

Low-Molecular-Weight Heparin vs Unfractionated Heparin for Perioperative Thromboprophylaxis in Patients With Cancer

A Systematic Review and Meta-analysis

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Background: The relative benefits and harms of low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) are required for judgments regarding the appropriate perioperative thromboprophylaxis in patients with cancer. We systematically reviewed the literature to quantify these effects.

Methods: The comprehensive searches included (1) an electronic search of MEDLINE, EMBASE, ISI the Web of Science, and CENTRAL (The Cochrane Central Register of Controlled Trials); (2) a hand search of relevant conference proceedings; (3) a reference check of included trials; and (4) use of the PubMed "Related Articles" feature. Outcomes of interest included mortality, deep venous thrombosis, pulmonary embolism, bleeding complications, and thrombocytopenia.

Results: Of 3986 identified citations, we included 14 randomized clinical trials in the meta-analysis (all using preoperative prophylactic anticoagulation). The overall meth-

odological quality was moderate. The meta-analysis showed no differences in mortality in patients receiving LMWH compared with UFH (relative risk [RR], 0.89; 95% confidence interval [CI], 0.61-1.28) or in clinically suspected deep venous thrombosis (RR, 0.73; 95% CI, 0.23-2.28). In a post hoc analysis including all studies assessing deep venous thrombosis, irrespective of the diagnostic strategy used, LMWH was superior to UFH (RR, 0.72; 95% CI, 0.55-0.94). There were no differences in rates of pulmonary embolism (RR, 0.60; 95% CI, 0.22-1.64), minor bleeding (RR, 0.88; 95% CI, 0.47-1.66), or major bleeding (RR, 0.95; 95% CI, 0.51-1.77).

Conclusions: We found no differences in mortality in patients with cancer receiving perioperative thromboprophylaxis with LMWH vs UFH. Further trials are needed to more carefully evaluate the benefits and harms of different heparin thromboprophylaxis strategies in this population.

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PATIENTS WITH CANCER UNDERGOING surgical procedures have a higher risk of venous thromboembolism than patients without cancer undergoing similar procedures.¹⁻³ Patients with cancer and venous thromboembolism also have a higher risk of death than patients with cancer alone or with venous thromboembolism alone.^{4,5} Moreover, thromboprophylaxis might be less effective in patients with cancer owing to the prothrombotic state associated with malignant neoplasms.^{2,6}

The American College of Chest Physicians recommends that patients with cancer undergoing surgery receive prophylaxis "that is appropriate for their current risk state," including the type of surgery.^{7(p372S)} Two systematic reviews^{8,9} have shown that heparins are superior to no anticoagulation in the prevention of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing colorectal and gen-

eral surgery, respectively. Mismetti et al⁹ showed that in general surgery, the efficacy and safety of low-molecular-weight heparin (LMWH) relative to unfractionated heparin (UFH) were similar in patients with vs those without cancer. However, estimates of the relative effects of the 2 medications in patients with cancer were not provided. Relative effects for benefits and harms are required to make judgments regarding the appropriate use of anticoagulants in this setting. The objective of this systematic review is to compare the efficacy and safety of LMWH with the efficacy and safety of UFH for perioperative thromboprophylaxis in patients with cancer.

METHODS

SEARCH

We conducted electronic searches (MEDLINE from 1966, EMBASE from 1980, ISI the Web of Science, and CENTRAL [The Cochrane

Central Register of Controlled Trials) in January 2007 without language restrictions. The search strategies combined terms for the anticoagulants of interest with terms for cancer with search filters for randomized controlled trials (RCTs) (eTable; <http://www.archinternmed.com>).¹⁰

We hand searched the conference proceedings of the American Society of Clinical Oncology (from 1982) and the American Society of Hematology (from 2003). We reviewed the reference lists of included articles, relevant articles, and related systematic reviews^{2,8,9} and used

the “Related Articles” feature in PubMed to identify additional citations.

SELECTION

Two reviewers (teams composed of many of us) independently screened the titles and abstracts for eligibility. We included studies that were RCTs, that enrolled patients with cancer, that compared LMWH with UFH, and that assessed the outcomes of interest (see the following subsection). We retrieved the full text of citations judged to be poten-

tially eligible by at least 1 reviewer. Two reviewers independently screened the full-text articles for eligibility and resolved disagreements by discussion. We included abstracts only if the investigators supplied the necessary data on methods and results.

METHODOLOGICAL QUALITY ASSESSMENT AND DATA ABSTRACTION

Two reviewers independently assessed the methodological quality of and abstracted data from each included trial using a pilot-tested and standardized form. They resolved disagreements by discussion, if necessary with help from an arbiter. We wrote to authors of included trials for incompletely reported data. The methodological criteria included allocation concealment, patient blinding, physician blinding, outcome assessor blinding, analyst blinding, percentage of follow-up, adherence to the principle of intention-to-treat analysis, a priori sample size calculation, and avoidance of early stoppage of the trial.

We aimed to collect data relating to the intervention and its control (type, dosing schedule, and duration), the cointerventions (including elastic stockings, pneumatic compressions, and early ambulation), participant characteristics (including type of cancer and surgery site), and outcome assessment (including type of screening and diagnostic tests).

