial symptomatic venous thromboembolic event was constructed such that the cumulative incidence of postphlebotic syndrome among survivors would be 7%, 14%, 20%, and 27%, respectively, at one, five, ten, and twenty years after a symptomatic VTE event.

The rates of postphlebotic syndrome following asymptomatic VTE are much more difficult to estimate. Among ninety-one patients noted to have proximal or distal DVT on routine predischarge venography in a study of 255 patients, five (5.5%) were noted to have postphlebotic syndrome develop over a mean follow-up period of 4.8 years³². This was not significantly different from the rate of postphlebotic syndrome (4.3%) that developed over a mean follow-up time of 5.5 years in the 164 patients who had not had any DVT noted on predischarge venography. We arbitrarily assumed a 5% cumulative incidence of postphlebotic syndrome over

twenty years in those subsets of individuals who develop asymptomatic DVT after total joint arthroplasty. This was modeled as a rate of 19% of the postphlebotic syndrome rate following a symptomatic VTE event. Wide sensitivity analyses were done around this estimate.

Obesity may be a risk factor for developing postphlebotic syndrome following DVT. Published estimates of the relative risk of postphlebotic syndrome in those with a body mass index (BMI) of >25 kg/m² compared with those with BMI below the cut point range from 1.5 to 3.5³³⁻³⁶. We chose a middle value, 1.9 for our estimate of the relative risk of postphlebotic syndrome in those with a BMI of ≥30 kg/m² compared with those with a BMI of <30³⁶.

Risks of Thrombocytopenia

Both a meta-analysis of heparin-induced thrombocytopenia (HIT) following total joint replacement and a separate registry study of HIT estimated the absolute incidence of HIT in those treated with LWMH to be 0.2%^{37,38}.

Relative Risks of Postoperative VTE Events Due to a History of VTE and Obesity

The risks of VTE events are crude rates regardless of the presence or absence of other risk factors such as history of VTE events. For the model to be applicable to subsets of the population defined by the presence or absence of these risks, the relative risks of VTE events as a function of age and sex, and in patients with compared to those without risk factors (such as obesity), are needed. Additionally, the prevalence of those risk factors needs to be taken into account as well.

We did not include age as a risk factor for VTE in this model. Although there is evidence among nonsurgical patients that age is risk factor for VTE, the evidence is contradictory among those undergoing total joint arthroplasty, with increasing age being a risk factor in some studies, not a risk factors in others, and protective against VTE in one.

History of VTE Events

The literature review for the recent American Academy of Orthopaedic Surgeons (AAOS) guideline for VTE prophylaxis following total joint arthroplasty noted that only a small handful of studies described estimates of the relative risk of VTE events following total joint arthroplasty in patients with compared to those without a history of VTE. One small study did not find any association of VTE events in patients with a history of VTE, but two much larger and better powered studies did. We used a relative risk of 8.1 based on the largest and highest-quality study (Pedersen et al.³⁹) as judged by the AAOS guideline review. We calculated costs per QALY gained without stratification by sex. The prevalence of a history of VTE events, of course, increases with increasing age. There are no published estimates of the prevalence of a history of VTE events, to our knowledge. We estimated the prevalence of prior VTE at each starting age of the model by running a reduced submodel with the population-based incidence rates of DVT and PE of the Rochester Epidemiology Project³⁰. With this reduced model, we could account for the competing risks of mortality from both PE and background causes. We ran this model from the age of thirty years until each of the starting ages for the main analyses with 100,000 trials each. A tracker variable was used to count the number of individuals per 100,000 who both developed VTE and were still alive at various ages. The estimated prevalences among men, among women, and among all regardless of sex at each age are shown in Table E-2.

