

# Once-daily vs. twice-daily dosing of enoxaparin for the management of venous thromboembolism: A systematic review and meta-analysis

JINGRONG NIU<sup>1</sup>, YIXIAO SONG<sup>2</sup>, CHUNMIN LI<sup>1</sup>, HUALIANG REN<sup>1</sup> and WANGDE ZHANG<sup>1</sup>

<sup>1</sup>Department of Vascular Surgery, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020; <sup>2</sup>School of Life Science, Tsinghua University, Beijing 100084, P.R. China

Received February 17, 2020; Accepted June 24, 2020

DOI: 10.3892/etm.2020.9036

**Abstract.** The present study aimed to determine whether there is any difference in the efficacy and safety of once-daily vs. twice-daily enoxaparin when used for the initial treatment of venous thromboembolism (VTE). The PubMed, Embase, Cochrane Central Register of Controlled Trials, Science Direct and Google Scholar databases were searched for studies comparing once-daily and twice-daily enoxaparin for the initial treatment of VTE added from inception up to 1st October 2019. Studies utilizing any other low-molecular-weight heparin and using enoxaparin for VTE prophylaxis were excluded. A total of 6 studies were included in the systematic review and 5 in the meta-analysis. Only one study was a randomized controlled trial (RCT). Pooled analysis of 460 patients receiving once-daily enoxaparin and 464 patients receiving twice-daily enoxaparin indicated no significant difference between the two dosing regimens regarding VTE recurrence [odds ratio (OR)=1.48, 95%CI: 0.75-2.89, P=0.26; I<sup>2</sup>=0%]. No significant difference in major hemorrhagic complications was noted (OR=1.21, 95%CI: 0.52-2.81, P=0.66; I<sup>2</sup>=0%). Sub-group analysis based on study type and use of enoxaparin for bridging therapy did not change the overall results. In cancer patients, no statistically significant difference in the recurrence of VTE was obtained between once-daily and twice-daily enoxaparin, but the confidence intervals were wide with a tendency to favor twice-daily dosing (OR=2.28, 95%CI: 0.91-5.75, P=0.08; I<sup>2</sup>=0%). The overall quality of the studies was determined to be average. To conclude, while the present results suggested no significant difference in efficacy and safety of once-daily vs. twice-daily enoxaparin when used for the initial treatment of VTE, the quality of the evidence

may not have been sufficiently high to support the conclusions with confidence. Further high-quality and adequately powered RCTs are required to corroborate the present results.

## Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a growing public health problem with an estimated incidence rate of 1.22 per 1,000 person-years (1). It is also the third most common cardiovascular condition after acute coronary syndromes and stroke (2). Early anti-coagulant therapy is necessary for managing the disease, as untreated VTE may lead to significant morbidity, functional disability and mortality. In the past two decades, low-molecular-weight heparin (LMWH) is being increasingly used in the initial management of VTE with a corresponding decrease in the use of unfractionated heparin (UFH) (3). As compared to UFH, LMWHs have a longer half-life and a more predictable anticoagulant response (4). Studies have suggested that LMWH is as effective as UFH with an advantage of home-based treatment and no requirement for monitoring the laboratory parameters of the patient (5). Despite LMWHs being the drug of choice for acute VTE, there is currently no consensus regarding the dosing strategy of LMWH for acute VTE (6). In studies evaluating the efficacy of LMWHs, clinicians have used both once-daily (7) and twice-daily (5) regimens of LMWH and demonstrated good results.

Several different LMWHs, including enoxaparin, dalteparin and tinzaparin, are available in the US. The different LMWHs, however, cannot be used interchangeably, as these drugs differ in their physicochemical and pharmacologic characteristics (8). While a once-daily dose of dalteparin (200 U/kg daily) is equivalent to twice-daily dosing (100 U/kg twice-daily) on a milligram basis, this does not apply for enoxaparin. Once-daily enoxaparin (1.5 mg/kg) provides 75% of the total drug received via twice-daily dosing (1 mg/kg) (9). The administration of 1 mg/kg twice-daily enoxaparin has been used for in-patient treatment of DVT with or without PE and outpatient treatment of acute DVT without PE as a bridge to warfarin (10). However, if a once-daily injection of enoxaparin is as efficacious as twice-daily dosing, such a regimen would

---

*Correspondence to:* Dr Wangde Zhang, Department of Vascular Surgery, Beijing Chao-Yang Hospital, Capital Medical University, 8 Gongti South Road, Beijing 100020, P.R. China  
E-mail: drwangde@vip.sina.com

**Key words:** low-molecular-weight heparin, anti-coagulant, thromboembolism, deep vein thrombosis, heparin

be more advantageous to patients, as it enables home-based therapy. A Cochrane review from 2013 last attempted to compare the efficacy and safety of once-daily and twice-daily LMWH therapy for the initial treatment of VTE (11). This review, however, included all types of LMWHs without specifically focusing on a single drug. Therefore, the purpose of the present review was to elucidate any difference in efficacy and safety of once-daily vs. twice-daily enoxaparin when used for the initial treatment of VTE.

## Materials and methods

**Study selection and search strategy.** In accordance with the Population, Intervention, Comparison, Outcome and Study design outline (12), an electronic literature search was performed for randomized controlled trials (RCTs), quasi-RCTs and prospective or retrospective cohort studies conducted on adult patients with acute VTE confirmed by diagnostic imaging ('Population'). Studies comparing weight-based once-daily administration of enoxaparin ('Intervention') with weight-based twice-daily administration of enoxaparin ('Comparison') for the initial treatment of the VTE were included. Studies reporting data on the recurrence of VTE and hemorrhagic complications ('Outcomes') were included. The definition of recurrence and major/minor hemorrhage was as specified in the included studies. No restrictions were applied regarding the location of VTE (DVT or PE). Studies were excluded if any of the following applied: i) Studies utilizing LMWHs other than enoxaparin; ii) studies comparing enoxaparin dosing strategy for VTE prophylaxis; iii) studies utilizing a fixed dose of the drug; iv) studies comparing <10 patients; v) studies not reporting relevant outcome data; vi) studies published in a language other than English; vii) in the case of duplicate reports, the study with the smaller sample size was excluded.