We extracted the outcome data necessary to conduct intention-to-treat analyses, and we collected data for all-cause mortality, DVT (detected by means of screening or diagnosed secondary to clinical suspicion), PE, major bleeding, minor bleeding, wound hematoma, subsequent surgery for bleeding, thrombocytopenia, and heparin-induced thrombocytopenia (HIT). For the evaluation

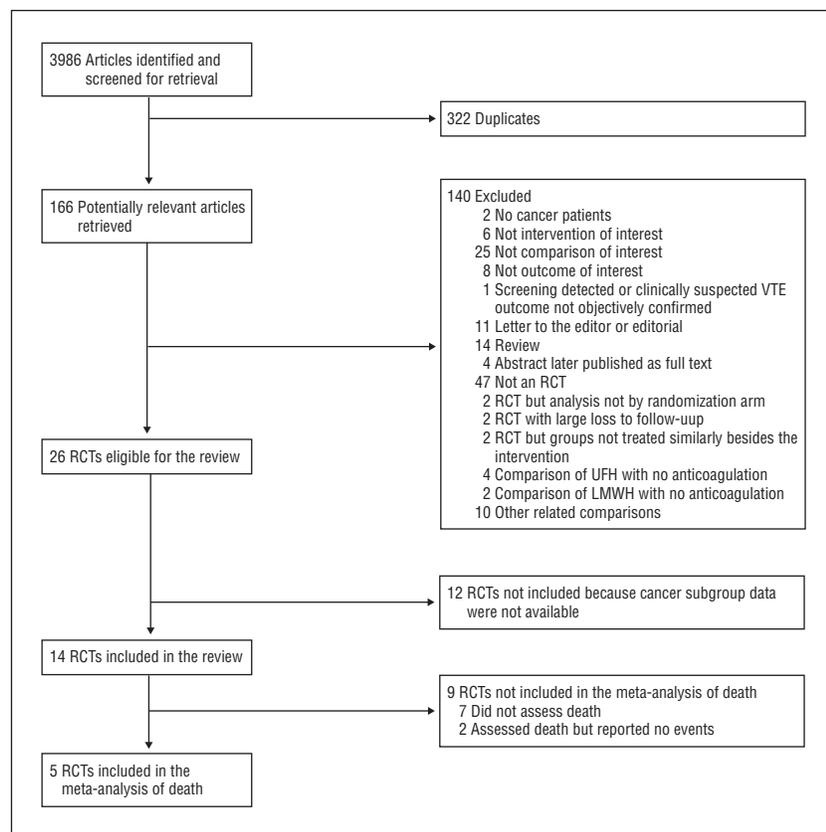


Figure 1. Systematic review flowchart. LMWH indicates low-molecular-weight heparin; RCT, randomized controlled trial; UFH, unfractionated heparin; and VTE, venous thromboembolism.

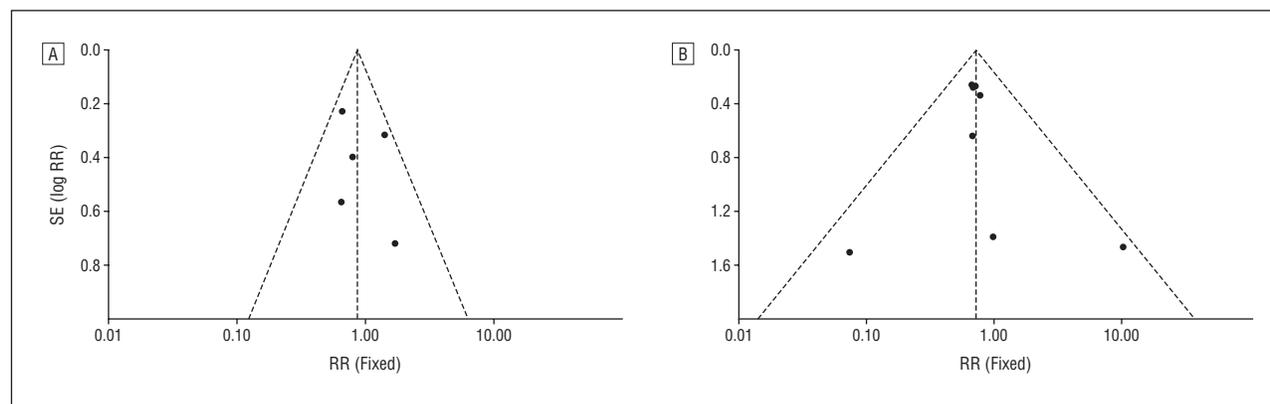


Figure 2. Inverted funnel plots for trials comparing the effect on mortality (A) and deep venous thrombosis (DVT) (B) of low-molecular-weight heparin and unfractionated heparin for perioperative thromboprophylaxis in patients with cancer. RR indicates relative risk.

of bleeding complications and thrombocytopenia, we accepted the authors' definitions as long as they were standardized within studies. We also collected data for intraoperative and postoperative blood loss, intraoperative and postoperative blood product transfusion, and surgical tube drainage.