The relative risks of VTE for those without a history of VTE compared with all of the same age and sex were calculated using the following equation:

$$RR_{NoPriorVTEvsAll} = 1 / (1 + [RR_{PriorVTEvsNoPriorVTE} - 1] * Prevalence_{PriorVTE}) = 1 / (1 + 7.1 * Prevalence_{PriorVTE})$$

Obesity

Sensitivity analyses were also run under the assumption that obesity (BMI of ≥30 g/m²) is a risk factor for both VTE events and for postphlebotic syndrome, should a VTE event occur. On the basis of several studies⁴⁰⁻⁴⁴, we estimated the relative risk of symptomatic VTE events in patients with a BMI of ≥30 kg/m² compared with those with a BMI of <30 kg/m² for these analyses to be 1.7. We estimated the prevalence of obesity in the population of interest (U.S. men and women fifty-five years of age and older) to be 43.2% using data from the National Health and Nutrition Examination Survey (NHANES) for 2007 to 2008 and the proportions of individuals in the U.S. population sixty-five years of age and older of different ethnic groups (www.cdc.gov/nchs/nhanes.htm).

Therefore, the relative risk for VTE events in the obese subset is estimated to be:

$$RR_{ObeseVsAll} = RR_{ObeseVsNonobese} / (1 + [RR_{ObeseVsNonobese} - 1] * Prevalence_{Obese}) = 1.7 / (1 + 0.7 * 0.432) = 1.31$$

In contrast, the relative risk for VTE events in the nonobese subset is:

$$RR_{NonobeseVsAll} = 1 / (1 + [RR_{ObeseVsNonobese} - 1] * Prevalence_{Obese}) = 1 / (1 + 0.7 * 0.432) = 0.77$$

Costs

All direct medical costs used in this modeling study were standardized to the latter half of 2010 U.S. dollars using the medical care part of the Consumer Price Index (CPI)⁴⁵.

DVT and Pulmonary Embolism

For 27,370 patients undergoing total hip arthroplasty and 39,535 undergoing total knee arthroplasty, the costs in 220 geographically diverse hospitals across the U.S. among those whose hospital stay was complicated by PE or DVT without PE were compared with those whose postoperative course was uncomplicated⁴⁶. Costs were derived from charges and the Medicare charge to cost ratios for those hospitals in late 1998. The cost attributable to postoperative PE and DVT were calculated as the differences between the costs of hospital stays with that complication minus the cost of a hospital stay uncomplicated by a VTE event. The costs were then adjusted to 2010 U.S. dollars using the medical component of the U.S. CPI. The mean incremental costs following total knee arthroplasty attributable to postoperative PE and DVT, respectively, were \$13,174 and \$4104. Similarly, the mean incremental costs following total hip arthroplasty attributable to postoperative PE and DVT, respectively, were \$14,539 and \$8262. Considering total knee and hip arthroplasties in aggregate (assuming that 59% are total knee arthroplasties and 41% are total hip arthroplasties)⁴⁶, the estimated costs for postoperative PE and DVT are, respectively, \$13,729 and \$5729.

The costs of hospitalization for recurrent DVT and PE occurring at times other than the immediate postoperative period (requiring a readmission to the hospital) were estimated from data of Bullano et al.⁴⁷. The cost of recurrent DVT, recurrent PE, and of both in 2005 U.S. dollars were estimated to be, respectively, \$11,419, \$11,014, and \$19,237. Assuming that 42% of those with PE also have symptomatic DVT and using the CPI for medical care to translate estimated costs to 2010 U.S. dollars, we estimated the costs of recurrent DVT and PE to be, respectively, \$14,816 and \$18,818.