The PubMed, Embase, Cochrane Central Register of Controlled Trials, Science Direct and Google Scholar databases were searched by two independent reviewers (YS and CL) from inception up to 1st October 2019 for publications with the following keywords: 'Low molecular weight heparin'; 'heparin'; 'enoxaparin'; 'anticoagulant'; 'venous thromboembolism'; 'thromboembolism'; 'pulmonary embolism'; 'deep vein thrombosis'; 'dosing'; 'twice daily'; 'once daily'; 'q.d' and 'b.i.d'. The references of included studies were also inspected for the identification of any further trials. After screening the search results at the title and abstract level, the full texts of selected papers were extracted for detailed analysis based on pre-defined inclusion/exclusion criteria. Any disagreements were resolved by discussion with the other two reviewers (HR and WZ). The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (12) and Cochrane Handbook for Systematic Reviews of Intervention (13) were followed during the conduct of this review.

**Risk of bias.** For quality assessment of randomized controlled trials (RCTs), the Cochrane Collaboration risk assessment tool for RCTs was used (14). Studies were rated as having low risk, high risk or unclear risk of bias for the following points: Random sequence generation, allocation concealment,

blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. Other studies were analyzed using the risk of bias assessment tool for non-randomized studies (15). Studies were rated as having low risk, high risk or unclear risk of bias for the following points: Selection of participants, confounding variables, intervention measures, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. Two authors conducted the risk of bias analysis independently (YS and CL). Any disagreements were resolved by discussion with the other two reviewers (HR and WZ).

**Data extraction and statistical analysis.** A total of two independent reviewers (HR and WZ) extracted data from the included trials using a data abstraction form. The following details were extracted: First author name, year of publication, patient inclusion/exclusion criteria, sample size, baseline comparability of the two groups, enoxaparin protocol, use of other anti-coagulants, details for risk of bias analysis, outcome definition, VTE recurrence, complications and follow-up. The corresponding authors were e-mailed to request any missing data. The primary outcome of interest was the recurrence of VTE assessed by diagnostic imaging. The secondary outcome was the incidence of major or minor hemorrhage.

All analyses were performed using Review Manager [RevMan, version 5.3; Nordic Cochrane Centre (Cochrane Collaboration); 2014]. Outcomes were summarized using the Mantel-Haenszel odds ratio (OR) with a 95%CI. Considering the methodological heterogeneity amongst the included studies, a random-effects model was used to calculate the pooled effect size. Between-study heterogeneity was calculated using the  $I^2$  statistic.  $I^2$  values of 25-50% represented low, values of 50-75% medium and >75% represented substantial heterogeneity. Furthermore, two sub-group analyses were performed: i) For RCT and non-RCTs and ii) Depending on the use of enoxaparin as a bridging therapy for warfarin or as a monotherapy. To assess the outcomes of once-daily vs. twice-daily enoxaparin in cancer patients, the results of studies conducted specifically on cancer patients were pooled separately. A sensitivity analysis was performed to assess the contribution of each study to the pooled effect size by sequentially excluding individual studies one at a time and recalculating the pooled OR estimates for the remaining studies. Publication bias was not assessed due to the small number of included studies (<10 studies).

## Results

**Search results.** A comprehensive literature search was performed and a total of 670 unique records were retrieved (Fig. 1). The full texts of 11 studies were retrieved. Subsequently, 5 studies were excluded (16-20). In one study, patients were not randomized to once-daily or twice-daily enoxaparin for the initial treatment of VTE (20), while in four trials, LMWHs other than enoxaparin were used (16-19). A total of six studies were finally included in the review (9,10,21-24). In one study (21), outcome data were not extractable and e-mails to the corresponding author did not elicit a response. This study was not included in the meta-analysis.