DATA ANALYSIS

We calculated the agreement between the 2 reviewers for the assessment of eligibility using the κ statistic, and we checked for possible publication bias using inverted funnel plots.¹¹ For categorical variables, we extracted the number of participants and the number of events by treatment arm, and we calculated a pooled relative risk (RR). For continuous variables, we extracted the mean and standard deviation by allocation arm, and we calculated the standardized mean difference (SMD). We measured homogeneity across trial results using the I^2 statistic,¹² and we considered the following classification of heterogeneity based on the value of I^2 : 0 to 30 indicates low; greater than 30 to 60, moderate and worthy of investigation; greater than 60 to 90, severe and worthy of understanding; and greater than 90 to 100, allowing aggregation only with major caution. We pooled the results using random effects. To explain heterogeneity, we attempted, whenever possible, to conduct subgroup analyses based on the characteristics of the participants, the interventions, and the outcomes. We conducted subgroup analyses for UFH administration 2 and 3 times daily and for abdominal surgery.

We defined a priori that we would conduct separate analyses for each diagnostic strategy (ie, studies using a diagnostic workup triggered by clinical suspicion were distinct from studies using a diagnostic workup triggered by a positive venographic result found by screening). Owing to the small number of trials using each of the specific diagnostic strategies and assuming that the relative effect is constant regardless of detection method, we conducted a post hoc analysis of the effect on DVT by pooling data from all the trials irrespective of whether they used the same strategy ("any diagnostic strategy"). For trials using more than 1 diagnostic strategy, we chose the data from 1 strategy using the following hierarchy: diagnostic workup triggered by clinical suspicion, diagnostic workup triggered by positive venography findings, diagnostic workup triggered by positive venous Doppler ultrasonographic findings, diagnostic workup triggered by a posi-

tive iodine 125-labeled fibrinogen uptake test result, and diagnostic workup triggered by positive impedance plethysmography findings.

RESULTS

SEARCH AND SELECTION OF TRIALS

The search strategy identified 3986 citations, including 322 duplicates. The title and abstract screening of the 3664 unique citations identified 166 as being potentially eligible for this review. The full-text screening of the 166 citations identified 26 eligible RCTs (**Figure 1**). We excluded 140 trials, as described in Figure 1. Agreement between reviewers for trial eligibility was excellent ($\kappa=0.94$).

Of the 26 eligible RCTs, 11 included patients with cancer exclusively ($n=4006$).¹³⁻²³ The remaining 15 trials included patients with cancer as subgroups: 2 trials^{24,25} reported the cancer subgroup data ($n=1341$), and we obtained cancer subgroup data from the authors²⁶ of 1 trial ($n=475$). We were not able to obtain cancer subgroup data for the remaining 12 trials²⁷⁻³⁸ ($n=3185$); thus, we did not include them in the meta-analysis. The inverted funnel plots for the outcomes of death at 1 year and DVT did not suggest publication bias (**Figure 2**).

METHODOLOGICAL QUALITY

In the **Table**, we present the characteristics of the 14 included trials. Of these trials, 6 concealed allocation, 8 reported blinding patients and physicians, 5 reported blinding outcome assessors, 4 reported blinding data analysts, 7 used intention-to-treat analysis, and 13 had follow-up greater than 80%. Five trials had a formal sample size calculation, but in 2 trials, patients with cancer constituted subgroups. One trial was published only as an abstract and did not meet most of the methodological quality criteria, probably owing to limited reporting secondary to space constraints. Otherwise, the overall methodological quality of the trials was moderate.

QUANTITATIVE DATA SYNTHESIS

Death

Seven trials^{13,14,17,19,21,23,24} reported death, but 2 of these reported no events in either group.^{13,14} The pooled analysis of the remaining 5 trials showed no significant survival benefit with LMWH compared with UFH (RR, 0.89; 95% confidence interval [CI], 0.61-1.28; $I^2=20\%$) (**Figure 3**). There were no differences in mortality in the subgroup of trials comparing LMWH with UFH administered 2 times daily (RR, 1.11; 95% CI, 0.55-2.25; $I^2=30\%$) or 3 times daily (RR, 0.74; 95% CI, 0.51-1.08; $I^2=0\%$). The difference between the RRs for the 2 subgroups was not significant ($P=.20$).

Deep Venous Thrombosis

Six trials reported data on DVT events that were initially clinically suspected and subsequently objectively confirmed (using venography in 4 studies,^{13,16-18} Doppler ultrasonography in 1 study,¹⁵ and either test in 1 study¹⁴); however, 4 trials reported no events.¹³⁻¹⁶ The pooled analysis of the remaining 2 trials,^{17,18} both administering UFH 3 times daily, showed no benefit with LMWH (RR, 0.73; 95% CI, 0.23-2.28; $I^2=0\%$).