Major Postoperative Bleeding

Vera-Llonch et al. reported results from the only investigation, to our knowledge, that has estimated the incidence, incremental lengths of stay, and incremental costs associated with operative site and nonoperative site major bleeding episodes following total knee and hip arthroplasty²⁸. Those investigators used the MQ-Profile database of discharges from 100 U.S. acute care hospitals from 1998 to 2000 inpatient charges for patients whose hospital stay was uncomplicated by any bleeding episode, for all who suffered any major bleeding, and for the subset who suffered bleeding at the operative site that required reoperation. We used a nationally weighted Medicare charge to cost ratio (calculated to be 0.52 from 1999 U.S. Medicare Cost Reports data)⁴⁸ to estimate costs from these charges, and used the medical care component of the U.S. CPI⁴⁵ to adjust the costs to 2010 U.S. dollars. We estimated costs following total knee arthroplasty attributable to operative site bleeding requiring reoperation and to all other major bleeding episodes to be, respectively, \$2932 and \$4888²⁸. Similarly, we estimated the incremental costs following total hip arthroplasty associated with operative site bleeding requiring reoperation and all other major bleeding episodes to be, respectively, \$12,608 and \$4332²⁸. Again assuming that 59% of all joint arthroplasties are of the knee and 41% are of the hip, the estimated incremental costs following total joint arthroplasty attributable to operative site bleeding requiring reoperation and to all other major bleeding episodes are, respectively, \$6867 and \$4662.

Postphlebotic Syndrome

On the basis of several sources, Caprini et al. used microcosting methods to determine the direct medical costs in 2000 U.S. dollars for management of mild to moderate and severe postphlebotic syndrome⁴⁹. Among all cases of postphlebotic syndrome, we estimated that 27% would be severe and 73%, mild to moderate⁵⁰. Of the severe cases, 31.5% at any given point in time have one or more open cutaneous ulcers that require more intensive management. Using data in the study by Caprini et al. and the U.S. CPI for medical care, we assumed first and subsequent year costs of \$1290 and \$524 (2010 U.S. dollars) for mild to moderate postphlebotic syndrome. For severe cases of postphlebotic syndrome, we assumed a first-year cost of \$5868 and costs for subsequent years of \$1435 for the patients without an open ulceration and \$5067 for those with one or more open ulcerations. Therefore, the average cost for postphlebotic syndrome was estimated to be \$2526 in the first year and \$1079 in subsequent years (in 2010 U.S. dollars).

Intracranial Hemorrhage

Costs for intracranial hemorrhage were estimated from a 5% sample of the U.S. Medicare population for 2005²⁷. Costs included the initial costs for the first three months (including the initial hospitalization) and then were estimated out for a total of four years. The cost was \$22,000 for the first quarter and \$28,015 for the subsequent fifteen quarters, or an average of \$1862 per quarter in 1997 U.S. dollars. Adjusted to 2010 U.S. dollars, the estimates for the first quarter (including the initial hospitalization) and per subsequent quarter are, respectively, \$37,705 and \$3201.

However, the estimated costs for the in-hospital phase for all nonoperative site bleeding episodes cited above from data of Vera-Llonch et al. presumably would include the initial costs for that small proportion whose site of nonoperative site bleeding is intracranial. For that reason, we applied only the downstream costs (\$3201 per quarter \times 15 quarters) in the post-intracranial hemorrhage state.

Thrombocytopenia

Estimates of costs attributable to heparin-induced thrombocytopenia have ranged from \$1135 (2004 U.S. dollars) to \$41,133 (2004 U.S. dollars) among medical patients who developed heparin-induced thrombocytopenia⁵¹⁻⁵³. Smythe et al. examined the incidence

of HIT among both surgical and medical patients receiving prophylactic LMWH⁵⁴. The incremental Medicare reimbursement (2004 U.S. dollars) for hospitalizations using prophylactic LMWH complicated by HIT compared with hospitalizations not complicated by HIT was \$15,089 (\$19,209 in 2010 U.S. dollars).

Medication Costs

We assumed the true cost of enoxaparin (30 mg subcutaneously) twice a day for 7.5 days to be the average wholesale cost according to the Thomson Reuters reference *RED BOOK* for 2010 (\$365), and aspirin (160 mg per day) to be \$0.20 for 7.5 days. For the small subset of patients who develop CTPH and are not able to be treated operatively (43.2%), there is no approved therapy in the United States⁵⁵. Nonetheless, it is common practice to treat these individuals with endothelin antagonists or phosphodiesterase inhibitors (85% in one study)⁵⁶. We assumed that those would be treated with sildenafil (50 mg three times a day) at cost of \$2249.10 per 100 50-mg tablets. The yearly cost of sildenafil, averaged over all patients who have initially survived CTPH is calculated to be \$9018.