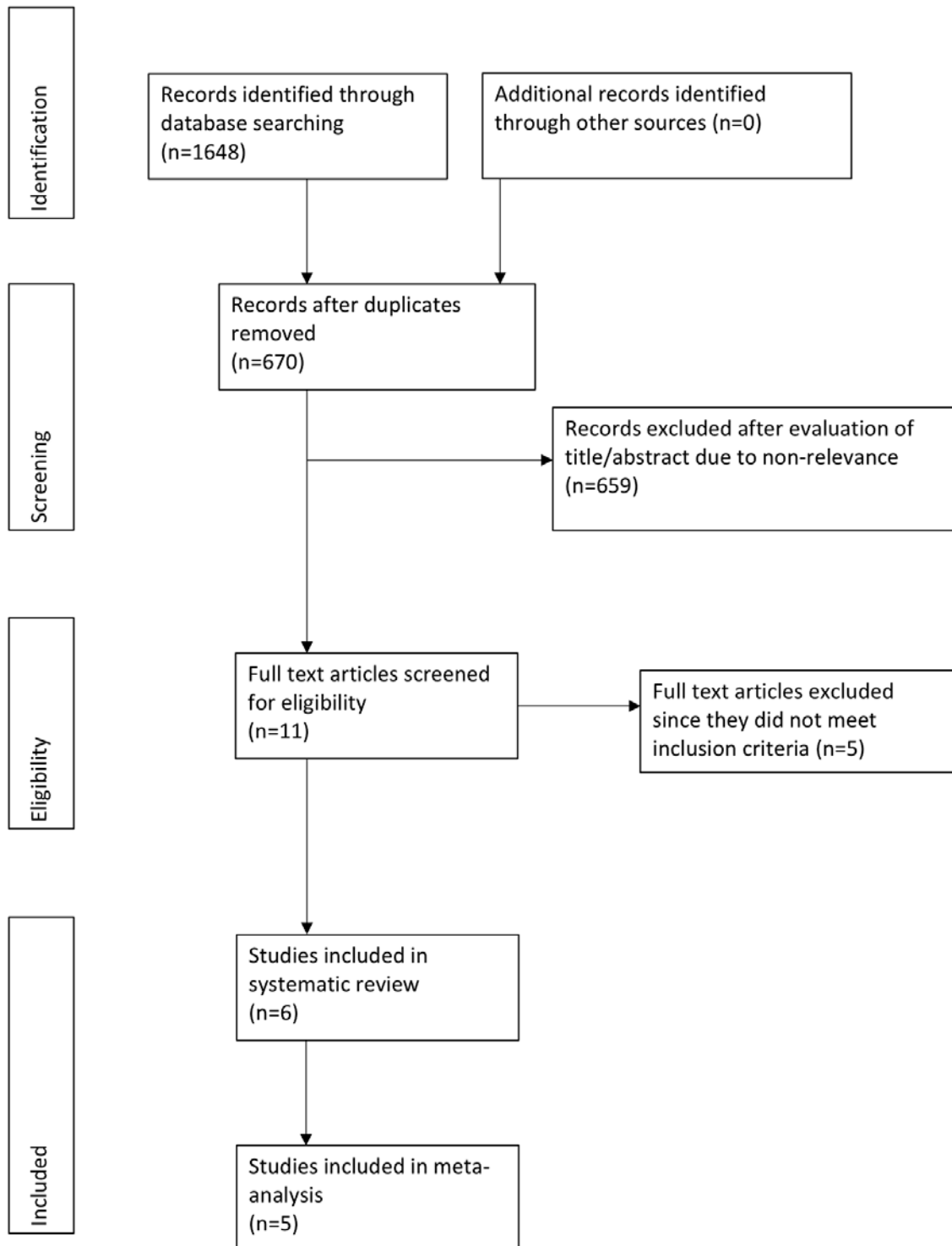


Figure 1. Study flow chart.

**Study characteristics.** The characteristics of individual studies are summarized in Table I. One study was an RCT (22) and two were prospective studies with historic control groups (10,23), while the remaining studies were retrospective studies (9,21,24). A total of two studies were performed specifically on cancer patients (9,24). VTE was confirmed by imaging in all studies. In addition, one study focused only on DVT (10), while another one focused only on PE (24). DVT and PE were both included in the definition of VTE for the

remaining studies. Inclusion/exclusion criteria, sample size and follow-up varied amongst the included studies. The enoxaparin dose was 1.5 mg/kg in the once-daily group and 1 mg/kg in the twice-daily group in all studies. The duration of enoxaparin treatment was not reported in four studies (9,21,23,24). In three studies (10,22,23), enoxaparin was used as bridging therapy to oral anti-coagulants. No major significant differences in baseline characteristics were reported by the included studies between the two study groups. There were

Table I. Characteristics of included studies.

Author (year)	Study type	Inclusion criteria	Exclusion criteria	Sample size		Enoxaparin dose		Duration of prophylaxis and treatment with other anti-coagulant drugs (Refs.)
				Once daily	Twice daily	Once daily	Twice daily	
Merli (2001)	RCT	Symptomatic DVT or PE confirmed by imaging	>24 h of previous treatment with heparin or warfarin, need for thrombolytic therapy, known hemorrhagic risk, active hemorrhage, angiodysplasia, eye/spinal/central nervous system surgery in past 1 month, renal/hepatic insufficiency, allergy to heparin/protamine/porcine products/iodine/contrast media, history of heparin-induced thrombocytopenia/skin necrosis, treatment with other investigational agents in <4 weeks, inferior vena cava interruption, pregnant or breastfeeding females	298	312	1.5 mg/kg	1 mg/kg	Duration of enoxaparin was at least 5 days. Warfarin started within 72 h of study drug administration and dose was adjusted to maintain INR between 2 and 3. Enoxaparin discontinued after target INR achieved.
Hacobian (2010)	Prospective with historic controls	Symptomatic DVT or PE confirmed by imaging	>72 h of hospitalization, PE with enlarged ventricle, high risk of bleeding, treated without warfarin, creatinine >2 mg/dl, recurrent VTE with anti-coagulation, life expectancy <3 months, scheduled for surgery during study period	40	80	1.5 mg/kg	1 mg/kg	Duration of enoxaparin not reported. Warfarin started on day 1 of study drug administration and dose adjusted to maintain INR at 2-3. Enoxaparin discontinued after target INR achieved.
King (2016)	Retrospective	Acute PE in cancer patients confirmed by imaging, enoxaparin dosing within 20 mg of body weight, >18 years of age, follow-up >6 months	In or transitioning to hospice, pregnant patients, patients weighing >190 kg, patients with <sup>3</sup> 1 enoxaparin dose held prior to completion of 30 days of drug administration, creatinine clearance <30 ml/min	48	48	1.5 mg/kg	1 mg/kg	NR

Table I. Continued.

Author (year)	Study type	Inclusion criteria	Exclusion criteria	Sample size		Enoxaparin dose		Duration of prophylaxis and treatment with other anti-coagulant drugs (Refs.)
				Once daily	Twice daily	Once daily	Twice daily	
Fuller (2018)	Retrospective	Adult cancer patients receiving enoxaparin for acute VTE event, follow-up >6 months	Creatinine clearance <30 ml/min, active hemorrhage or fibrinolytic therapy <3 days prior to enoxaparin initiation, anticoagulation started >48 h after diagnosis, >5 days treatment with another anti-coagulant, >15% divergence in the enoxaparin dose when prescribed according actual body weight, patients switching between the two study groups, discontinuing the study drug or shifting to another anti-coagulant	85	38	1.5 mg/kg	1 mg/kg	NR (9)
Trujillo-Santos (2017)	Retrospective	Symptomatic DVT or PE confirmed by imaging	NR	864	1,407	1.5 mg/kg	1 mg/kg	NR (21)
Yusuf (2019)	Prospective with historic controls	Symptomatic DVT confirmed by imaging	Prolonged hospitalization for >15 days, PE, high risk of bleeding, renal impairment, pregnancy, malignancy	40	40	1.5 mg/kg	1 mg/kg	Duration of enoxaparin was at least 5 days. Warfarin started on day 1 of study drug administration and dose adjusted to maintain INR at 2-3. Enoxaparin discontinued after target INR achieved. (10)

NR, not reported; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; RCT, randomized controlled trial; INR, international normalization ratio.