In 2 trials,^{17,26} DVT was diagnosed based on venography screening. The pooled analysis showed no difference using LMWH compared with UFH (RR, 0.78; 95% CI, 0.57-1.06; $I^2=0\%$). In 6 trials,^{13,16,18,19,24,25} a DVT diagnostic workup was triggered by a positive isotopic screening (iodine 125-labeled fibrinogen uptake test) result and was subsequently confirmed by venography in all but 1 trial.²⁴ The pooled analysis of the 5 trials reporting events showed a significantly lower DVT rate with LMWH compared with UFH (RR, 0.72; 95% CI, 0.52-0.99; $I^2=0\%$). The reduction was not significant in either of the 2 subgroups comparing LMWH with UFH administered 2 times daily (RR, 0.70; 95% CI, 0.48-1.01; $I^2=0\%$) or 3 times daily (RR, 0.79; 95% CI, 0.41-1.50; $I^2=0\%$). The difference between the RRs for the 2 subgroups was not significant ($P=.39$).

Table. Characteristics of the 14 Included Trials

Source	Funding	Methodological Quality	Intervention	Participants	Outcomes ^a
Onarheim et al, ¹³ 1986	Private for profit	AC, not clear; blinding, patient, physician, outcome assessor, and analyst; ITT analysis; sample size not calculated a priori; follow-up, 100%	Dalteparin sodium, 5000 U, 2 h preoperatively, then once daily for 6 d, vs heparin (Kabi 2165), 5000 U, 2 h preoperatively, then twice daily for 6 d	52 Patients undergoing surgery for abdominal malignant neoplasms; aged >40 y	Death, DVT (isotopic), DVT (venography), DVT (clinical), PE (clinical), major bleeding, wound hematoma, thrombocytopenia, perioperative blood loss, and subsequent surgery for bleeding
Fricker et al, ¹⁸ 1988	Not reported	AC, adequate; blinding, none; ITT analysis; sample size not calculated a priori; follow-up, 100%	Dalteparin sodium, 2500 U, 2 h preoperatively and 12 h after, then 5000 U/d for 10 d, vs UFH, 5000 U, 2 h preoperatively and then 5000 U 3 times daily for 10 d	80 Patients undergoing surgery for abdominal and pelvic malignant neoplasms; aged >40 y	DVT (isotopic), DVT (clinical), and PE (clinical)
European Fraxiparin Study (EFS) Group, ²⁵ 1988	Not reported	AC, not clear; blinding, none reported; analysis not ITT; sample size not calculated a priori; follow-up, 99%	Nadroparin calcium, 7500 U, 2 h before and 8 h after surgery, then once daily for 7 d, vs UFH, 5000 U, 2 h before and 8 h after surgery at 8-h intervals for 7 d	704 Patients with cancer undergoing abdominal surgery (study subgroup); aged >40 y	DVT (isotopic), PE (clinical), and postoperative drain volume
Bergqvist et al, ²⁴ 1990	Governmental	AC, not clear; blinding, none reported; analysis not ITT; sample size calculated a priori but not for cancer subgroup; follow-up, 96%	Dalteparin sodium, 5000 U, at 10 PM on preoperative night, then 5000 U/d for 5-8 d, vs UFH, 5000 U, 2 h preoperatively, then twice daily for 5-8 d	637 Patients with cancer undergoing abdominal surgery (study subgroup); aged >40 y	DVT (isotopic), PE (clinical), and death
Dahan et al, ¹⁶ 1990	Not reported	AC, not clear; blinding, none; ITT analysis; sample size not calculated a priori; follow-up, 100%	Nadroparin calcium, 7500 U, 12 h preoperatively and 12 h postoperatively until postoperative day 2, then 10 000 U once daily on postoperative days 3-7, vs UFH, 5000 U, 2 h preoperatively and 12 h postoperatively, then 3 times daily until postoperative day 2, then a dose adjusted to aPTT on postoperative days 3-7 given twice daily	100 Patients undergoing thoracic cancer surgery; aged >18 y	DVT (isotopic), DVT (clinical), PE (clinical), major bleeding, perioperative blood loss, postoperative blood loss, perioperative blood transfusion, and postoperative blood transfusion
Gallus et al, ¹⁹ 1993	Private for profit	AC, adequate; blinding, patient, physician, outcome assessor, and analyst; sample size calculated a priori; ITT analysis; follow-up, 95%	Danaparoid sodium, 750 U, 1-2 h preoperatively, then at 12-h intervals for 6 d, vs UFH, 5000 U, 1-2 h preoperatively, then at 12-h intervals for 6 d	514 Patients undergoing abdominal or thoracic cancer surgery; aged >40 y	DVT (isotopic), PE (clinical), intraoperative bleeding, and death
Godwin et al, ²⁰ 1993 (abstract)	Not reported	AC, not clear; blinding, none reported; analysis not ITT; not clear whether sample size calculated a priori; follow-up, 86%	RD heparin (Normiflo), 50 U, 2 h preoperatively and then 90 U once or twice daily vs UFH, 5000 U, 2 h preoperatively and then 5000 U twice daily	904 Patients undergoing abdominal or pelvic cancer surgery	DVT (IP or US), PE (clinical), and thrombocytopenia

(continued)

Twelve trials^{13-20,22,24-26} assessed DVT outcome using any diagnosis strategy. In the post hoc analysis pooling data from 8 of these trials^{17-20,22,24-26} that reported events, LMWH was superior to UFH (RR,

0.72; 95% CI, 0.55-0.94; $I^2=0\%$) (Figure 4). The benefit was significant in the subgroup of trials comparing LMWH with UFH administered 2 times daily (RR, 0.66; 95% CI, 0.44-0.99) but not in the

subgroup comparing LMWH with UFH administered 3 times daily (RR, 0.78; 95% CI, 0.53-1.15; $I^2=0\%$). The difference between the RRs for the 2 subgroups was not significant ($P=.28$).

