

Management of Venous Thromboembolism: A Systematic Review for a Practice Guideline

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Background: New treatments are available for treatment of venous thromboembolism.

Purpose: To review the evidence on the efficacy of interventions for treatment of deep venous thrombosis (DVT) and pulmonary embolism.

Data Sources: MEDLINE, MICROMEDEX, the Cochrane Controlled Trials Register, and Cochrane Database of Systematic Reviews from the 1950s through June 2006.

Study Selection: Randomized, controlled trials; systematic reviews of trials; and observational studies; all restricted to English-language articles.

Data Extraction: Paired reviewers assessed study quality and abstracted data. The authors pooled results about optimal duration of anticoagulation.

Data Synthesis: This review includes 101 articles. Low-molecular-weight heparin (LMWH) is modestly superior to unfractionated heparin at preventing recurrent DVT and is at least as effective as unfractionated heparin for treatment of pulmonary embolism. Outpatient treatment of venous thromboembolism is likely to be effective

and safe in carefully chosen patients, with appropriate services available. Inpatient or outpatient use of LMWH is cost-saving or cost-effective compared with unfractionated heparin. In observational studies, catheter-directed thrombolysis safely restored vein patency in select patients. Moderately strong evidence supports early use of compression stockings to reduce postthrombotic syndrome. Limited evidence suggests that vena cava filters are only modestly efficacious for prevention of pulmonary embolism. Conventional-intensity oral anticoagulation beyond 12 months may be optimal for patients with unprovoked venous thromboembolism, although patients with transient risk factors benefit little from more than 3 months of therapy. High-quality trials support use of LMWH in place of oral anticoagulation, particularly in patients with cancer. Little evidence is available to guide treatment of venous thromboembolism during pregnancy.

Limitations: The authors could not address all management questions, and excluded non-English-language literature.

Conclusions: The strength of evidence varies across the study questions but generally is strong.

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Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism, is a prevalent disease treated by internists. The incidence of VTE is about 7 per 10 000 person-years among community residents (1, 2). The condition recurs in about 20% of patients after 5 years, but the rate varies depending on the presence of risk factors (3, 4). A community-wide study from the 1980s reported an incidence rate of pulmonary embolism, with or without DVT, of 2.3 per 10 000 (5). Pulmonary embolism limits the short- and long-term survival of patients with VTE (6). Postthrombotic syndrome, another prevalent complication of DVT, may result in lifelong morbidity with limb pain and edema (4). Treatment of VTE, with anticoagulants and thrombolytic therapies, is associated with its own risks.

Given the prevalence of this condition and its associated morbidity, we reviewed the evidence on optimal treatment of VTE. We sought to summarize the evidence to inform the guidelines developed by the American Academy of Family Physicians and the American College of Physicians for management of patients with VTE. The foundation of this background paper was a previous systematic review of diagnosis and management of VTE (7). For this paper, we addressed the following questions: 1) Is heparin or low-molecular-weight heparin (LMWH) safer and more efficacious for initial treatment of VTE? 2) Is outpatient treatment of VTE safe and effective when compared with inpatient treatment? 3) Is LMWH cost-effective compared

with heparin? 4) Does catheter-directed thrombolysis reduce VTE recurrences and the incidence of postthrombotic syndrome? 5) Does use of compression stockings reduce the incidence of postthrombotic syndrome? 6) Do vena cava filters alter the incidence of pulmonary embolism and recurrent DVT? 7) What is the optimal duration of therapy with vitamin K antagonists for VTE? 8) Does evidence support use of LMWH instead of vitamin K antagonists? 9) What is the best therapy for pregnant women with VTE?

METHODS

The methods used in our systematic review are completely described in a detailed evidence report (7). The methods specific to this article are briefly described in the following section.

See also:

Print

Related article. 204
Summary for Patients. I-43

Web-Only

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Appendix Tables
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Table 1. Assessing Quality of Evidence*

Study Quality	Regarding Treatment, Prevention, and Screening
Level 1: good-quality patient-oriented evidence	Systematic review/meta-analysis or randomized, controlled trial with consistent findings High-quality individual randomized, controlled trial† All-or-none study‡
Level 2: limited-quality patient-oriented evidence	Systematic review/meta-analysis of lower-quality clinical trials or of studies with inconsistent findings Lower-quality clinical trial Cohort study Case-control study
Level 3: other evidence	Consensus guidelines; extrapolations from bench research; usual practice; opinion; disease-oriented evidence (intermediate or physiologic outcomes only); or case series for studies of diagnosis, treatment, prevention, or screening

* Based on Strength of Recommendation Taxonomy (SORT) (9).

† High-quality randomized, controlled trial: allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (>80%).

‡ In an all-or-none study, the treatment causes a dramatic change in outcomes, such as antibiotics for meningitis or surgery for appendicitis, which precludes study in a controlled trial.

Data Sources

To identify relevant articles, we searched literature-indexing systems, including MEDLINE, MICROMEDEX, the Cochrane Controlled Trials Register, and the Cochrane Database of Systematic Reviews, beginning in the 1950s. We also examined reference lists from material identified through the electronic searching and from discussion with experts, and we reviewed recent tables of contents of the pertinent journals. For our previous report, we searched for citations through March 2002. For the current review, we extended the search through June 2006.

Data Selection

Our criteria for article inclusion are listed in Appendix 1 (available at www.annals.org). Two team members independently reviewed the titles and abstracts and excluded those that did not meet the eligibility criteria. For primary literature, the article must have been in English, addressed one of the chosen questions, not involved prevention only, included original human data, and not have been a single-patient case report. For our review of systematic reviews, we used these criteria but also stipulated that the article have included a systematic review, meta-analysis, or cost-effectiveness analysis. Data published only in abstract form were excluded. Each question had additional eligibility criteria. If both reviewers agreed about eligibility, we reviewed the article.

In our previous review, we evaluated 64 systematic reviews and 148 primary studies. Of these, 16 systematic reviews and 32 primary studies were relevant to our questions about management of VTE. In our additional searching, we identified another 3 systematic reviews and 13 primary studies on the questions that were in the previous review. We also reviewed 515 additional abstracts to identify 46 primary studies on 5 additional questions covered in this review. Seven studies, previously included for question 7 above, were eliminated; they were published before 1995 and were inconsistent in their use of objective tests for diagnosing VTE.

Data Extraction and Quality Assessment

A single reviewer abstracted data, and a co-investigator did a secondary review to verify accuracy. We summarized data in evidence tables and assessed the quality of the article by using validated instruments, where appropriate (8).

Two authors graded evidence according to the Strength of Recommendation Taxonomy (SORT) developed by a consortium of editors of U.S. family medicine and primary care journals (9). As shown in Table 1, level 1 indicates good-quality patient-oriented evidence, level 2 indicates limited-quality patient-oriented evidence, and level 3 indicates when there is other evidence.

Data Synthesis and Analysis

We pooled risk ratios across studies about duration of oral anticoagulation and generated CIs around the risk ratios with a random-effects model using the method of DerSimonian and Laird; the estimate of heterogeneity was taken from the Mantel-Haenszel model (Stata 9.0, Stata-Corp., College Station, Texas). The I^2 statistic was calculated as $100\% \times (Q - \text{degrees of freedom})/Q$, where Q is the measure of heterogeneity (10). Because the I^2 statistic suggested heterogeneity between trials, we do not report pooled results.

Role of the Funding Sources

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DATA SYNTHESIS

Is Heparin or LMWH Safer and More Efficacious for Initial Treatment of VTE?

Numerous trials have compared the safety and efficacy of LWMHs to those of unfractionated heparin in the treatment of VTE. We report on 17 systematic reviews of these trials, published between 1994 and 2003, which reviewed

rates of recurrent VTE, major bleeding, or death (11–27). Five included only trials of patients with an isolated DVT, 1 review focused on patients with pulmonary embolism with or without concomitant DVT (23), and 1 evaluated the adequacy of dosing of unfractionated heparin (24).