Table II. Outcomes of studies included in the meta-analysis.

Study	VTE definition	VTE outcomes (n/N)		Hemorrhage	Outcomes (n/N)		(Refs.)
		Once daily	Twice daily		Once daily	Twice daily	
Merli (2001)	Recurrent DVT or PE within 3 months of randomization. DVT confirmed with venography, USG or both. PE confirmed with lung perfusion scanning, pulmonary angiography or both.	11/247	8/258	Major hemorrhage was defined as being associated with at least one of the following: A decrease in hemoglobin level of at least 20 g/l; need for transfusion of at least two units of blood; retroperitoneal, intracranial or intraocular bleeding; other associated serious clinical event; need for surgical or medical intervention; or death. Minor hemorrhages were other hemorrhages that were clinically overt but did not meet the criteria for major hemorrhage.	Major hemorrhage: 5/298 Minor hemorrhage: 41/298	Major hemorrhage: 4/312 Minor hemorrhage: 50/312	(22)
Hacobian (2010)	Definition not specified. Outcomes assessed at 30 days.	1/40	3/80	Major hemorrhage defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria	0/40	3/80	(23)
King (2016)	Recurrent PE was defined as a new embolism or extension of a current embolism on CT pulmonary angiography or lung perfusion scanning or symptoms requiring anticoagulation medication changes such as an increased strength in dosing, increased frequency of dosing, or a change to an alternative anticoagulant. Maximum follow-up of 6 months	6/48	3/48	Major hemorrhage defined as an intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intramuscular with compartment syndrome, or intra-articular bleed, a drop in hemoglobin by $\geq 2$ g/dl from baseline, a requirement of $\geq 2$ units of packed red blood cells, or any bleed requiring major medical or surgical intervention.	7/48	3/48	(24)
Fuller (2018)	Recurrent VTE confirmed by diagnostic imaging. Outcomes evaluated at 30, 90 and 180 days.	30 day: 7/85 90 day: 5/72 180-day: 0/48	30 day: 1/38 90 day: 0/25 180-day: 2/14	Major bleeding as defined by the International Society on Thrombosis and Hemostasis, which includes fatal bleeding, bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), hemoglobin decrease by $\geq 2$ g/dl from baseline as a result of bleeding,	Major hemorrhage: 30 days, 1/85; 90 days, 2/72; 180 days, 2/48	Major hemorrhage: 30 days, 1/38; 90 days, 1/25; 180 days, 1/14	(9)

Table II. Continued.

Study	VTE definition	VTE outcomes (n/N)		Hemorrhage	Outcomes (n/N)		(Refs.)
		Once daily	Twice daily		Once daily	Twice daily	
Yusuf (2019)	Assessment of DVT carried out using clinical, radiological and laboratory tests at 30 days	1/40	2/40	or patients requiring $\geq 2$ units of blood or red cells as a result of bleeding. Non-major bleed defined as hemorrhage leading to medical intervention, hospitalization and increased level of care or necessitating a face-to-face evaluation Major hemorrhage was defined as overt bleeding that required a transfusion of $\geq 2$ units of blood, was retroperitoneal, spinal or intracranial, or was fatal.	30 days, 1/85; 90 days, 4/72; 180 days, 4/48	30 days, 1/38; 90 days, 1/25; 180 days, 0/14	(10)
n, number of events; N, total number of patients evaluated; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; USG, ultrasonography.							

no significant differences in baseline risk factors for VTE between the two groups in all studies. In one study (24), the two groups differed significantly in mean body weight, while in another study (9), the groups differed in their mean body mass index. One study (21) used propensity score matching for the two groups but did not report exact data on the outcome definition and relevant outcomes. A total of 864 patients on once-daily enoxaparin were matched with 1,407 patients on twice-daily enoxaparin in this study. The authors reported a similar incidence of recurrent VTE at 15 days [hazard ratio (HR)=1.26, 95%CI: 0.25-6.36]. A lower rate of major hemorrhage was seen in patients with once-daily enoxaparin at 15 days (HR=0.30, 95%CI: 0.10-0.88) and at 30 days (HR=0.16, 95%CI: 0.04-0.68). Outcome definitions and data reported by the remaining five studies are presented in Table II.

**Meta-analysis.** Data of 460 patients receiving once-daily enoxaparin and 464 patients receiving twice-daily enoxaparin were pooled for meta-analysis on VTE recurrence. The results indicated no significant difference between the two dosing regimens in terms of VTE recurrence (OR=1.48, 95%CI: 0.75-2.89,  $P=0.26$ ;  $I^2=0\%$ ; Fig. 2). Similar non-significant results were observed for sub-group analysis of non-RCTs (OR=1.50, 95%CI: 0.57-3.97,  $P=0.41$ ;  $I^2=0\%$ ) and the lone RCT (OR=1.46, 95%CI: 0.58-3.68,  $P=0.43$ ; Fig. 2). A total of 511 patients on once-daily enoxaparin and 518 patients on twice-daily enoxaparin were evaluated in the included studies for major hemorrhage. Meta-analysis demonstrated no significant difference in major hemorrhagic complications between once-daily and twice-daily enoxaparin (OR=1.21, 95%CI: 0.52-2.81,  $P=0.66$ ;  $I^2=0\%$ ; Fig. 3). The results were non-significant for non-RCTs (OR=1.08, 95%CI: 0.34-3.42,  $P=0.90$ ;  $I^2=5\%$ ) as well as the included RCT (OR=1.31, 95%CI: 0.35-4.94,  $P=0.69$ ; Fig. 3). On grouping studies based on the use of enoxaparin as bridging therapy for warfarin, no significant difference in recurrent VTE (Fig. 4) and major hemorrhage (Fig. 5) was obtained between once-daily and twice-daily enoxaparin for both sub-groups (bridging therapy vs. no-bridging therapy).