Health State Utilities

DVT and PE

DVT and PE are postulated to cause loss of quality of life only through the time period of acute treatment, except for that proportion of individuals who develop postphlebotic syndrome. We assume total loss of quality of life for the extra days of hospitalization required for those who suffer DVT or PE after total hip or knee arthroplasty. Ollendorf et al. estimated the average incremental length of stay due to DVT following total knee and total hip arthroplasty, respectively, to be 2.5 and 4.7 days⁴⁶. Similarly, they estimated the incremental length of stay attributable to postoperative PE following total knee and total hip arthroplasty, respectively, to be 6.3 and 6.2 days. Given that nearly twice as many knee as hip replacements are done each year, we calculated an average incremental weighted length of stay for DVT and PE (with or without clinical DVT) following total joint arthroplasty to be, respectively, 3.39 days and 6.26 days. If we assume total loss of quality of life (0.76 QALY in the healthy state) during these days in hospital, these correspond to QALY losses of 0.007 years attributable to postoperative DVT and 0.013 attributable to postoperative PE.

For those who are readmitted with recurrent DVT or PE, respectively, Caprini et al. estimated the length of stays to be 5.9 and 7.1 days, respectively, corresponding to QALY losses of 0.0123 and 0.0148⁴⁹.

While it is true that these estimated QALY losses do not include loss of quality of life due to long-term complications or time lost due to additional physician appointments after discharge, the former is addressed by separate estimations of quality of life loss due to postphlebotic syndrome, and the latter is compensated by the fact that we assume total quality of life loss during incremental hospitalization.

Postphlebotic Syndrome

Caprini et al. estimated the quality of life for those with severe postphlebotic syndrome (with open or healed cutaneous ulcers) to be 93% of expected, and for mild to moderate postphlebotic syndrome to be 98% of expected, on the basis of the study by Lenert and Soetikno estimating quality of life loss associated with postphlebotic syndrome with a standard gamble⁵⁷. Seventy-three percent of all cases of postphlebotic syndrome are estimated to be mild to moderate, and 27% are estimated to be severe, on the basis of a long-term follow-up study of 528 patients with symptomatic DVT for at least five years⁵⁰. Another follow-up study, however, has estimated the proportion of postphlebotic syndrome cases that are severe to be about 10%⁵⁸. To be conservative, we assumed 27% of cases of postphlebotic syndrome to be severe.

Major Postoperative Bleeding

Among patients followed after total hip arthroplasty, Vera-Llonch et al. documented an increased length of stay of 1.7 days for all who had a major bleeding episode in the postoperative period, and an increased length of stay of 4.0 days for the subset (26.1%) who had a major bleeding episode at the operative site that required another surgery³⁸. Following major knee surgery, those who had a major bleeding episode in the postoperative period had an incremental length of stay (LOS) of 1.7 days regardless of whether or not another surgery was required. Therefore, the incremental length of stay in all of those who did not require a reoperation following total hip arthroplasty is as follows:

$$\text{Incremental LOS}_{\text{BleedNoReop}} = (1.7 - 4.0 * 0.261) / (1 - 0.261) = 0.89 \text{ day}$$

As shown earlier, we estimated that 42.4% of all major bleeding episodes at the operative site require reoperations. From this percentage, we can calculate the incremental length of stay to be a mean of 2.67 days for major bleeding at the operative site following total hip arthroplasty and to be a mean of 0.89 day for major bleeding at nonoperative sites. Again assuming total loss of quality of life from excess hospital stays due to bleeding, we assigned disutilities of 0.0043 and 0.0019 QALYs for operative site

bleeding and nonoperative site bleeding, respectively, following total hip arthroplasty. We assigned a disutility value of 0.0035 to major bleeding at any site complicating total knee arthroplasty. Considering total knee (59%) and total hip (41%) arthroplasties together, we assigned disutilities of -0.0039 for operative major bleeding and -0.0028 for nonoperative site major bleeding.