Thirteen LMWHs were compared with unfractionated heparin, almost always given intravenously. The LMWHs most often included were enoxaparin (13 reviews), dalteparin (12 reviews), nadroparin (11 reviews), tinzaparin (10 reviews), reviparin (9 reviews), and CY222 (8 reviews). The quality of the systematic reviews was generally good, although only 5 evaluated the quality of trials (14, 17, 23, 26, 28). Description of the search strategies and methods of combining results were weaker in the earlier reviews. Five reviews were descriptive and did not pool results (11, 18, 19, 22, 24).

As expected, many of the same articles were included in multiple reviews. The reviews fell into 3 clusters depending on which trials they included. **Table 2** summarizes the pooled trial results by these clusters. The cluster containing the most recent trials, cluster C, has odds ratios closer to 1.0 than the cluster containing only the earliest trials. **Appendix Table 1** (available at www.annals.org) describes the individual trials within each review.

The 5 descriptive reviews had discordant results (11, 18, 19, 22, 24). Among the 11 reviews that pooled trial results (with many trials in common), none showed heparin to be superior to LMWH in preventing recurrent DVT. In addition, patients treated with LMWH had fewer episodes of major bleeding than those treated with unfractionated heparin. All but 1 of 10 reviews showed that LMWH significantly reduced mortality during the 3 to 6 months of follow-up compared with unfractionated heparin (23). Only 4 reviews reported summary results separately for patients with pulmonary embolism; these reviews concluded that LMWH was as effective as unfractionated heparin in this population (16, 18, 23, 29).

In summary, evidence is ample that LMWH is superior to unfractionated heparin for the treatment of DVT, particularly for reducing mortality and the risk for major bleeding during initial therapy. The magnitude of benefit from LMWH, while significant in many of these reviews, appears to be lower than was estimated in the earliest reviews. Additional trials are needed to examine the efficacy

of LMWH for the treatment of pulmonary embolism, but reviews of existing trials indicate that LMWH is at least as effective as unfractionated heparin for these patients as well. This is level 1 evidence.

Is Outpatient Treatment of VTE Safe and Effective When Compared with Inpatient Treatment?

Thirteen studies compared the outcomes of patients with VTE treated with LMWH administered at home with outcomes of those treated with unfractionated heparin in the hospital (30–42). Four of these were randomized trials (30–32, 42); 9 were cohort studies. An additional 5 studies, including 2 randomized trials (43, 44), compared outcomes and costs for patients receiving LMWH at home with those for patients receiving LMWH in the hospital (43–47).

The studies used subcutaneous enoxaparin, nadroparin, tinzaparin, or dalteparin at varying dosages, and then an oral anticoagulant during follow-up. At least 8 studies allowed a brief inpatient admission for stabilization of patients randomly assigned to the outpatient group.

Three studies permitted enrollment of patients with concomitant pulmonary embolism (38, 41, 47), while 1 prospective cohort study required stable patients with pulmonary embolism (45). The remaining studies excluded these patients. Inclusion criteria were restrictive—investigators screened far more patients than they enrolled. Most studies excluded patients with previous VTE, thrombophilic conditions, or significant comorbidity; pregnant patients; and patients unlikely to adhere to outpatient therapy. Few studies reported on the adequacy of anticoagulation with heparin during the heparin treatment period or in the oral anticoagulation period.

Across all groups, the percentages of patients having recurrent DVT ranged from 0% to 9%, with minimal differences according to treatment. Pulmonary embolism rarely occurred in any group in any study. The incidence of major bleeding ranged from 0% to 4%, and the percentage of patients dying during follow-up ranged from 0% to 18%, with minimal differences between groups. The cohort study that exclusively enrolled patients with pulmonary embolism found no significant difference in event rates (45). All these studies, however, may have been underpowered to detect a difference in event rates between

Table 2. Systematic Reviews Comparing Low-Molecular-Weight Heparin with Unfractionated Heparin (n = 10)*

Outcome	Range of Odds Ratios†		
	Cluster A (17, 21)	Cluster B (14, 16, 20, 25, 28)	Cluster C (23, 26, 27)
Recurrent venous thromboembolism	0.47–0.53 (relative risks)	0.77–0.85	0.66–0.76
Major bleeding	0.28–0.47 (relative risks)	0.57–0.71	0.56–0.67
Death	0.54–0.56 (relative risks)	0.68–0.76	0.68–0.78

* Five descriptive studies were not included in these results (11, 18, 19, 22, 24); also excluded were references 12 and 15. In column headings, numbers in parentheses are reference citations.

† <1 favors low-molecular-weight heparin. "Cluster" = systematic reviews containing common primary articles.

Table 3. Catheter-Directed Thrombolysis for Deep Venous Thrombosis*

Study, Year (Reference)	Lytic Agent	Patients, n	Significant Lysis, %†	Partial Lysis, %	Complete Lysis, %	Major Bleeding, %	Minor Bleeding, %
Randomized trials							
Elsharawy and Elzayat, 2002 (48)	SK	35	SK: 100 AC: 0	SK: 39 AC: 0	SK: 61 AC: 0	0	0
Cohort studies							
Grunwald and Hofmann, 2004 (63)	t-PA	82	97–100	26–50	50–71	3–8	10–16
Sugimoto et al., 2003 (58)	t-PA or UK	54	t-PA: 87 UK: 83 (<i>P</i> = 0.69)	t-PA: 29 UK: 47 (<i>P</i> = 0.56)	t-PA: 58 UK: 47 (<i>P</i> = 0.39)	t-PA: 2† UK: 2† (<i>P</i> = 0.96)	t-PA: 9† UK: 10‡ (<i>P</i> = 0.80)
Castaneda et al., 2002 (55)	r-PA	25	92	0	92	4	0
Razavi et al., 2002 (53)	TNK	36	83	33	50	2†	7†
Horne et al., 2000 (56)	t-PA	28	UE: 59 LE: 90	UE: NR LE: 50	UE: 59 LE: 40	0	21
Ouriel et al., 2000 (57)	r-PA	11	NR	NR	73	9	18
Mewissen et al., 1999 (49)	UK	303	NR	52	31	11	16
Raju et al., 1998 (54)	UK	24	71	17	NR	8	8
Bjarnason et al., 1997 (51)	UK	87	NR	NR	79	6	13
Semba and Dake, 1994 (52)	UK	27	92	20	72	0	NR
Ogawa et al., 2005 (60)	UK	24	54	33	21	0	0
Laiho et al., 2004 (61)	r-PA	16	81	NR	NR	13	25
Sillesen et al., 2005 (62)	r-PA	45	93	NR	NR	2	9
Acharya et al., 2005 (59)	r-PA	5 (postpartum)	100	20	80	NR	NR

* AC = anticoagulant; LE = lower extremity; NR = not reported; r-PA = reteplase; SK = streptokinase; t-PA = tissue plasminogen activator; TNK = tenecteplase; UE = upper extremity; UK = urokinase.
 † Significant lysis is the sum of partial lysis and complete lysis.
 ‡ Combined complication rates from treatment of arterial and venous occlusions.

treatment groups. Fewer inpatient days accrued in the treatment groups that used LMWH after a brief inpatient stay or entirely at home than in the groups using unfractionated heparin in the hospital.

Ten of these 17 studies reported on treatment costs (30, 33, 34, 37–39, 41, 43, 44, 46), including an analysis of hospital discharge data (38). Nine of the 10 studies suggested cost savings with outpatient therapy when compared with inpatient therapy. Each study included different items in the tabulations of costs, thereby limiting comparison of the savings across studies.

While outcomes did not differ between groups, equivalency cannot be definitively claimed. It is important to note that many presenting patients were denied enrollment in these trials. In addition, in observational studies, sicker patients are more likely to be treated as inpatients, potentially confounding the results. Still, the direction of the results was consistent. It is likely that LMWH at home is at least as safe as inpatient treatment for DVT, in appropriately chosen patients if required support services are in place. Little evidence exists regarding outpatient treatment of pulmonary embolism. This is level 1 evidence for DVT treatment.

Is It Cost-Effective or Cost-Saving to Use LMWH rather than Unfractionated Heparin for Initial Treatment of VTE?

This question is addressed in Appendix 2 (available at www.annals.org). The evidence strongly supports that use of LMWH is cost-saving or, at a minimum, cost-effective

compared with use of unfractionated heparin for VTE, generally regardless of treatment setting.