Table. Characteristics of the 14 Included Trials (cont)

Source	Funding	Methodological Quality	Intervention	Participants	Outcomes ^a
Enoxacan Study Group, ¹⁷ 1997	Governmental	AC, not clear; blinding, patient, physician, and outcome assessor; analysis not ITT; sample size calculated a priori; follow-up, 57%	Enoxaparin sodium, 40 mg, 2 h preoperatively, then once daily for a mean (SD) of 10 (2) d, vs UFH, 5000 U, 2 h preoperatively, then 3 times daily for a mean (SD) of 10 (2) d	1116 Patients undergoing abdominal, gynecologic, and urologic cancer surgery; aged >40 y; minimum life expectancy of 6 mo	Death, DVT (venography), DVT (clinical), PE (clinical), major bleeding, and minor bleeding
von Tempelhoff et al, ²² 1997	Not reported	AC, not clear; blinding, patient and physician; ITT analysis; sample size not calculated a priori; follow-up, 100%	Certoparin sodium, 3000 anti-Xa U, 2 h preoperatively, then once daily for 7 d (plus 2 placebo injections), vs UFH, 5000 IU/d 2 h preoperatively, then at 8-h intervals for 7 d	60 Patients with ovarian cancer undergoing surgery; undergoing chemotherapy	DVT (IP)
Heilmann et al, ²¹ 1998	Not reported	AC, adequate; blinding, patient and physician; analysis not ITT; sample size calculated a priori; follow-up, 91%	Certoparin sodium, 3000 U, 2-5 h preoperatively, then once daily for 7 d, vs UFH, 5000 U, 2-5 h preoperatively, then 3 times daily for 7 d	358 Patients undergoing breast and pelvic cancer surgery; aged >40 y	Death, PE (clinical), major bleeding, minor bleeding, thrombocytopenia, wound hematoma, and subsequent surgery for hematoma
von Tempelhoff et al, ²³ 2000	Private for profit	AC, adequate; blinding, patient and physician; analysis not ITT; sample size not calculated a priori; follow-up, 93%	Certoparin sodium, 3000 U, 2 h preoperatively, then once daily for 7 d, vs UFH, 5000 U, 2 h preoperatively, then 3 times daily for 7 d	350 Patients undergoing breast and pelvic cancer surgery; aged >40 y; minimum life expectancy, 3 mo; undergoing chemotherapy and radiotherapy	Death
Baykal et al, ¹⁴ 2001	Private for profit	AC, adequate; blinding, patient, physician, outcome assessor, and analyst; ITT analysis; sample size not calculated a priori; follow-up, 100%	Enoxaparin sodium, 2500 U, 2 h preoperatively, then once daily, vs UFH, 5000 U, 3 times daily	102 Patients undergoing surgery for gynecologic malignant neoplasms; aged >40 y	Death, DVT (clinical), PE (clinical), intraoperative blood loss, and catheter drainage
Boncinelli et al, ¹⁵ 2001	Not reported	AC, not clear; blinding, none reported; ITT analysis; sample size not calculated a priori; follow-up, 100%	Nadroparin calcium, 7500 U, 12 h preoperatively, then once daily during hospital stay, vs UFH, 5000 U, 2 h preoperatively, then 3 times daily during hospital stay	50 Patients undergoing prostatectomy for prostate cancer	DVT (clinical), PE (clinical), major bleeding, and hematoma
McLeod et al, ²⁶ 2001	Private for profit	AC, adequate; blinding, patient, physician, outcome assessor, and analyst; analysis not ITT; sample size calculated a priori but not for cancer subgroup; follow-up, 94%	Enoxaparin sodium, 40 mg, 2 h preoperatively, then 40 mg/d for 10 d, vs UFH, 5000 U, 2 h preoperatively, then 5000 U every 8 h for 10 d	475 Patients with cancer undergoing colorectal cancer surgery (study subgroup)	DVT (venography), PE, major bleeding, and minor bleeding

Abbreviations: AC, allocation concealment; aPTT, activated partial thromboplastin time; DVT, deep venous thrombosis; ITT, intention-to-treat; PE, pulmonary embolism; UFH, unfractionated heparin.

^aIsotopic, venography, US, and IP refer to detection of DVT through screening via iodine 125-labeled fibrinogen uptake testing, venography, venous Doppler ultrasonography, and impedance plethysmography, respectively; clinical refers to DVT assessed based on clinical suspicion. For the evaluation of bleeding complications and thrombocytopenia, we accepted the authors' definitions as long as they were standardized within the studies.