Intracranial Hemorrhage

Lee et al. used the EuroQoL-5D (EQ-5D) to estimate preference-weighted quality of life following a stroke in 486 individuals, including fifty-three with intracranial hemorrhage⁵⁹. At a mean 3.7 years after the stroke, the mean EQ-5D index score using U.S. weights (rescaled up to 1.0) was 0.60 for those who had had an intracranial hemorrhage. Given that our top score for patients who have had an uncomplicated recovery from total joint arthroplasty is 0.76, therefore we assumed a utility weight of 0.45 for the time period after a person has recovered as much as they will after intracranial hemorrhage. However, it takes about one year to reach this level, and hence we used the utility value of 0.29 derived using a standard gamble among patients by O'Meara et al. for the first quarter after an intracranial hemorrhage⁶⁰, a value of 0.45 for the fourth and all subsequent quarters after an intracranial hemorrhage, and estimated values for the second and third quarters by linear interpolation between these two values.

Thrombocytopenia

Creekmore et al. estimated the incremental hospital length of stay attributable to heparin-induced thrombocytopenia to be 12.5 days⁵¹. If we assume total loss of quality of life (0.76 QALY per year in the healthy state), this corresponds to a QALY loss of -0.026 QALYs.

Distributions for Probabilistic Sensitivity Analyses (Table E-3)

Cost and QALYs Due to Bleeding and VTE Events in the Immediate Postoperative Period

We estimated these costs primarily on excess length of stay attributable to these events. These excess lengths of stay were based on 160 individuals (in the case of postoperative bleeding) and 395 individuals (in the case of postoperative PE). Assuming a normal distribution to each, the standard error of excess length of stay attributable to VTE events is $([12.4-9.8]/12.4)/\sqrt{(395)} = 0.01$, and for length of stay attributable to bleeding episodes is $(0.5/6.1)/3.92$ (Vera-Llonch et al.²⁸ reported 95% confidence intervals for standard error), which is equal to 0.02.

This does not account for the error in estimating length of stay for those with no VTE or bleeding events. Moreover, this does not account for error due to systematic biases that are very difficult to eliminate from any observational data analysis, and hence, to be conservative, we set disutilities attributable to VTE events and major bleeding to be from 50% to 150% of the base case assumptions along triangular distributions, with the likeliest being the base case value, the minimal being 50% of the base case value, and the maximal being 150% of the base case value.

Incidence of VTE, Major Bleeding, and Postphlebotic Syndrome

The cumulative incidence of postphlebotic syndrome following a VTE event is uncertain, particularly following asymptomatic VTE. Therefore, conservatively, we also allowed the rate of postphlebotic syndrome following an asymptomatic VTE event to vary from 50% to 150% of that of the base case along a uniform distribution. Following a symptomatic VTE event, where better data are available, we assumed the cumulative incidence of postphlebotic syndrome to follow a binomial distribution. Given the sample size of 1527 individuals with 245 developing postphlebotic syndrome while alive, the standard error is 5% of the mean. Using a normal approximation to the mean, the incidence of postphlebotic syndrome following a symptomatic VTE event was allowed to vary along a normal distribution with a standard deviation of 5% of the mean.

The distributions of symptomatic DVT, asymptomatic DVT, and symptomatic PE were established as normal approximations to the binomial distributions from the data from the systematic review by Brown¹. Hence, the rates of symptomatic PE, symptomatic DVT, and asymptomatic DVT were estimated to be normally distributed with standard deviations equal to 18%, 10%, and 3%, respectively, of the mean. In order to allow the rates of symptomatic DVT and PE to be fully correlated, we created a variable with a mean of 1.0 and a standard deviation of 0.18 and multiplied all rates of symptomatic DVT and PE by this value.