Does Catheter-Directed Thrombolysis for Treatment of DVT Reduce Recurrence Rates and Reduce the Incidence of Postthrombotic Syndrome Relative to Standard Anticoagulation?

Catheter-directed thrombolysis involves administration of thrombolytics directly through the side ports of a catheter traversing the thrombus. Only 1 randomized trial has evaluated catheter-directed thrombolysis. It compared catheter-directed thrombolysis followed by 6 months of warfarin with use of intravenous heparin followed by warfarin (48). This study enrolled 35 of 207 screened patients with acute iliofemoral DVT; most exclusions were due to recent surgery. Some patients had already received heparin at the time of enrollment. Six months after treatment, the patency rate was significantly higher in the group that received catheter-directed thrombolysis (13 of 18 [72%] vs. 2 of 17 [12%]), and the prevalence of venous reflux was significantly lower (2 of 18 [11%] vs. 7 of 17 [41%]).

Fourteen studies of catheter-directed thrombolysis were observational (Table 3). The largest series, from the National Deep Venous Thrombosis Registry, involved 287 patients enrolled from 63 centers for treatment of symptomatic iliofemoral and femoral–popliteal DVT with catheter-directed thrombolysis (49). Greater than 50% lysis was achieved in 83% of cases. The degree of lysis correlated with long-term outcomes: 100%, 50% to 99%, and under 50% lysis resulted in 1-year patency rates of 79%, 52%,

and 32%, respectively. Acute occlusions were more thoroughly lysed than were chronic occlusions (34% vs. 19% for complete lysis; 86% vs. 68% for significant lysis). Patients with iliofemoral DVT had significantly greater 1-year patency rates than patients with femoral–popliteal DVT (64% vs. 47%). To assess health-related quality of life, Comerota and colleagues (50) recruited 68 patients from the Venous Registry who had undergone thrombolysis. After a mean 16 months, patients treated with catheter-directed thrombolysis reported significantly better overall physical functioning, less stigma, less health distress, and fewer postthrombotic symptoms than patients treated with anticoagulation alone.

The other published studies were single-institution case series that involved a total of 802 patients (51–63). The enrolled patients were heterogeneous, consisting of those with upper- or lower-extremity DVT, and most series had minimal long-term follow-up. The rates of complete thrombolysis (>95% lysis) ranged from 40% to 92% across series, and rates of complete or partial thrombolysis (defined as 50% to 100% lysis) ranged from 50% to 100%. Besides the Venous Registry, just 4 studies reported on the long-term results of catheter-directed thrombolysis, with generally favorable results for vein patency, the postthrombotic syndrome, and venous competence (51, 60–62). The rates of major bleeding in these case series ranged from 0% to 13%, and rates of minor bleeding ranged from 0% to 25%, with no uniformity in assessment methods. In the Venous Registry, 1 fatal intracranial hemorrhage and 1 subdural hematoma occurred. No other study reported intracranial hemorrhage.

The literature suggests that catheter-directed thrombolysis may be efficacious in well-chosen patients. Additional randomized trials are needed to confirm that the outcomes of patients treated with catheter-directed thrombolysis are superior to those in patients receiving standard anticoagulation, to better define which patients may benefit most from this therapy, and to more thoroughly evaluate the risks of this procedure. Evidence on how the magnitude of clot burden influences response to catheter-directed thrombolysis is limited. This is level 2 evidence.

Are Compression Stockings Efficacious at Reducing the Incidence of the Postthrombotic Syndrome?

Three randomized, controlled trials have examined the efficacy of compression stockings for prevention of postthrombotic syndrome after DVT (64–66). The diagnosis of postthrombotic syndrome does not have a widely accepted set of criteria, so these trials used different instruments for diagnosis. All the trials documented eligibility criteria, had objective measures of the outcome (postthrombotic syndrome), and masked the outcome assessors to group assignment. Follow-up lasted nearly 5 years in each of these trials.

The earliest and largest trial, with 194 patients, involved custom-made compression stockings that patients

began wearing within the first month of developing proximal DVT and continued wearing for at least 2 years (64). After 5 years of follow-up, the incidence of postthrombotic syndrome in the stocking group was significantly lower than in the no-stocking group (20% vs. 47%, respectively, had mild to moderate postthrombotic syndrome, and 11% vs. 23%, respectively, had severe postthrombotic syndrome). The second trial involved 47 patients who were randomly assigned to graded compression stockings beginning 1 year after the index DVT event or to stockings without hemodynamic compression (65). This trial did not demonstrate benefit with use of compression stockings. The most recent trial enrolled 180 patients randomly assigned to over-the-counter, sized-to-fit compression stockings beginning 1 week after the event or to no stockings (66). The cumulative incidence of postthrombotic syndrome at the end of 2 years was 25% in the stocking group and 49% in the control group (hazard ratio, 0.49 [95% CI, 0.29 to 0.84]). Severe postthrombotic syndrome developed in 3% of patients in the stocking group and in 11% of those in the control group. Most postthrombotic syndrome end points were reached within the first 6 months (cumulative incidence at 6 months, 21% and 40%, respectively), events that were not counted in the other 2 studies.

Thus, the 2 trials that enrolled patients early demonstrated a reduction in the incidence of the postthrombotic syndrome among patients wearing compression stockings, whether over-the-counter stockings or more expensive custom-fit stockings (64, 66). Most diagnoses of the postthrombotic syndrome occurred within the first 1 or 2 years. This is level 1 evidence.

What Are the Incidences of Pulmonary Embolism and DVT Recurrences after Placement of Vena Cava Filters?

Vena caval interruption has been used in treatment of DVT to prevent pulmonary embolism since the early 1970s. We identified a single randomized trial (67) and 1 population-based study (68) that addressed this question. Elsewhere, we have reviewed in detail 107 case series reporting on the outcomes of patients receiving vena cava filters (69).

Decousus and colleagues (67) used a 2 × 2 factorial design to randomly assign 400 patients with proximal DVT with or without pulmonary embolism judged to be at high risk for pulmonary embolism; the 2 treatments were a vena cava filter or no filter along with unfractionated heparin or enoxaparin, followed by a vitamin K antagonist. Patients did not have contraindications to heparin therapy. Pulmonary ventilation–perfusion scanning was performed within 48 hours of enrollment and again after 8 or 12 days if no symptomatic pulmonary embolism had occurred. After 12 days, filter recipients had significantly fewer total (symptomatic and asymptomatic) pulmonary emboli than the group without filters (Table 4). Filter placement, however, was not associated with a reduction in incident symptomatic pulmonary embolism. After 8 years,

Table 4. Randomized, Controlled Trial of Vena Cava Filter Placement with Anticoagulation Compared with Anticoagulation Alone*

Type of Outcome	Outcomes at 12 Days, %			Outcomes at 2 Years, %			Outcomes at 8 Years, %		
	Filter plus Anticoagulation	Anticoagulation Alone	P Value	Filter plus Anticoagulation	Anticoagulation Alone	P Value	Filter plus Anticoagulation	Anticoagulation Alone	P Value
Pulmonary embolism	1.1	4.8	0.03	NR			NR		
Symptomatic pulmonary embolism	1.1	2.6	0.25	3.4	6.3	0.16	6.2	15.1	0.008
Recurrent deep venous thrombosis	NR			20.8	11.6	0.02	35.7	27.5	0.042
Major bleeding	4.5	3.0	0.44	8.8	11.8	0.41	15.4	18.5	0.52
Death	2.5	2.5	0.99	21.6	20.1	0.65	48.1	51.0	0.83

* From references 67 and 70. NR = not reported.

significantly fewer filter recipients had a symptomatic pulmonary embolism than patients without filters. However, DVT was significantly more common among the patients in the filter group, and mortality was similar in both groups. Only 35% of patients received vitamin K antagonists over the study period (70). At the time this study was initiated, extended-duration anticoagulation was not used for patients at high risk for recurrence as often as it is today. In addition, this study provides no information about the effectiveness of filters for the patient who does not receive early anticoagulation, the typical patient for whom filter placement is considered.