Pulmonary Embolism

Twelve trials assessed PE,^{13-21,24-26} but 5 of them reported no events.^{13-16,25}

The pooled analysis of the remaining 7 trials showed no difference comparing LMWH with UFH (RR, 0.60; 95% CI, 0.22-1.64; $I^2=26\%$). The dif-

ference between LMWH and UFH was not significant in the 2 subgroups administering UFH 2 times daily (RR, 0.41; 95% CI, 0.11-1.55;

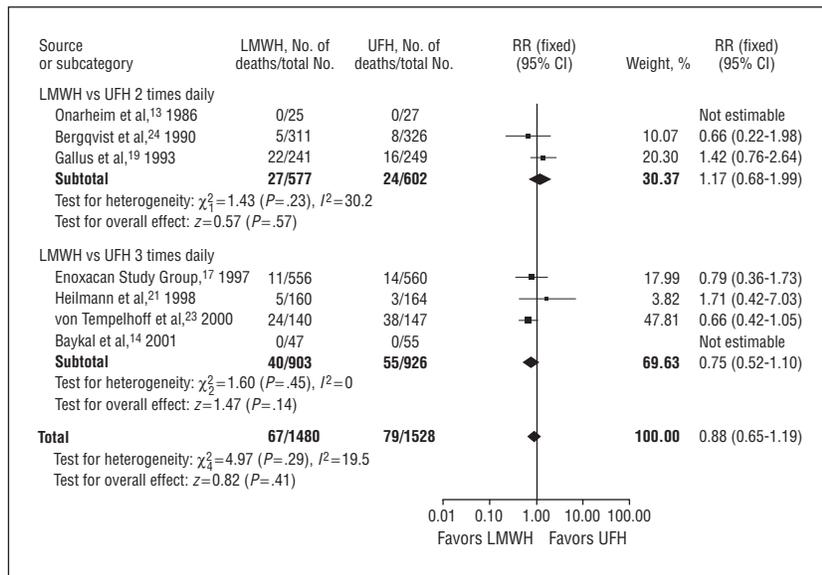


Figure 3. Deaths in patients with cancer receiving perioperative thromboprophylaxis with low-molecular-weight heparin (LMWH) vs unfractionated heparin (UFH). CI indicates confidence interval; RR, relative risk.

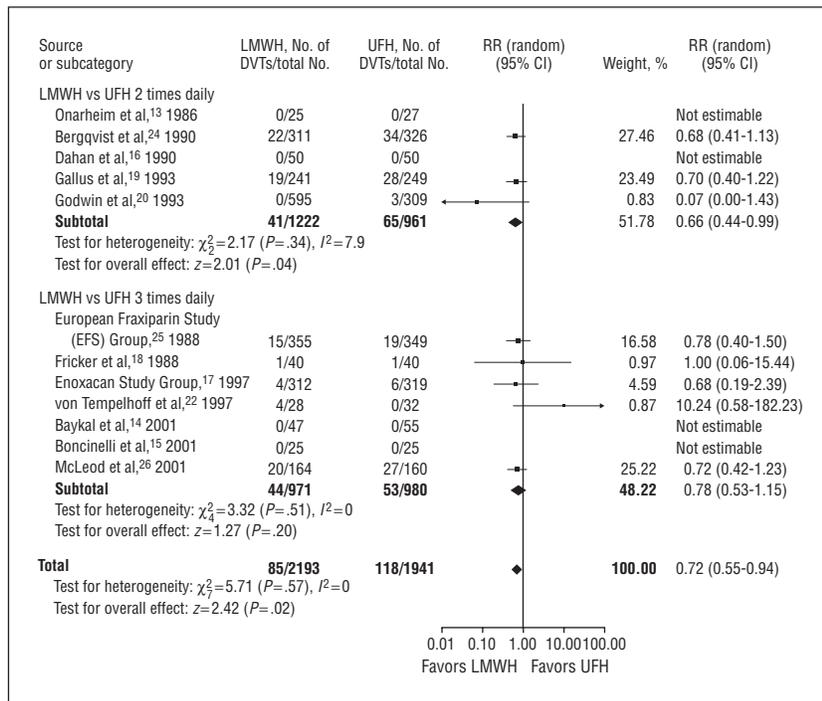


Figure 4. Deep venous thrombosis (DVT) (any diagnostic strategy) in patients with cancer receiving perioperative thromboprophylaxis with low-molecular-weight heparin (LMWH) vs unfractionated heparin (UFH). CI indicates confidence interval; RR, relative risk.

$I^2=0\%$) or 3 times daily (RR, 0.70; 95% CI, 0.14-3.57; $I^2=45\%$). The difference between the RRs for the 2 subgroups was not significant ($P=.13$).

Bleeding Outcomes

Only 3 trials^{17,21,26} reported minor bleeding; the pooled analysis showed

no difference in minor bleeding (RR, 0.88; 95% CI, 0.47-1.66). Heterogeneity was severe ($I^2=75\%$). Similarly, there were no differences in the 6 trials assessing major bleeding (RR, 0.95; 95% CI, 0.51-1.77). Heterogeneity was moderate ($I^2=42\%$).

Three trials^{13,15,21} reported wound hematoma as an outcome. The

pooled analysis showed no difference in LMWH- and UFH-treated patients (RR, 0.65; 95% CI, 0.39-1.09; $I^2=0\%$). Only 2 trials^{13,21} assessed subsequent surgery for bleeding as an outcome. The pooled analysis showed no difference in groups (RR, 0.70; 95% CI, 0.06-7.89). Heterogeneity was moderate ($I^2=40\%$).