Data of two studies (9,24) performed specifically on cancer patients and the cancer sub-group of the RCT (22) were pooled together for a meta-analysis on recurrent VTE in cancer patients. The results demonstrated no difference between once-daily and twice-daily enoxaparin regarding the recurrence of VTE in cancer patients (OR=2.28, 95%CI: 0.91-5.75,  $P=0.08$ ;  $I^2=0\%$ ; Fig. 6). Data on hemorrhagic complications in cancer were not available from the RCT (22); hence, no meta-analysis was conducted on bleeding complications with just two studies.

The incidence of minor hemorrhage was reported only by two studies (9,22). While one trial (22) did not report any significant difference in minor hemorrhage between the two groups, the other study did not have sufficient statistical power to detect a significant difference (9).

**Sensitivity analysis and risk of bias assessment.** On sensitivity analysis, there was no change in the results of recurrent VTE and major hemorrhage on the sequential exclusion of all studies (data not shown). The authors' judgment of the risk of bias in studies included in the meta-analysis is presented in



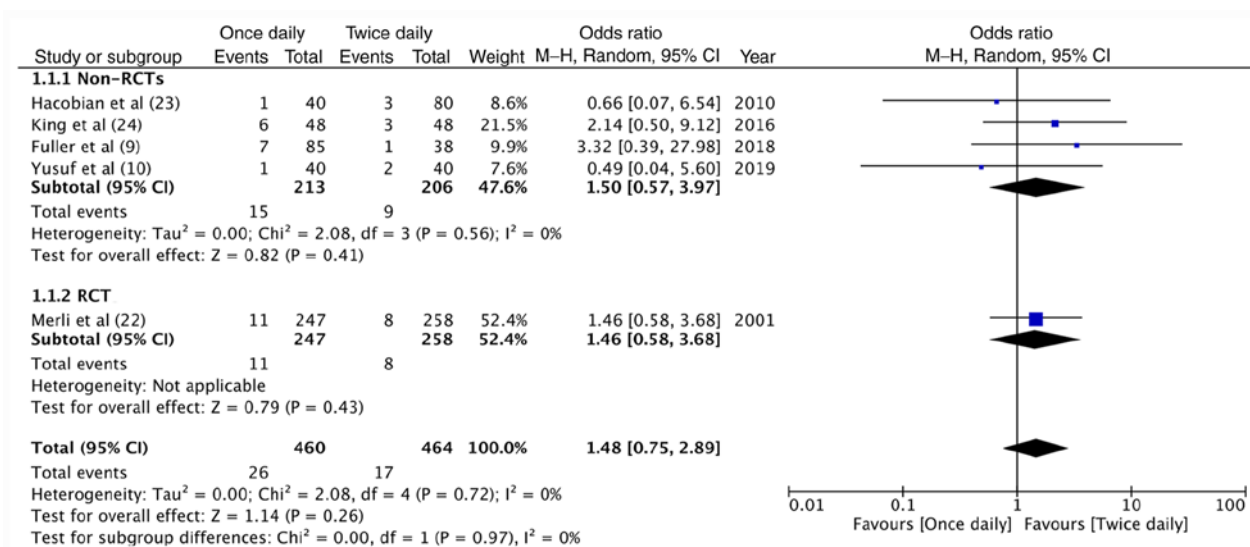


Figure 2. Forest plot of recurrent venous thromboembolism with sub-group analysis of the single RCT and non-RCTs. RCT, randomized controlled trial; M-H, Mantel-Haenszel; df, degrees of freedom.

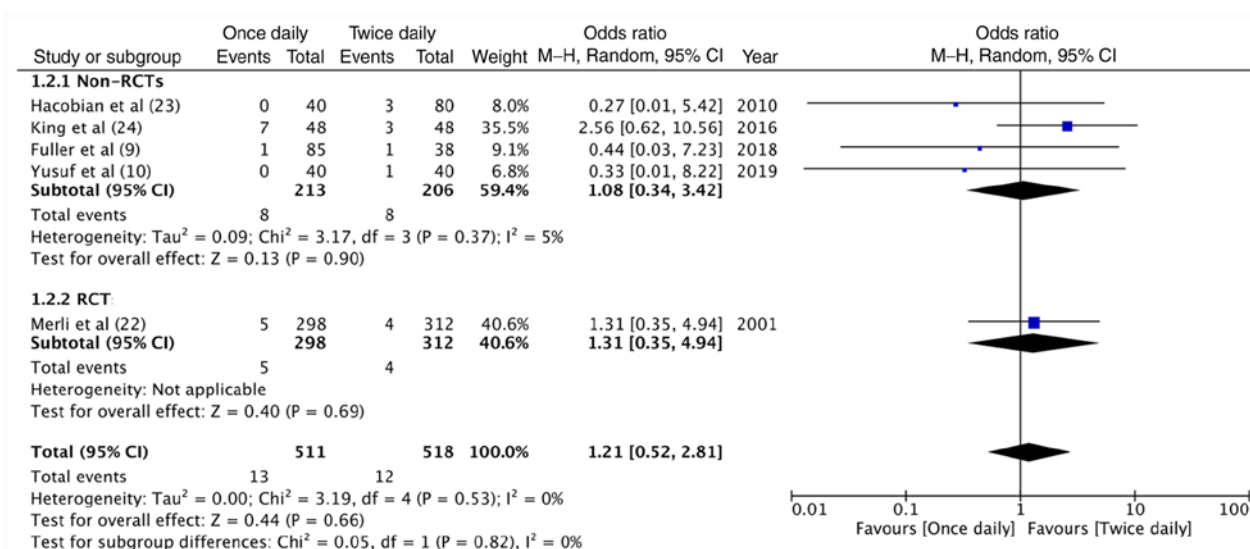


Figure 3. Forest plot of major hemorrhage with sub-group analysis of the RCT and non-RCTs. RCT, randomized controlled trial; M-H, Mantel-Haenszel; df, degrees of freedom.