White and colleagues (68) conducted a population-based observational study of patients with VTE. Using administrative data, the authors identified patients with VTE who did and did not receive vena caval filters between January 1991 and December 1995. No information on medication use, including anticoagulants, was available in the source data. After adjustment for risk factors associated with recurrent VTE, recipients of vena caval filters were as likely as nonrecipients to be admitted for pulmonary embolism. Filter placement was associated with a twofold increase in the relative hazard of subsequent DVT, although only among patients with an initial pulmonary embolism. The time to recurrent pulmonary embolism was similar in filter recipients and nonrecipients. Among patients without a previous hospitalization for VTE treatment, mortality was higher for filter recipients than control patients (relative hazard ratio, 1.71 [CI, 1.55 to 1.88]). Since 1973, 107 case series have reported on the outcomes of 9533 patients who received 1 of 9 different vena caval filters (69). The case series data are severely limited by the absence of a control group, significant differences between studies in population characteristics, and the varying durations and completeness of follow-up.

Recently, several retrievable vena caval filters have been approved for use in the United States. These filters may be an attractive alternative to permanent vena caval filters for patients with a temporary contraindication to anticoagulation. Outcome data for retrievable filters are limited to case series; further information is necessary before their efficacy relative to permanent filters can be established (71).

In summary, the evidence suggests that vena caval filters may be only modestly efficacious in reducing recurrence of pulmonary emboli and do not affect mortality. This is level 2 evidence.

What Is the Optimal Duration of Vitamin K Antagonist Therapy for VTE Treatment, and What Is the Optimal International Normalized Ratio for Extended-Duration Therapy?

We identified trials that randomly assigned patients to different durations of VTE treatment with a vitamin K antagonist. We restricted our review to 10 trials, published since 1995, that used objective radiologic documentation of VTE and measured therapeutic intensity by using the international normalized ratio (INR). Patients with cancer or patients at high risk for bleeding were excluded from all but 1 study (72). Anticoagulation management generally was performed in specialized anticoagulation clinics. These trials included 4240 patients (72–81).

As shown in Table 5, we separated the arms of the studies by duration of treatment to examine event rates across trials. The rates of recurrent DVT in these trials varied depending on whether enrolled patients had had idiopathic DVT (75, 78–80); DVT in the setting of a transient risk factor (81); or a permanent risk factor for recurrent DVT, including a history of thromboses (74). The incidence of recurrent VTE declined stepwise as the duration of anticoagulation increased from 3 or fewer months to longer than 12 months (extended-duration therapy) with conventional-intensity therapy (INR, 2 to 3). The incidence of major bleeding increased from 0.4 bleeding episode per 100 patient-years among patients receiving 3 or fewer months of anticoagulation to 1.5 bleeding episodes per 100 patient-years among patients receiving extended-duration therapy. Total adverse events (recurrent VTE or major bleeding or death) declined as duration of therapy increased.

In the single study of calf vein DVT, recurrent VTE was similar among patients treated for 6 or 12 weeks with a vitamin K antagonist (1.9 episodes of VTE per 100 patient-years [CI, 0.2 to 6.9] vs. 3.5 episodes of VTE per 100 patient-years [CI, 1 to 9.9], respectively) (77). In the only

study that exclusively enrolled patients presenting with a second episode of VTE, extended-duration conventional-intensity therapy (INR, 2.0 to 2.85) was associated with fewer recurrences than was termination after 6 months of therapy (0.7 VTE episode per 100 patient-years [CI, 0.1 to 1.9] vs. 5.2 VTE episodes per 100 patient-years [CI, 3.3 to 7.8]) (74). A trend toward more major bleeding was noted among patients receiving extended-duration therapy. Only 1 study, which was stopped early for slow accrual, examined the duration of therapy for patients with provoked VTE (81). Rates of recurrence and bleeding were similar in the group treated for 1 month and the group treated for 3 months.

While some studies randomly assigned patients at the initiation of oral anticoagulation therapy (73,74, 77), most studies assigned patients after the completion of 1 or more months of oral therapy (72, 75,76, 78–81). Since the first 3 months of therapy are the highest-risk period for recurrent thromboembolism and for bleeding during anticoagulation, this design would underestimate recurrent VTE and bleeding rates, although it is unclear how this affects the comparison between treatment groups. Three of the 4 studies of extended-duration anticoagulation enrolled patients after at least 3 months of therapy (75, 78, 80). However, because 80% to 90% of recurrent VTE episodes occurred after discontinuation of therapy, this design should not have influenced the trial results substantially. Of note,

the results from the extended-duration anticoagulation studies reflect follow-up of fewer than 4 years. It is unclear whether the risk–benefit ratio of extended-duration conventional-intensity anticoagulation diminishes during longer treatment. No study assessed bleeding rates among patients who resumed anticoagulation after recurrent VTE.

In summary, level 1 evidence suggests that extended-duration conventional-intensity oral anticoagulation may be optimal treatment for patients with unprovoked VTE or following a second episode of VTE. Level 2 evidence indicates that patients with a provoked episode of VTE may be well served with just 3 months of anticoagulation.

What Is the Evidence to Support Use of LMWH in Place of a Vitamin K Antagonist for Treatment of VTE?

We identified 10 randomized trials that compared the safety and efficacy for LMWH versus oral vitamin K antagonists for treatment of VTE (82–91). We also reviewed 1 large prospective cohort study (92). These 10 trials, published between 1994 and 2005, are high-quality studies that completely described the patient populations, radiographically documented the index VTE, and clearly described either active surveillance for VTE recurrence or methods for identifying symptomatic recurrences. The documentation of losses to follow-up was excellent. Most studies had extensive eligibility criteria that limited generalizability, and all were open-label. The percentage of time

Table 5. Event Rates by Duration of Anticoagulation after Venous Thromboembolism*

Study, Year (Reference)	Recurrent VTE (95% CI)	Major Bleeding (95% CI)	Total Adverse Events (95% CI)†
Anticoagulation ≤ 3 mo			
Levine et al., 1995 (72)	9.7 (5.9–15.2)	0.5 (0–2.8)	19.3 (14–26)
Schulman et al., 1995 (73)	10.2 (8.2–12.5)	0.1 (0–0.6)	12.8 (10.5–15.3)
Kearon et al., 1999 (75)	27.3 (15.9–43.8)	0 (0–5.9)	32.1 (19.6–49.6)
DOTAVK Study, 2001 (77)	7.8 (4.8–11.9)	1.9 (0.6–4.3)	NR
Warfarin Optimal Duration Italian Trial, 2001 (76)	5.1 (3.2–7.8)	0.5 (0–1.8)	7.3 (5.1–10.4)
Warfarin Optimal Duration Italian Trial, 2003 (79)	4.1 (2.4–6.5)	0.2 (0–1.3)	6.6 (4.6–9.4)
Kearon et al., 2004 (81)	5.5 (2.4–10.9)	0 (0–2.5)	6.2 (2.9–11.8)
Anticoagulation 4–12 mo			
Schulman et al., 1995 (73)	4.7 (3.4–6.4)	0.6 (0.3–1.4)	7.2 (5.5–9.1)
Schulman et al., 1997 (74)	5.2 (3.3–7.7)	0.7 (0.2–2.1)	9.5 (6.8–12.7)
DOTAVK Study, 2001 (77)	8.6 (5.4–12.8)	2.6 (1–5.4)	
Warfarin Optimal Duration Italian Trial, 2001 (76)	5 (3.1–7.6)	1 (0.2–2.4)	7.6 (5.2–10.7)
Warfarin Optimal Duration Italian Trial, 2003 (79)	3.1 (1.7–5.2)	0.6 (0.1–1.8)	6.3 (5.2–8.9)
Continuous anticoagulation (INR, 1.5–2)			
Extended Low-Intensity Anticoagulation for Thrombo-Embolic, 2003 (80)	1.8 (1–2.9)	1 (0.5–1.9)	4.6 (3.3–6.3)
PREVENT, 2003 (78)	2.6 (1.4–4.4)	0.9 (0.3–2.2)	4.3 (2.7–6.4)
Continuous anticoagulation (INR, 2–3)			
Schulman et al., 1997 (74)	0.7 (0.2–1.9)	2.2 (1.0–4.0)	5 (3.1–7.4)
Kearon et al., 1999 (75)	1.3 (0–7.1)	3.8 (0.8–11.1)	6.3 (2.1–14.8)
Extended Low-Intensity Anticoagulation for Thrombo-Embolic, 2003 (80)	0.7 (0.2–1.5)	0.9 (0.4–1.8)	2.5 (1.6–3.8)

* Values are rate of events per 100 patient-years. DOTAVK = Durée Optimale du Traitement AntiVitamines K; INR = international normalized ratio; NR = not reported; PREVENT = Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients; VTE = venous thromboembolism.