For the outcomes of intraoperative blood loss (SMD, -0.06; 95% CI, -0.25 to 0.13), postoperative drain volume (SMD, 0.05; 95% CI, -0.08 to 0.19), and postoperative transfusion (SMD, 0.26; 95% CI, -0.18 to 0.70), there were no differences between LMWH and UFH. Based on 1 trial,¹⁶ intraoperative transfusion volume was higher with LMWH (SMD, 1.16; 95% CI, 0.69-1.62).

Thrombocytopenia

Three trials^{13,20,21} reported thrombocytopenia rates, but 1 reported no occurrence of thrombocytopenia.¹³ The pooled analysis from the 2 remaining trials showed no difference (RR, 1.18; 95% CI, 0.49-2.81). None of the studies reported HIT.

Subgroup Analysis: Abdominal Surgery

For patients undergoing abdominal surgery, subgroup data were available for some outcomes from 4 studies.^{13,24-26} Results were similar to those of the primary analysis. There was no difference between LMWH and UFH in effect on DVT diagnosed after isotopic screening (RR, 0.73; 95% CI, 0.49-1.08), PE (RR, 0.74; 95% CI, 0.06-9.83), or death (RR, 0.66; 95% CI, 0.22-1.98). The LMWH was superior to UFH in effect on DVT using any diagnostic strategy (RR, 0.72; 95% CI, 0.52-0.99).

COMMENT

This systematic review showed no significant difference in the effect on survival between LMWH and UFH for perioperative thromboprophylaxis in patients with cancer. The main analysis showed no differences in DVT, PE, and bleeding rates. Although the absence of a statistically significant difference might re-

flect a true absence of effect, it could also be related to the lack of power to detect important differences.

In a subgroup analysis of trials comparing LMWH with UFH administered 2 times daily rather than 3 times daily, DVT rates were lower. This subgroup analysis should be interpreted cautiously because it fails 2 important criteria of the 7 criteria for a credible subgroup difference³⁹: the effect is not suggested by comparisons within rather than between studies and the effect is not statistically significant. We found no trials directly comparing 2 times with 3 times daily UFH dosing regimens in this population. Indirect comparisons, even when adjusted, do not always agree with the results of head-to-head comparisons.⁴⁰

There are several strengths to this systematic review, including the rigorous search strategy without language restrictions and the assessment of publication bias. We conducted study selection in duplicate to minimize the likelihood of missing relevant trials, and we had excellent agreement. We evaluated methodological quality and abstracted data in duplicate to minimize random and systematic error. The overall methodological quality of the included trials was moderate.

Although we used a comprehensive search strategy, a potential limitation of this review is the restriction of the electronic search strategy to patients with cancer; indeed, some of the data included in this review were from trials not restricted to patients with cancer. However, the search strategy identified all trials included in earlier systematic reviews on the same topic unrestricted to patients with cancer.² We could not obtain data for 12 trials including subgroups of patients with cancer. These trials could have contributed 3185 additional participants to the meta-analyses, whereas 5822 are included in the present analysis. If the treatment effect estimated from those 12 trials was different from the true effect, these results would be biased.

Another limitation is that the included studies varied in the types of malignant neoplasms, types of surgical procedures, dosing of anticoagulant medications, follow-up pe-

riods, and measurement of end points. This might be a particular concern with older studies. Because of the limited number of studies, we could not explore in subgroup analyses the impact of all of these characteristics. In addition, this meta-analysis lacked sufficient power to detect a statistically significant and meaningful difference between the RR of LMWH and UFH 2 and 3 times daily, if one exists.

The event rate of PE was relatively low (0.6%). Thus, even now, individual trials, and even meta-analyses of these trials, remain underpowered to show statistically significant and meaningful differences in PE rates. On the other hand, the event rate of DVT in the control group (UFH) is lower when DVT is symptomatic (1.6%) rather than asymptomatic and detected by screening (8.1% for the iodine 125-labeled fibrinogen uptake test and 16.5% for venography). Consequently, the post hoc analysis pooling DVT data from all the trials (any diagnostic strategy) includes more events from studies incorporating screening (ie, DVTs that are asymptomatic and detected by screening), but it likely has relatively little effect on relative estimates of effect (ie, the RR), expressed by the low heterogeneity.

All included studies comparing LMWH with UFH started anticoagulant drug treatment preoperatively. Thus, it is not certain how the results apply to settings in which anticoagulant drug treatment is started postoperatively. The results suggest that physicians should consider preoperative rather than postoperative use. Further support for preoperative use comes from studies that did not find statistically significant differences in the amount of blood loss when patients were randomized to a first dose of enoxaparin sodium 12 hours before surgery vs postoperatively.⁴¹

A systematic review⁸ of thromboprophylaxis in colorectal surgery (search date: 2003) showed that LMWH and UFH were similarly effective in preventing DVT and PE (odds ratio, 1.01; 95% CI, 0.67-1.52); however, DVT and PE were not analyzed separately. A systematic review⁴² of thromboprophylaxis in gynecologic surgery (search

date: 2005) showed no statistically significant difference between LMWH and UFH on DVT.