Similarly, the rates of postoperative bleeding were assumed to be normally distributed. Using the binomial distributions inherent in the data presented by Brown, the standard deviations of these proportions were assumed to be 10% and 7%, respectively, of the mean for nonoperative site bleeding and operative site bleeding.

Model Validation

Monte Carlo microsimulations were run using tracker variables to count the cumulative incidence of symptomatic PE, symptomatic DVT, asymptomatic VTE, operative site bleeding, nonoperative site bleeding, and postphlebotic syndrome following symptomatic VTE, assuming no specific risk profile of VTE. The model estimated values are close to published values (Table E-4).

Additional Analyses

Expanded Model

We did secondary analyses expanding the model to include two additional adverse outcomes of total joint replacement: periprosthetic joint infection and chronic thromboembolic pulmonary hypertension.

Chronic Thromboembolic Pulmonary Hypertension (CTPH)

Rates

Recent evidence has suggested that over a two-year period after a PE, 3.8% of patients develop pulmonary hypertension due to persistent pulmonary artery obstruction⁶¹. The risk is particularly high among those whose PE is unexplained by any specific risk factors; the relative risk in those with idiopathic PE compared with those with PE due to a known cause was 5.7. In the study by Pengo et al., the proportion of all patients with a first PE without a known cause was 37.2%⁶¹. Therefore, the relative risk of CTPH in those with PE due to a known cause compared with all with a first PE was:

$$RR_{CTPH_Known} = 1 / (1 + [RR_{CTPH_KnownVsUnknown} - 1] * Prevalence_{PE_Unknown}) = 1 / (1 + [5.7 - 1] * 0.372) = 0.364$$

Since venous thromboembolism following total joint arthroplasty is not idiopathic, we assumed the proportion of those who have a PE after surgery and go on to have CTPH to be $0.038 * 0.364 = 0.0138$.

We assigned this proportion of the patients who survive a postoperative PE immediately to the CTPH without postphlebotic syndrome health state, so that mortality following development of CTPH could be modeled as a function of model stage rather than a time-dependent tracker variable. This allowed us to still estimate the model as a Markov cohort rather than using microsimulation.

Mayer et al. recently reported that the thirty-day mortality following pulmonary artery endarterectomy for CTPH was 7%⁶². Although the prognosis for patients considered to have an inoperable condition a couple of decades ago was thought to be very poor (with a five-year survival rate of only 30%)⁶³, since 2003 with medical treatment (using phosphodiesterase inhibitors or vascular endothelin inhibitors), five-year survival is approximately 75%⁵⁶. For patients undergoing pulmonary artery endarterectomy, five-year survival among those surviving the perioperative period was 94%. On the basis of Mayer et al., we assumed that 56.8% of those developing CTPH would be surgical candidates and would receive surgery. We assumed the five-year survival rate for CTPH overall to be the weighted average of the surgery survivors and those not considered surgical candidates (85.6%). We therefore assumed a mortality rate of 0.8% per three-month period among survivors reaching the start of each three-month period alive; this yields a modeled five-year survival rate of the population of those developing CTPH after a clinically evident PE of 85.2%. For those surviving five years, we then assumed only background mortality equal to that of those who do not have CTPH.

Costs of CTPH

We assumed that the costs of CTPH would be primarily due to the cost of pulmonary artery endarterectomy for that subset undergoing the procedure. Of 679 patients in a CTPH registry from multiple Canadian and European Centers for CTPH, 58.6% underwent the procedure⁶². The mean Medicare reimbursement for surgeon's fees for the second half of 2010 for pulmonary artery endarterectomy (Current Procedural Terminology, Fourth Edition [CPT-4] code 33916) was \$1905⁶⁴. Pulmonary artery endarterectomy can be associated with discharge Diagnosis-Related Group (DRG) codes 166, 167, 168, 237, and 238. The cost of a hospitalization for pulmonary artery endarterectomy for 2009 was estimated to be the weighted mean Medicare DRG reimbursement for hospitalization for these five DRGs, which was \$19,216 (\$19,792 in 2010 U.S. dollars)⁶⁵. The total cost of pulmonary artery endarterectomy was estimated to be the sum of the surgeon's fees and hospital DRG reimbursement (\$21,697).