Table III. The included RCT (20) was of high quality with low risk of bias in all domains.

For non-RCTs, only one study (24) had low risk of bias for selection of participants. None of the studies took into account confounding factors or had blinded outcome assessment. Therefore, the overall the quality of included studies was determined to be average.

## Discussion

LMWHs are among the most commonly used drugs for the prevention and management of VTE. In a Moroccan study, >90% patients with VTE were managed by LMWHs (25). LMWHs are a class of chemically distinct compounds with products differing in their polysaccharide chain lengths, mean molecular weights, as well as pharmacological properties.

In the absence of any consensus with regards to the clinical equivalence of different LMWHs, it is proposed that clinicians should follow manufacturer-recommended dosing guidelines when using these drugs (26). Amongst the three available LMWHs in the US, enoxaparin has the widest range of FDA-approved indications with established efficacy and safety in multiple patient populations (2,24,26).

Despite the broad utilization of enoxaparin, there is no consensus on the optimal dosing strategy of the drug (11,27). At present, two dosing regimens are approved by the FDA for the management of DVT with or without PE in hospitalized patients: 1 mg/kg every 12 h or 1.5 mg/kg every 24 h (27). Twice-daily administration of enoxaparin has been historically used for the treatment of VTE, with initial trials demonstrating equivalence of twice-daily enoxaparin and UFH (28). In a recent study, Trujillo-Santos *et al* (21) demonstrated that the



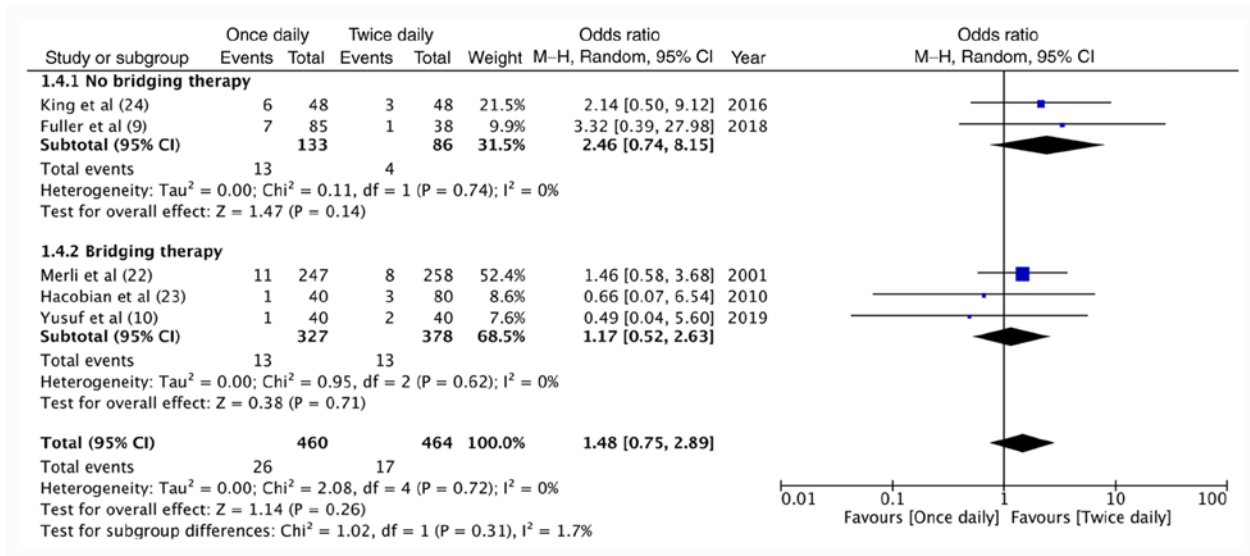


Figure 4. Forest plot of recurrent venous thromboembolism with sub-group analysis based on bridging therapy. M-H, Mantel-Haenszel; df, degrees of freedom.