† Refers to recurrent episodes of venous thromboembolism or major bleeding or death.

that the INR was in a therapeutic range was not particularly high and is probably similar to the degree of control achieved by patients receiving usual clinical care.

The largest trial (336 patients in each group) treated patients with cancer and normal serum creatinine levels for 6 months with dalteparin or warfarin (85). The recurrence rates were high but were significantly lower in the patients receiving LMWH than those receiving warfarin (4% vs. 11% for DVT and 4% vs. 5% for pulmonary emboli), with no significant difference in the prevalence of bleeding. The other trial with a restricted patient population was a trial in 100 patients older than 75 years of age (89). Patients received enoxaparin or acenocoumarol for 3 months (or for 6 months for those with a history of DVT) and reported symptom recurrences for 1 year. Seven events occurred in the enoxaparin group and 5 in the acenocoumarol group, with 2 bleeding episodes in the acenocoumarol group. The 7 other trials (with 50 to 100 patients per group) were similar in design; most randomly assigned patients to 3 months of LMWH or an oral anticoagulant after initial, standard treatment. In no trial did the rates of recurrence of VTE substantially differ between the groups. The bleeding rates in all the LMWH groups were either similar to or below the rates in the oral anticoagulant groups.

The 1 large prospective cohort study followed 410 patients receiving dalteparin and 244 patients receiving warfarin after initial treatment with dalteparin (92). Patients were treated for 3 months after DVT and for 6 months after pulmonary embolism. The two groups differed in their risk factors for the index event, and patients with higher bleeding risk were assigned to the LMWH group. Nine patients in the dalteparin group (2.2%) and 5 patients in the warfarin group (2.0%) had VTE recurrences. Three patients bled while receiving dalteparin and 2 bled while receiving warfarin. Four vertebral fractures were reported in the LMWH group. The authors concluded that long-term therapy with LMWH is effective and safe.

The evidence supports the use of LMWH instead of oral anticoagulation for VTE in select patients. Low-molecular-weight heparin LMWH may be a useful treatment for patients in whom INR control is difficult and may be as efficacious as or more efficacious than oral anticoagulants in patients with cancer. The most recent trial included cost data and demonstrated modest savings with use of tinzaparin, largely because of a reduction in initial hospital days (91). However, a high-quality cost-effectiveness analysis that modeled the use of 6 months of dalteparin compared with 6 months of warfarin demonstrated that LMWH was relatively expensive (incremental cost-effectiveness ratio, \$149 864/quality-adjusted life-year) (93). The LMWH strategy could be cost-effective if the daily drug cost was less than \$18 per day. This is level 1 evidence.

What Are the Optimal Therapies for Pregnant Women with VTE?

Risk for VTE is 5 times higher than that of nonpregnant women. The absolute risk for symptomatic VTE during pregnancy is between 0.5 and 3.0 per 1000 woman (94). We identified 30 studies that evaluated treatment of VTE during pregnancy. After we excluded studies that evaluated only prophylaxis, very small studies, and those without clinical outcomes, we had 14 studies for review (95–108).

Studies were published between 1985 and 2003. All were observational studies. Most were underpowered for all outcomes. Most studies evaluated the use of LMWH on maternal thrombosis-related end points, although 2 included fetal outcomes (95, 99). Three studies evaluated the safety of vena caval interruption (100–102). The largest study was a retrospective review of the safety of enoxaparin in 624 pregnancies, including 49 women with acute VTE (99).

The total number of women treated exclusively with LMWH was 195. Across all studies, few patients had recurrent VTE or severe bleeding. Three of the authors commented that the fetal deaths were thought not to be related to heparin or LMWH (97, 99, 104). The relationship between drug dose and anti-factor Xa levels varied across studies, so the need for monitoring and dosage adjustment in this population is not known.

In 3 case series, Aburahma and colleagues evaluated the use of vena cava filters in pregnant women with acute DVT (100–102). The latest study evaluated filter placement in 18 women and followed them for a mean 78 months (100). Three of the 7 patients receiving filters close to delivery had extension of DVT, but no pulmonary emboli, bleeding events, or fetal morbidity occurred. The authors also reviewed the outcomes for patients who had been treated with heparin or with heparin plus filter placement (101, 102). Pulmonary emboli and bleeding occurred only in the group receiving heparin without a filter. These series probably included many of the same patients.

The 3 other studies reported on patients treated in the era before LMWH. Rosfors and colleagues (106) retrospectively identified patients who had VTE during pregnancy and reviewed medical records for up to 16 years after the event. Six of 25 patients had a second episode of VTE, and many had mild symptoms of venous disease. Tawes and coworkers (107) looked at patients who received intravenous heparin compared with those who received subcutaneous heparin, and Berquist and colleagues (108) reported on outcomes for women treated with intravenous heparin followed by subcutaneous heparin. Few events occurred in these 2 small studies.

While LMWH as a prophylactic therapy for pregnant women has been extensively studied, fewer than 200 pregnant women have been treated with LMWH in observational studies of treatment of DVT or pulmonary embolism. The case series describing vena cava filters provide

weak evidence to support filter use. The evidence on management of VTE during pregnancy is level 3.

DISCUSSION

The evidence indicates that LMWH is modestly superior to unfractionated heparin for initial treatment of DVT and is at least as effective as unfractionated heparin for treatment of pulmonary emboli. Outpatient therapy is probably safe and effective in well-chosen patients when appropriate support services are available. From a third-party payer's perspective, LMWH use is cost-saving or cost-effective compared with unfractionated heparin for treatment of VTE. Catheter-directed thrombolysis is efficacious in carefully selected patients, although this evidence is not strong. The literature supports early use of compression stockings to reduce postthrombotic syndrome. Vena cava filters may be only modestly efficacious for preventing pulmonary emboli, and there is little evidence to support their use. Extended-duration, conventional-intensity oral anticoagulation is the optimal treatment for patients with unprovoked VTE, although patients with transient risk factors appear not to benefit from more than 3 months of therapy. High-quality randomized trials support the use of LMWH instead of oral anticoagulation, particularly in patients with malignant conditions. Little evidence exists regarding treatment of VTE during pregnancy.

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APPENDIX 1

1. Articles were *excluded* if any of the below were true:

- A. Article is not in English
- B. Article does not include human data
- C. Article is a meeting abstract (no full article for review)
- D. Article focuses on prevention of VTE
- E. Article does not apply to a key question
- F. Article is a case report with only 1 patient

2. Additional, question-specific criteria

1) *Is heparin or LMWH safer and more efficacious for initial treatment of VTE?*

Systematic reviews or meta-analysis; primary articles in reviews must have included trials with outcomes of death, recurrent VTE, or bleeding.

2) *Is outpatient treatment of VTE safe and effective when compared with inpatient treatment?*

Must have included outcomes of death, recurrent VTE, or bleeding; randomized, controlled trials or cohort studies included, but studies must have included a comparison group.

3) *Is LMWH cost-effective when compared with heparin?*

Studies must have included modeled analyses of this comparison.

4) *Does catheter-directed thrombolysis reduce VTE recurrences and the incidence of postthrombotic syndrome?*

- a. Uses a thrombolytic medication.
- b. Thrombolytic medication is administered to the lesion via a catheter in at least 1 group of patients.
- c. At least 10 patients with venous disease are treated.
- d. Outcomes include bleeding, venographic response, or symptoms.
- e. Most patients are *not* included in a more recent publication.
- f. Streptokinase is not currently used for thrombolytic therapy because of risks.

5) *Does use of compression stockings reduce the incidence of the postthrombotic syndrome?*

Randomized, controlled trials with outcome of the postthrombotic syndrome.

6) *To what extent do vena cava filters alter the incidence of pulmonary embolism and recurrent DVT?*

Randomized, controlled trials or cohort study; case series were excluded.