Another systematic review⁴³ compared the risk of thrombocytopenia and HIT with UFH and LMWH thromboprophylaxis. Most of the studies enrolled patients undergoing orthopedic surgery. Only 2 trials prospectively examined HIT, and they identified only 10 events overall (all in the UFH group); a meta-analysis of these 2 RCTs measuring HIT showed an odds ratio of 0.10 (95% CI, 0.01-0.82), and a meta-analysis of 15 studies measuring thrombocytopenia showed an odds ratio of 0.47 (95% CI, 0.22-1.02), favoring LMWH. Furthermore, a recent meta-analysis⁴⁴ comparing therapeutic doses of UFH with LMWH found only 2 trials examining this outcome, and no differences in HIT rates were found (RR, 1.33; 95% CI, 0.77-2.30). Although none of the prophylaxis trials included in this review reported HIT, the thrombocytopenia rates were similar (RR, 1.18; 95% CI, 0.49-2.81).

Evidence of a survival benefit of anticoagulation in patients with cancer mediated through an antineoplastic effect is accumulating.^{45,46} However, it is unclear whether a short course of lower-dose perioperative heparin thromboprophylaxis can exert such an effect. We postulate that longer-term treatment with heparin may be required to realize this potential benefit.

As the American College of Chest Physicians recommends, patients with cancer should receive prophylaxis that is appropriate for their current surgical risk.⁷ For example, Andtbacka et al⁴⁷ showed that in patients undergoing breast cancer surgery and treated with mechanical antiembolic devices and early ambulation, venous thromboembolism is rare (0.16% per procedure in 60 days).

In conclusion, this systematic review suggests no survival benefit and no harm associated with LMWH compared with UFH for thromboprophylaxis in patients with cancer undergoing surgery. In choosing one or the other agent, physicians should consider factors such as cost, ease of administration, and patient preferences. Further randomized trials are

needed to confirm or refute the hypothesis that if UFH is used, 3 times daily dosing may be more effective in DVT prevention than 2 times daily dosing.

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Correction

Error in Byline. In the Original Article by Hassan et al titled "Computed Tomographic Colonography to Screen for Colorectal Cancer, Extracolonic Cancer, and Aortic Aneurysm: Model Simulation With Cost-effectiveness Analysis," published in the April 14, 2008, issue of the *Archives* (2008;168[7]:696-705), there were errors in the names of 2 authors in the byline. "Perry Pickhardt, MD" should be "Perry J. Pickhardt, MD," and "Daniel Kim, MD" should be "David H. Kim, MD."

eTable. Search Strategies Used for the Electronic Databases

Database and Search No.	Search Strategy
MEDLINE	
1	Heparin/
2	Heparin.tw
3	Heparin, Low-Molecular-Weight/
4	(LMWH or low molecular weight heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran).tw
5	1 or 2 or 3 or 4
6	Coumarins/
7	Warfarin/
8	(warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw
9	6 or 7 or 8
10	(fondaparinux or Arixtra).tw
11	(ximelagatran or Exanta).tw
12	5 or 9 or 10 or 11
13	Neoplasms/
14	(malignan\$ or neoplasm\$ or cancer or carcinoma\$ or adenocarcinoma or tumour or tumor).tw
15	13 or 14
16	clinical trial.pt. or random:.tw. or tu.xs.
17	animals/not human/
18	16 not 17
19	12 and 15 and 18
EMBASE	
1	Heparin/
2	heparin.tw
3	Low Molecular Weight Heparin/
4	(LMWH or low molecular weight heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran).tw
5	1 or 2 or 3 or 4
6	Coumarin derivative/
7	Warfarin/
8	(warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin k antagonist or VKA).tw
9	6 or 7 or 8
10	fondaparinux/
11	(fondaparinux or Arixtra).tw
12	ximelagatran/
13	(ximelagatran or Exanta).tw
14	5 or 9 or 10 or 11 or 12 or 13
15	Neoplasm/
16	(malignan\$ or neoplasm\$ or cancer or carcinoma\$ or adenocarcinoma or tumour or tumor).tw
17	15 or 16
18	Random:.tw. or clinical trial:.mp. or exp health care quality
19	animals/not human/
20	18 not 19
21	14 and 17 and 20
ISI (International Scientific Information) the Web of Science	
1	heparin or low molecular weight heparin or LMWH or low-molecular-weight heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran
2	Coumarins or Warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA
3	fondaparinux or Arixtra
4	ximelagatran or Exanta
5	1 or 2 or 3 or 4
6	malignan\$ or neoplasm\$ or cancer or carcinoma\$ or adenocarcinoma or tumour or tumor
7	random\$ or placebo\$ or versus or vs or double blind or double-blind or compar\$ or controlled
8	5 and 6 and 7
CENTRAL (The Cochrane Central Register of Controlled Trials)	
1	heparin or low molecular weight heparin or LMWH or low-molecular-weight heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran
2	Coumarins or Warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA
3	fondaparinux or Arixtra
4	ximelagatran or Exanta
5	1 or 2 or 3 or 4
6	malignan\$ or neoplasm\$ or cancer or carcinoma\$ or adenocarcinoma or tumour or tumor
7	5 and 6