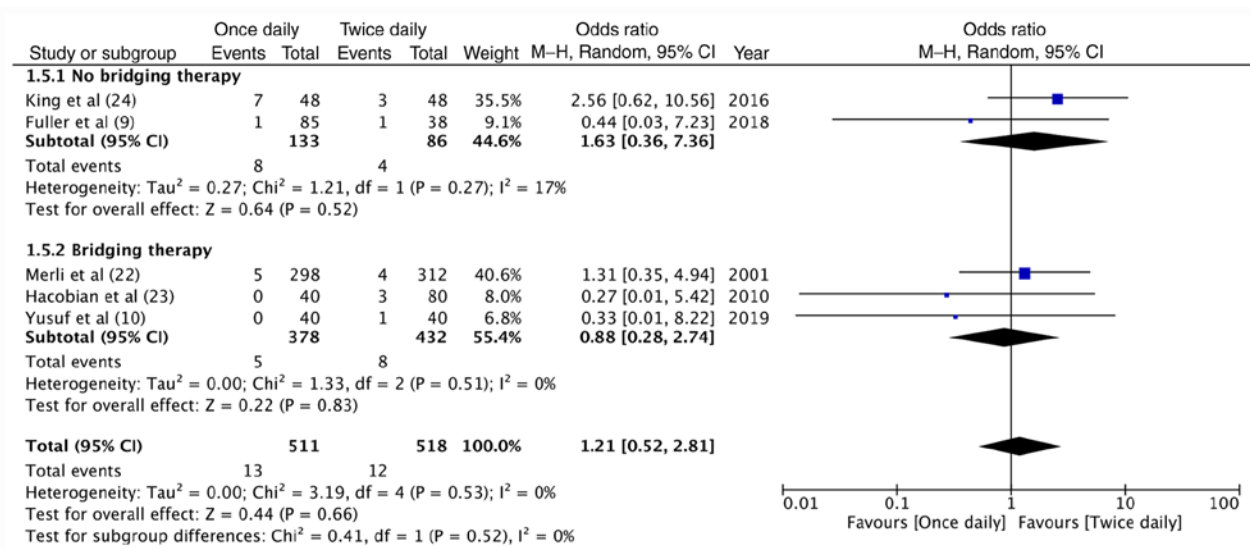


Figure 5. Forest plot of major hemorrhage with sub-group analysis based on bridging therapy. M-H, Mantel-Haenszel; df, degrees of freedom.

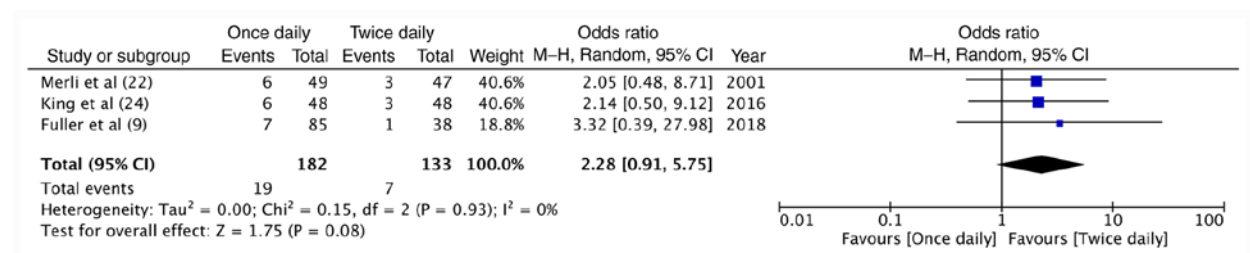


Figure 6. Forrest plot of recurrent venous thromboembolism for patients with cancer. M-H, Mantel-Haenszel; df, degrees of freedom.

twice-daily regimen is generally preferred for the treatment of acute VTE with >70% patients receiving dual injections. Whilst a twice-daily dosing regimen may theoretically provide a more stable anti-coagulation profile, the once-daily dose may be preferred by patients. Such a dosing strategy may halve the number of injections, reduce treatment costs and promote

outpatient department-based management protocols (10). The once-daily dose may also reduce hemorrhagic complications due to a reduced dose but may also potentially increase the recurrence of VTE.

According to the systematic search of the present study, a total of six studies published to date have performed a

Table III. Risk of bias assessment.

A, Randomized studies						
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Merli <i>et al</i> (22)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
B, Non-randomized studies						
Study	Selection of participants	Confounding variables	Intervention measures	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Hacopian <i>et al</i> (23)	High risk	Unclear risk	Low risk	High risk	Low risk	Low risk
King <i>et al</i> (24)	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk
Fuller <i>et al</i> (9)	Unclear risk	Unclear risk	Low risk	High risk	Low risk	Low risk
Yusuf <i>et al</i> (10)	High risk	Unclear risk	Low risk	High risk	Low risk	Low risk

head-to-head comparison of the two dosing strategies of enoxaparin for the management of acute VTE. In a pooled analysis of five studies, the present results indicated no difference in the incidence of recurrent VTE (OR=1.48, 95%CI: 0.75-2.89) and major bleeding complications (OR=1.21, 95%CI: 0.52-2.81) between once-daily and twice-daily enoxaparin. The present results concur with the last meta-analysis of Bhutia and Wong (11), which indicated no difference in terms of recurrent VTE (OR=1.21, 95% CI: 0.52-2.81) and major hemorrhagic complications (OR=0.77, 95%CI: 0.40-1.45) with once-daily and twice-daily LMWHs. It is important to note that while Bhutia and Wong (11) pooled results of only RCTs (total of two RCTs for VTE and four RCTs for major hemorrhage), only one RCT was included in the present analysis. This is because the present review was focused specifically on enoxaparin, unlike the past review, which pooled data of different LMWHs. Furthermore, the confidence interval of the pooled OR was wider as compared to that of the previous meta-analysis for the same outcomes. This, along with the inclusion of retrospective studies whose quality was not high, reduced the quality of evidence of the present analysis.

Several baseline risk factors are able to influence outcomes of acute VTE management, including age, history of VTE, cancer, obesity, trauma, congestive heart failure, pregnancy, infection, placement of venous catheters and duration of therapy (27). The use of suitable methods of randomization in RCTs usually nullifies the influence of such confounding variables on the study results; however, comparability is difficult to achieve in retrospective studies. Propensity-score matching has been used to reduce the bias of observational studies and was used in one study included in the present review (21). However, due to the absence of extractable data, the study was not included in the meta-analysis. Despite the remaining retrospective studies reporting no difference in the baseline characteristics of their study participants, a sub-group analysis for the single RCT and non-RCTs was performed to test the

validity of the present results. The sub-group analysis demonstrated no difference between the two groups for primary or secondary outcome variables. A similar sub-group analysis of enoxaparin bridging therapy and monotherapy also yielded a non-significant result.