7) *What is the optimal duration of therapy with vitamin K antagonists for VTE?*

- a. Study includes a comparison group and was published since 1995.
- b. All patients have radiologic documentation of index VTE.
- c. Intensity of therapy monitored with the INR.

8) *Is there evidence to support use of LMWH in place of vitamin K antagonists?*

Randomized, controlled trials or prospective cohort studies.

9) *What is the best therapy for pregnant women with VTE?*

Randomized, controlled trials or cohort studies.

APPENDIX 2: COST-EFFECTIVENESS

Is It Cost-Effective or Cost-Saving To Use LMWH Rather than Unfractionated Heparin for the Initial Treatment of VTE?

We identified 14 studies that used decision analysis methods to address the costs of treatment with LMWH compared with unfractionated heparin, regardless of setting (109–122). These were published between 1997 and 2006. As detailed in **Appendix Table 2**, 7 studies were designed as cost-effectiveness studies (110–113, 115, 118, 122), 6 were cost-minimization studies (109, 114, 116, 117, 120, 121), and 1 used a decision model that could not be classified as either (119). A societal perspective was used in quantifying costs in 3 studies (110, 113, 117), whereas the other 11 took the perspective of a third-party payer or the provider.

The comparisons fell into 2 categories. Seven of the studies modeled the use of LMWH compared with unfractionated heparin, with all drugs administered in the hospital (109–111, 113, 115, 116, 120). The other studies modeled the use of LMWH at home compared with unfractionated heparin in the hospital (112, 114, 117, 119, 121, 122). The source of the estimates for the costs used in the models varied, with half of the studies using actual costs measured in the setting of a clinical trial. The others used costs obtained from databases maintained by the government or a payer, or used costs abstracted from literature review. Similarly, the rates of events included in the models came from actual data observed in trials or from the literature. For the models, 3 of the studies assumed, on the basis of earlier work, that the rates of recurrent thromboses and adverse events were equivalent for LMWH and unfractionated heparin (114, 116, 121).

Appendix Table 3 details the results of these studies. Of the 3 cost-minimization studies that compared inpatient low-molecular-weight heparin treatment to inpatient unfractionated heparin treatment, 1 projected a 57% cost savings with use of nadroparin instead of unfractionated heparin (116), and 1 projected a 32% savings with dalteparin rather than unfractionated heparin (120). The other study found no difference in costs between treatment with enoxaparin and unfractionated heparin,

cautioning that these costs were accrued in the setting of a clinical trial; as a result the costs were greater than those that would be seen in usual practice, particularly in the enoxaparin group (109). One of the 4 cost-effectiveness studies of this comparison found that inpatient tinzaparin was both less costly and more efficacious than unfractionated heparin (115); similarly, 1 found that inpatient bempaparin dominated unfractionated heparin in the cost-effectiveness analysis (111). The high-quality cost-effectiveness study by Gould and colleagues modeled the use of enoxaparin and unfractionated heparin in the hospital and found that although enoxaparin treatment is more expensive, it is cost-effective compared with unfractionated heparin because of the gain in quality-adjusted life-years (113). In a secondary analysis, the authors modeled costs if some of the patients receiving enoxaparin were treated as outpatients. They found that if only 8% of the patients were treated as outpatients, this treatment would be not just cost-effective but even cost-saving. A very similar analysis by Aujesky and colleagues reported comparable findings, with cost savings anticipated if just 8% of patients using LMWH are discharged from the hospital early (within 3 days) or if the daily cost of LMWH is under \$51 (in 2005 U.S. dollars) (110).

All of the studies investigating outpatient LMWH compared with inpatient unfractionated heparin found that use of LMWH in outpatients was less costly than hospitalization for unfractionated heparin. The cost-effectiveness study by Estrada and colleagues (112) found that use of LMWH at home for clinically stable patients and in the hospital for unstable patients yielded a 10% cost savings over use of unfractionated heparin in the hospital for all patients. The authors noted that the cost savings were largely due to savings on inpatient costs. Rodger and colleagues similarly found a cost savings of 23% when this comparison was made (118). The 3 cost-minimization studies found outpatient LMWH to yield a cost savings of 57% (117), 64% (114), and 91% (121) compared with inpatient unfractionated heparin.

The cost-effectiveness studies were consistent in suggesting that LMWH is either cost-saving or cost-effective compared with unfractionated heparin.

Appendix Table 1. Individual Studies Included in Systematic Reviews*

Study, Year	Green et al., 1994 (15)	Hirsh et al., 1995 (17)	Lensing et al., 1995 (21)	Leizorovicz, 1996 (20)	Howard, 1997 (18)	Brewer, 1998 (11)	Hettiarachchi et al., 1998 (16)	Hunt, 1998 (19)	Martineau and Tawil, 1998 (22)	Gould et al., 1999 (14)	Dolovich et al., 2000 (28)	Rocha et al., 2000 (25)	van Den Belt et al., 2000 (26)	van der Heijden et al., 2000 (27)	Raschke et al., 2003 (24)	Quinlan et al., 2004 (23)	Mismetti et al., 2005 (12)
Levine, 1991	x							x									
Lassen, 1991	x							x									
Turpie, 1986	x							x									
Hull, 1993	x							x									
Leyvraz, 1991	x							x									
Spiro, 1991	x																
Danish Enoxaparin Study Group, 1991	x																
Eriksson, 1991	x																
Leyvraz, 1992	x																
German Hip Arthroplasty Trial Group, 1992	x																
Planes, 1989	x																
Hoek, 1989	x																
Dechiavanne, 1989	x																
RD Heparin Arthroplasty Group (in review)	x																
Simonneau et al., 1993		x	x	x			x	x	x	x	x	x	x	x	x		
Hull et al., 1992		x	x	x			x	x	x	x	x	x	x	x	x		
Prandoni, 1992		x	x	x			x	x	x	x	x	x	x	x	x		
Lopaciuk, 1992		x	x	x			x	x	x	x	x	x	x	x	x		
Bratt, 1990		x	x	x				x	x	x	x	x	x	x	x		
Holm, 1986		x	x	x				x	x	x	x	x	x	x	x		
Bratt, 1985		x	x	x				x	x	x	x	x	x	x	x		
Lindmarker, 1994		x	x	x			x	x	x	x	x	x	x	x	x		
Duroux, 1991		x	x	x			x	x	x	x	x	x	x	x	x		
Favre, 1988		x	x	x			x	x	x	x	x	x	x	x	x		
Albada, 1989		x	x	x				x	x	x	x	x	x	x	x		
Thery, 1992		x	x	x				x	x	x	x	x	x	x	x		
Handeland, 1990		x	x	x													
Favre, 1987			x														
Levine, 1996			x	x	x	x	x	x	x	x	x	x	x	x	x		x
Koopman, 1996			x	x	x	x	x	x	x	x	x	x	x	x	x		x
European Multicenter Study, 1991			x	x	x	x	x	x	x	x	x	x	x	x	x		x
Notarbartolo, 1988			x	x	x	x	x	x	x	x	x	x	x	x	x		x
Harenberg, 1990			x	x	x	x	x	x	x	x	x	x	x	x	x		x
Tedoldi, 1993			x	x	x	x	x	x	x	x	x	x	x	x	x		x
Etude Multicentrique Francaise, 1989			x	x	x	x	x	x	x	x	x	x	x	x	x		x
Znaghi, 1988			x	x	x	x	x	x	x	x	x	x	x	x	x		x
Lindmarker, 1993			x	x	x	x	x	x	x	x	x	x	x	x	x		x
Loumanmaki, 1994			x	x	x	x	x	x	x	x	x	x	x	x	x		x
Flessinger, 1994			x	x	x	x	x	x	x	x	x	x	x	x	x		x
Kakkar, 1993								x									
Caen, 1988								x									
Kakkar, 1986								x									
Harti, 1990								x									
Bergqvist et al., 1986								x									