Disutility of CTPH

Since successful pulmonary artery endarterectomy restores normal or nearly normal cardiopulmonary function, we assumed no quality-of-life loss among those who would undergo and survive this procedure⁶⁶. Among the 43% who would not be considered operative candidates⁶², however, we assumed a QALY value of 0.48 corresponding to a New York Heart Association class III status using the CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) preference-weighted quality-of-life scale specific for pulmonary hypertension⁶⁶. The weighted QALY average between those who survive endarterectomy and those who do not undergo the procedure is 0.63, compared with 0.76 for those who have an uneventful recovery from total joint arthroplasty.

Subsequent Periprosthetic Joint Infection Following Surgical Drainage of a Postoperative Hematoma Following Total Joint Arthroplasty

Rates

Following total joint arthroplasty, 0.5% to 2.5% of patients develop an infection around a joint prosthesis^{67,68}. While many have postulated that postoperative bleeding around a prosthetic joint increases the risk of periprosthetic joint infection, there are no

robust estimates of the incremental risk. Galat et al. estimated that among patients who have undergone total knee arthroplasty, the proportion of those who require a repeated operation to evacuate a postoperative hematoma who then go on to develop an infection around a prosthetic knee joint is 4.9% by six months after surgery, 10.5% by two years after surgery, and 13.6% by five years after surgery⁶⁹. In contrast, among those not requiring surgical evacuation of a hematoma after surgery, only 0.8% by two years and 1.4% by five years develop an infection around a prosthesis. We plotted the incremental proportion of patients who develop a periprosthetic infection among those who require surgery for a hematoma compared with those who do not as a function of time, and assigned the incremental risk for each three-month time period between surgery and the five-year time point after surgery. However, only 0.24% of all total knee arthroplasties required reoperation specifically to evacuate a postoperative hematoma. It is unclear, however, how many of the entire cohort were treated with full anticoagulation after surgery and what proportion were not. According to the data of Vera-Llonch et al.²⁸ and Brown¹, an estimated 1.24%, or (0.0292×0.424) , of all of those undergoing total joint arthroplasty would require reoperation, which is fivefold higher than the rate in the study by Galat et al.⁶⁹ who estimated that 0.24% would require surgery specifically to evacuate a hematoma at the operative site. However, it is unclear from the data of Vera-Llonch et al. that all reoperations specifically were done to evacuate a hematoma in the joint space. On the other hand, Galat et al. did not address whatever incremental periprosthetic joint infection risk might be present in those with postoperative bleeding at the operative site who did not require evacuation of a hematoma. Darwiche et al. estimated that twenty of sixty patients requiring a reoperation for any reason within ninety days of a total hip arthroplasty developed a periprosthetic joint infection⁷⁰. However, it would not be appropriate to apply these rates to patients who have a repeat bleeding episode since many of these reoperations were for reasons other than hemorrhage.

Therefore, for the primary analysis, we conservatively estimated that the incremental risk of infection over a five-year time period following total joint arthroplasty would apply to only 0.24% of all patients receiving aspirin prophylaxis, and that this rate would be increased in those receiving LMWH because of the increased risk of bleeding by a factor of 1.37 (inverse of 0.729). Wide sensitivity analyses around these estimates were done.