Continued on following page

Appendix Table 1—Continued

Study, Year	Green et al., 1994 (15)	Hirsh et al., 1995 (17)	Lensing et al., 1995 (21)	Leizorovitz, 1996 (20)	Howard, 1997 (18)	Brewer, 1998 (11)	Hettiarachchi et al., 1998 (16)	Hunt, 1998 (19)	Martineau and Tawil, 1998 (22)	Gould et al., 1999 (14)	Dolovich et al., 2000 (28)	Rocha et al., 2000 (25)	van Den Belt et al., 2000 (26)	van der Heijden et al., 2000 (27)	Raschke et al., 2003 (24)	Quinlan et al., 2004 (23)	Mismetti et al., 2005 (12)
Bergqvist et al., 1995	x																
Bergvist, 1990	x																
Koller et al., 1986	x																
Ockelford, 1989	x																
Borstad, 1992	x																
Fricke, 1988	x																
Bounameau, 1993	x																
Flessinger, 1996							x	x	x	x	x	x	x	x	x	x	x
Columbus Investigators, 1997				x	x	x	x	x	x	x	x	x	x	x	x	x	x
Simoneau et al., 1997				x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lounanmaki, 1996				x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lensing, 1995				x													
Decousis, 1998							x						x			x	x
Warkentin, 1995								x				x					
Meyer, 1995								x								x	
Gick, 1996								x									
Cairns, 1996								x									
Bergmann, 1996								x									
Planes, 1996								x									
Spiro, 1994								x									
Leizorovitz, 1994								x									
Gazzaniga, 1993								x									
Kikta, 1993								x									
Rasmussen, 1994								x									
FRISC Study Group, 1996								x									
Planes, 1986								x									
Stables and Sigwart, 1996								x									
Kay, 1994								x									
Bergvist, 1996								x									
Clagett, 1995								x									
Slocum, 1996								x									
Lechler, 1996								x									
Falon, 1994								x									
Leizorovitz, 1992								x									
Hull and Pineo, 1994								x									
Partsch, 1996								x									
Kay, 1995								x									
Leclerc, 1994								x									
Hirsch, 1995								x									
Pan, 1996								x									
Preisack, 1993								x									
Gurfinkel, 1995								x									
Braunwald, 1994								x									
Turpie, 1990								x									
Numohamed, 1992								x									
RISC Group, 1990								x									

Appendix Table 1—Continued

Study, Year	Green et al., 1994 (15)	Hirsh et al., 1995 (17)	Lensing et al., 1995 (21)	Leizorovitz, 1996 (20)	Howard, 1997 (18)	Brewer, 1998 (11)	Hettiarachchi et al., 1998 (16)	Hunt, 1998 (19)	Martineau and Tawil, 1998 (22)	Gould et al., 1999 (14)	Dolovich et al., 2000 (28)	Rocha et al., 2000 (25)	van Den Belt et al., 2000 (26)	van der Heijden et al., 2000 (27)	Raschke et al., 2003 (24)	Quinlan et al., 2004 (23)	Mismetti et al., 2005 (12)
Cohen, 1997							x										
Heilmann, 1989								x									
Prandoni, 1990									x								
Harenberg, 2000																	
Merli, 2001																	
Breddin, 2001																	
Belcaro, 1999																	
Kirchmaier, 1998																	
Riess, 2003																	
Findk, 2002																	
Goldhaber, 1998																	
Ninet, 1991																	
Breddin, 1999																	
Campbell, 1998																	
Kuijjer, 1995																	

* FRISC = Fragmin during Instability in Coronary Artery Disease; RISC = Research Group on Instability in Coronary Disease.

Appendix Table 2. Designs of the Modeled Analyses of the Costs of Using Low-Molecular-Weight Heparin Compared with Unfractionated Heparin for Treatment of Venous Thromboembolism *

Study, Year (Reference)	Aims	Design	Perspective and Time Horizon	Comparisons	Sources of Cost Estimates	Sources of Event Rate Estimates	Units of Benefits
Hull et al., 1997 (115)	To perform an economic evaluation comparing tinzaparin to UFH for inpatient treatment of proximal DVT	CE	Third-party payer; 3 mo	Inpatient tinzaparin therapy (175 U/kg daily) Inpatient UFH	Direct medical costs in patients enrolled (1992 Canadian and U.S. dollars)	Observed in trial	Deaths averted, recurrences averted
Rodger et al., 1998 (118)	To assess the cost-effectiveness of LMWH and unfractionated heparin using data from a meta-analysis and patient-specific case-costing data	CE	Third-party payer; 3 mo	Outpatient LMWH if eligible; inpatient LMWH if not Outpatient LMWH if eligible; inpatient UFH if not Inpatient LMWH Inpatient UFH	Case-costing using an online reimbursement-based patient-specific cost accounting system (1995 Canadian dollars)	Systematic literature review	Deaths averted
Goold et al., 1999 (14)	To evaluate the costs and health effects of LMWH compared with unfractionated heparin for inpatient treatment of acute DVT	CE	Societal; death or age 99 y	Inpatient enoxaparin (1 mg/kg twice daily) Inpatient UFH (includes secondary analyses of outpatient enoxaparin)	Medicare reimbursement rates, therapy costs, wholesale prices (1997 U.S. dollars); analysis included 3%/y discounting	From the literature, also used U.S. lifetable to construct survival curves	Quality-adjusted and unadjusted life-years
Estrada et al., 2000 (112)	To evaluate the overall inpatient cost of treating acute VTE with enoxaparin versus unfractionated heparin	CE	Third-party payer; 3 mo	Outpatient LMWH if eligible, inpatient LMWH if not Outpatient LMWH if eligible, inpatient UFH if not Inpatient UFH	Direct medical costs taken from literature review, institutional accounting, and costs to Medicare (1996 U.S. dollars)	Literature	Deaths averted, recurrences averted
Lloyd et al., 1997 (116)	To evaluate the inpatient cost of treating DVT with nadroparin compared with UFH	CM	Third-party payer; 5 d	Inpatient nadroparin (weight-based, twice daily) Inpatient UFH (2 routes: SC or IV)	Direct costs measured as hospital charges to payer (Swiss sickness fund), list prices of drugs	Assumed equivalent in all arms	U.S. dollars
van den Belt et al., 1998 (114)	To assess the cost consequences of outpatient management in the treatment of DVT	CM	Third-party payer; 6 mo	Outpatient fraxiparine (weight-adjusted) Inpatient UFH	Direct medical costs measured in 1 site of multi-center clinical trial (1993 Dutch guilders)	Rates observed in all trial sites, considered equivalent in both groups	Guilders

Study, Year (Reference)	Aims	Design	Perspective and Time Horizon	Comparisons	Sources of Cost Estimates	Sources of Event Rate Estimates	Units of Benefits
O'Brien et al., 1999 (117)	To evaluate the costs of treating a patient with proximal DVT with outpatient enoxaparin versus unfractionated heparin as inpatient therapy	CM	Societal; 3 mo	Outpatient enoxaparin (1 mg/kg twice daily) Inpatient UFH	Canadian national data systems, local labor and therapy costs (1997 Canadian dollars)	Observed in trial, measured health-related quality of life	Canadian dollars (also reported health-related quality of life)
DeLissovoy et al., 2000 (109)	To perform an economic evaluation comparing LMWH with unfractionated heparin for treating a DVT in inpatients and outpatients	CM	Third-party payer; 3 mo	Inpatient enoxaparin (1.5 mg/kg daily or 1.0 mg/kg twice daily) Inpatient UFH	Direct medical costs from 33 U.S. sites participating in multicenter trial (1997 U.S. dollars)	Observed in the 33 U.S. trial sites	U.S. dollars
Tillman et al., 2000 (119)	To evaluate the clinical and economic outcomes associated with implementation of outpatient DVT treatment with LMWH	Decision model	Third-party payer; 3 mo	Outpatient enoxaparin (1 mg/kg twice daily) Inpatient UFH	Direct medical cost measured in outpatients in HMO; source of inpatient costs is unclear (1998 U.S. dollars)	Measured in outpatients	U.S. dollars
Boucher et al., 2003 (121)	To compare the cost of contemporary outpatient and historical inpatient management of proximal lower-limb DVT	CM	Hospital; 7 days	Outpatient tinzaparin or dalteparin Inpatient UFH	Direct hospital costs measured in 1 hospital (2000 Canadian dollars)	Assumed equivalent in both arms	Canadian dollars
Caro et al., 2002 (122)	To evaluate economic and health implications of tinzaparin versus UFH in treatment of DVT	CE	Third-party payer; 3 mo and 50 y	Outpatient tinzaparin once daily Inpatient UFH	Direct medical costs from administrative data, fee schedules, survey data, literature (1999 U.S. dollars)	Event rates from the literature and patient-level data from Massachusetts	Quality-adjusted life-years
Avritscher et al., 2004 (120)	To determine whether the use of dalteparin or UFH is less expensive for inpatient management of patients with cancer who have DVT	CM	Provider (hospital), time horizon not specified; presumed to be duration of hospitalization	Inpatient dalteparin, once daily Inpatient UFH	Two retrospective cohorts of patients in 1 institution, included a process flow analysis (2003 U.S. dollars)	Two retrospective cohorts of patients in 1 institution; assumed equivalent in both arms	U.S. dollars
Aujesky et al., 2005 (110)	To compare medical and economic outcomes for PE treatment with LMWH or UFH	CE	Societal; 6 mo	Inpatient enoxaparin (1 mg/kg twice daily for 6 d) Inpatient IV UFH	Direct medical costs from literature, Medicare reimbursement data (2002 U.S. dollars)	Literature (meta-analysis)	Quality-adjusted life-years

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Appendix Table 2—Continued

Study, Year (Reference)	Aims	Design	Perspective and Time Horizon	Comparisons	Sources of Cost Estimates	Sources of Event Rate Estimates	Units of Benefits
Gómez-Outes et al., 2006 (111)	To compare costs and cost-effectiveness of 2 regimens with LMWH to UFH and oral anticoagulation for treatment of DVT	CE	Payer; 3 mo	Inpatient bempiparin (115 U/d) and oral anticoagulant Inpatient bempiparin (115 U/d) and long-term bempiparin Inpatient UFH and oral anticoagulant	Published medical resource cost data (2002 euros)	Clinical trial by authors	Quality-adjusted life-years, also reported cost per recurrence avoided

* CE = cost-effectiveness; CM = cost minimization; DVT = deep venous thrombosis; HMO = health maintenance organization; IV = intravenous; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SC = subcutaneous; UFH = unfractionated heparin; VTE = venous thromboembolism.

Appendix Table 3. Results of the Modeled Analyses of the Costs of Using Low-Molecular-Weight Heparin Compared with Unfractionated Heparin for Treatment of Venous Thromboembolism *

Study, Year (Reference)	Least Costly Strategy	Strategy with Greatest Benefits	Incremental Cost-Effectiveness	Cost Savings	Sensitivity Analysis	Comments
Hull et al., 1997 (115)	Inpatient tinzaparin	Inpatient tinzaparin	Tinzaparin dominates	\$401 per person with tinzaparin, (11% savings)	Robust to all 1-way analyses; when cost of tinzaparin is 5.8 times base cost it is not cost-saving	If 37% of patients are treated as outpatients, cost saving of \$913 per person
Rodger et al., 1998 (118)	Outpatient LMWH if eligible and inpatient LMWH if not	Either LMWH inpatient or outpatient LMWH if eligible and inpatient LMWH if not	LMWH dominates whether outpatient or inpatient	\$767 per person with LMWH outpatient/inpatient relative to UFH (23% savings)	Using "worst-case" estimates, cost-effectiveness of inpatient LMWH relative to inpatient UFH is \$25 667 per life saved at 3 mo	If one assumes equivalent efficacy and safety in all arms, LMWH is cheaper to deliver in any setting and dominates
Goold et al., 1999 (114)	Inpatient UFH	Inpatient enoxaparin	\$6910 per LY or \$7820 per QALY with enoxaparin	Cost-saving when 8% of enoxaparin-treated patients are outpatients, or when 13% have an early discharge; sensitive to frequency of late complications, robust to other variables	Robustly cost-effective; becomes cost-saving if LMWH-treated patients are outpatients	
Estrada et al., 2000 (112)	Outpatient LMWH and inpatient UFH	Outpatient and inpatient LMWH	\$9600 per recurrence averted; \$80 000 per death averted with outpatient/inpatient LMWH relative to LMWH outpatient	\$310 per person for LMWH outpatient and inpatient relative to UFH (10% savings)	Sensitive to the percentage of patients eligible for outpatient therapy; if fewer than 14%, UFH lower cost than LMWH outpatient/inpatient; model sensitive to costs of UFH	Lower costs primarily due to saving hospitalization costs
Lloyd et al., 1997 (116)	Inpatient nadroparin	Assumed to be equivalent for model	NA	\$153 per person with nadroparin (57% savings)	Robust to all 1-way analyses; cost-savings less if nadroparin-treated patients are required to have APTT measurement	
van den Belt et al., 1998 (114)	Outpatient fraxaparine	Assumed to be equivalent for model	NA	5528 Dutch guilders per person with fraxaparine (64% savings)	Fraxaparine is cost-saving even if 50% of patients require home care visits; cost-saving even if 50% require inpatient care	
O'Brien et al., 1999 (117)	Outpatient enoxaparin	Higher social functioning on SF-36 with enoxaparin, otherwise no difference in health-related quality-of-life measures or events	NA	\$3045 per person with enoxaparin (57% savings)	Robust to all 1-way analyses	
Delissovoy et al., 2000 (109)	Not stated	Inpatient enoxaparin twice daily; fewest readmissions for recurrent DVT and for all causes	NA	None	Robust to all 1-way analyses	Blood testing and costs of medication offset by fewer readmissions with enoxaparin
Tillman et al., 2000 (119)	Outpatient enoxaparin	Unknown	NA	\$2828 per person with enoxaparin (60% savings)	Enoxaparin not cost-saving if drug cost increases 750% or hospitalization costs drop 77%	Rates of events in the UFH arm not explicitly stated
Boucher et al., 2003 (121)	Outpatient LMWH	Assumed to be equivalent for model	NA	\$1578 Canadian per person with outpatient treatment (91% savings)	"Worst-case scenario," 87% savings with outpatient treatment	Acknowledges that some of the savings is shifted to patients who must purchase LMWH

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Appendix Table 3—Continued

Study, Year (Reference)	Least Costly Strategy	Strategy with Greatest Benefits	Incremental Cost-Effectiveness	Cost Savings	Sensitivity Analysis	Comments
Caro et al., 2002 (122)	Outpatient tinzaparin	Outpatient tinzaparin	Tinzaparin dominates	\$5016 per person with outpatient treatment (49% savings); short-term costs only \$4890 (34% with inclusion of subsequent costs)	Tinzaparin is cost-saving even if all patients are treated as inpatients, or if price is increase up to 2.8 times; robust to varying management costs, discount rate, and event rates up to a 55% increase in rates	Suggests that strong results favoring tinzaparin are due to tinzaparin's superior efficacy relative to that of other LMWHs, although based on only 1 trial
Avritscher et al., 2004 (120)	Dalteparin	Assumed to be equivalent for model	NA	\$1569 per person with dalteparin (32% savings)	Robust in all 1-way analyses; costs of dalteparin would need to increase 5-fold to match costs of UFH	Savings from shorter hospital stays, lower laboratory costs, less intensive monitoring, some cost-shifting after discharge
Aujesky et al., 2005 (110)	Inpatient UFH	Inpatient LMWH	\$1209 per QALY favoring LMWH	None	Robust to all 1-way analyses; cost-saving if LMWH costs <\$51 daily; cost-saving if 8% of LMWH are discharged early	
Gómez-Outes et al., 2006 (111)	Inpatient bempiparin followed by long-term bempiparin	Inpatient bempiparin followed by oral anticoagulant	Both bempiparin arms dominate over the UFH arm	\$769 A vs. C (19% savings) \$908 B vs. C (22% savings)†	Robust in all 1-way analyses, most sensitive to rate of recurrence	Savings mostly due to lower hospital-stay costs

* APTT = activated partial thromboplastin time; DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; LY = life-year; NA = not available; QALY = quality-adjusted life-year; SF-36 = Short Form-36 Health Survey; UFH = unfractionated heparin.

† A = inpatient bempiparin (115 U/d) and oral anticoagulant; B = inpatient bempiparin (115 U/d) and long-term bempiparin; C = inpatient UFH and oral anticoagulant.