Costs of Periprosthetic Joint Infection

Several studies have examined the costs attributable to infection after total joint arthroplasties⁷¹⁻⁷³, but only one of them examined both inpatient and outpatient downstream costs relative to an uninfected control group using data relevant to the U.S. This was a single-center study that collated the costs over one calendar year for twenty-five patients who developed an infection at the site of a prosthesis following total hip arthroplasty. All were treated with a two-stage procedure: removal of the prosthesis followed by intravenous antibiotics and then reimplantation of a prosthesis. Costs were presented as true hospital costs (\$96,166) and as outpatient charges (\$48,348) for March 2001 through the end of 2002⁷³. The institutional cost-to-charge ratio in 2002 (0.31) for the institution (University of California, San Francisco) was used to estimate the Medicare 2002 reimbursement (\$14,989) for these outpatient costs⁷⁴. The sum of the inpatient and outpatient costs (\$111,155) was then divided by 0.716 to reflect the increase in the costs of medical care services from 2002 to 2010, yielding a final estimated cost for one year of \$155,244 in 2008 dollars.

Disutility of Periprosthetic Joint Infections

Cahill et al. estimated quality of life with the Short Form-36 (SF-36) and the Assessment of Quality of Life instrument (AQoL) among sixty-two patients who had uncomplicated total joint arthroplasty and thirty-four patients who had total joint arthroplasty complicated by periprosthetic joint infection⁷⁵. The AQoL⁷⁶ is a fifteen-item preference-weighted instrument that has been calibrated to estimate QALY utility values. Those who had a periprosthetic joint infection had an AQoL utility value of 0.4 (at an average time of fifty-seven months after the total joint arthroplasty) compared with 0.6 for those with uncomplicated arthroplasty. Hence, we assumed, on the basis of a QALY value (0.51) equal to two-thirds that of the health state after total joint arthroplasty (0.76), that this disutility would last for four years. We assumed that the QALY value more than four years after total joint arthroplasty to be that of the healthy state after total joint arthroplasty.

Results of Analyses with Expanded Model Compared with Base Model

As can be seen in Table E-5, the estimated costs per QALY gained for LMWH compared with aspirin using the expanded model are very similar to those using the simpler model.

Two-Way Sensitivity Analyses (Figs. E-1A through E-1D)

Allowing the rates of VTE and major bleeding events to vary between zero and three times the rates of the base case analysis illustrates how unlikely LMWH is to be cost-effective compared with low-dose aspirin following total hip arthroplasty (Fig. E-1A). For example, even if rates of VTE events following total hip arthroplasty were 1.4 times as high as we estimated, the rates of major bleeding events would have to be half of what we estimated for the base case analyses for LMWH to be cost-effective. Similarly, if the

relative risk of bleeding events on aspirin compared with LMWH was only 0.9, the relative risk of VTE events would have to be ≥ 2.0 for LMWH to be cost-effective following total hip arthroplasty (Fig. E-1C).

Following total knee arthroplasty, moderate changes in the rates of VTE and bleeding events could change the optimal choice of VTE prophylaxis on the ground of cost-effectiveness. For example, if the rate of VTE events is 25% lower than what we assumed for the base case and the rate of major bleeding events is 25% higher, then aspirin becomes the agent of choice. The optimal choice following total knee arthroplasty is particularly sensitive to changes in the relative risks of VTE and major bleeding events on aspirin compared with LMWH. For example, if the relative risk of bleeding on aspirin compared with LMWH is 0.6 instead of 0.73, as we estimated for the base case, then aspirin appears to be the optimal choice if the relative risk of VTE events on aspirin compared with LMWH is ≤ 1.75 .

We believe these results, combined with the probabilistic sensitivity analyses described in the main paper, indicate that a randomized controlled trial of aspirin versus LMWH following total knee arthroplasty would be helpful in defining optimal management of VTE risk after total knee arthroplasty. In contrast, in light of these two-way sensitivity analyses and the probabilistic sensitivity analyses, we believe that it is highly unlikely that LMWH following total hip arthroplasty in patients without a history of VTE is cost-effective, and that it is quite unlikely that such a randomized controlled trial of aspirin versus LMWH following total hip arthroplasty would be fruitful.

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