Specific sub-groups of patients, e.g. those with cancer, have an increased risk of developing VTE (9). Despite anti-coagulant therapy, cancer patients have a three-fold risk of developing recurrent VTE as compared to patients without malignancy (29). In addition, the risk of hemorrhagic complications is higher when cancer patients receive anti-coagulation therapy (24,27). In the present review, the studies of King *et al* (24) and Fuller *et al* (9) were specifically performed on cancer patients. These two studies individually reported a higher incidence of recurrent VTE with once-daily enoxaparin compared to twice-daily enoxaparin; however, the studies were not statistically powered to detect differences between the two groups. Similarly, a limited sub-set analysis in the RCT of Merli *et al* (22) also demonstrated a two-fold increased incidence of recurrent VTE with once-daily enoxaparin but was statistically underpowered. On the pooling of data, a higher incidence of recurrent VTE was obtained with the once-daily compared to the twice-daily dosing regimen of enoxaparin (10.4 vs. 5.2%). The OR, however, included the null value of 1 with a wide CI (OR=2.28, 95%CI: 0.91-5.75).

There are certain limitations to the present review which require to be considered when interpreting the results. First, a limited number of included studies with only one RCT and preponderance of retrospective studies are significant drawbacks of the present review. The inherent drawbacks associated with retrospective studies, including selection bias and lack of blinding, may have skewed the results. Furthermore, the majority of studies were statistically underpowered to detect significant differences between the two groups. In addition, there were certain methodological differences between the included studies in terms of variation in inclusion/exclusion

criteria, duration of anti-coagulant therapy, differences in definition and evaluation of outcomes, and non-inclusion of DVT or PE in the definition of VTE. Also, there was a significant difference in follow-up amongst the studies included in the meta-analysis, with none comparing the hazard ratio of the two study groups. In addition, long-term follow-up data were not available for meta-analysis. Furthermore, outcomes including improvement of thrombus size and incidence of heparin-induced thrombocytopenia were not reported by the included trials. Finally, the present meta-analysis did not stratify the results based on specific risk factors for recurrent VTE. A sub-group analysis was possible only for cancer patients but with a limited number of studies.

To the best of our knowledge, the present study was the first systematic review and meta-analysis comparing once-daily and twice-daily enoxaparin for the management of VTE. Unlike previous reviews, the present study focused on a single drug that was compared using the same dosing protocol in all included studies. Sub-group and sensitivity analyses were performed to provide clarity on the overall results of the present review.

To conclude, despite the present results indicating similar rates of recurrent VTE and major hemorrhagic complications with once-daily and twice-daily enoxaparin when used for the treatment of VTE, the overall quality of evidence was not high, limiting the confidence of the conclusions. Although there was a tendency favoring twice-daily dosing over once-daily dosing, particularly for cancer patients, the results on efficacy and safety of the two dosing regimens of enoxaparin may not be reliable due to the limited number of available studies. Further high-quality and adequately powered RCTs are required to corroborate the present results, particularly in cancer patients.

### Acknowledgements

Not applicable.

### Funding

No funding was received.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

JN conceived and designed the study. YS and CL performed the literature search. HR and WZ collected the data. YS and CL assessed the risk of bias of included studies. HR and WZ were involved in interpretation of results. JN was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### References

1. Tagalakakis V, Patenaude V, Kahn SR and Suissa S: Incidence of and mortality from venous thromboembolism in a Real-world population: The Q-VTE study cohort. *Am J Med* 126: 832.e13-e21, 2013.
2. Spencer FA, Emery C, Lessard D, Anderson F, Emami S, Aragam J, Becker RC and Goldberg RJ: The worcester venous thromboembolism study: A population-based study of the clinical epidemiology of venous thromboembolism. *J Gen Intern Med* 21: 722-727, 2006.
3. Huang W, Goldberg RJ, Cohen AT, Anderson FA, Kiefe CI, Gore JM and Spencer FA: Declining Long-term risk of adverse events after First-time Community-presenting venous thromboembolism: The Population-based Worcester VTE study (1999 to 2009). *Thromb Res* 135: 1100-1106, 2015.
4. Hirsh J and Levine MN: Low molecular weight heparin. *Blood* 79: 1-17, 1992.
5. Robertson L and Jones LE: Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. *Cochrane Database Syst Rev* 2: CD001100, 2017.
6. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, *et al*: Antithrombotic therapy for VTE disease: CHEST Guideline and expert panel report. *Chest* 149: 315-352, 2016.
7. Lindmarker P, Holmström M, Granqvist S, Johnsson H and Lockner D: Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. *Thromb Haemost* 72: 186-90, 1994.
8. Collignon F, Frydman A, Caplain H, Ozoux ML, Le Roux Y, Bouthier J and Thébaud JJ: Comparison of the pharmacokinetic profiles of three low molecular mass heparins-dalteparin, enoxaparin and nadroparin-administered subcutaneously in healthy volunteers (doses for prevention of thromboembolism). *Thromb Haemost* 73: 630-40, 1995.
9. Fuller K, Malecki S, Anselmo L, Borrego ME, Jakeman B and Burnett A: Once-daily versus Twice-daily enoxaparin for the treatment of acute venous thromboembolism in cancer patients. *Ann Pharmacother* 52: 257-262, 2018.
10. Yusuf M, Gouda M, Herz-Allah A, Alkhoully M and Samir A: Once-daily versus twice-daily enoxaparin for the initial treatment of acute deep venous thrombosis: A case-control study. *J Med Sci Res* 2: 144-147, 2019.
11. Bhutia S and Wong PF: Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. *Cochrane Database Syst Rev* 2013: CD003074, 2013.
12. Moher D, Liberati A, Tetzlaff J, Altman DG and PRISMA Group: Preferred reporting items for systematic reviews and Meta-analyses: The PRISMA statement. *PLoS Med* 6: e1000097, 2009.
13. Higgins JPT and Green S (eds): *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.
14. Higgins J, Altman D and Sterne J: *Cochrane statistical methods group and the cochrane bias methods group*. Chapter 8: Assessing risk of bias in included studies. In: *Cochrane handbook for systematic reviews of interventions*, version 5. The Cochrane Collaboration, 2011.
15. Kim SY, Park JE, Lee YJ, Seo HJ, Sheen SS, Hahn S, Jang BH and Son HJ: Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol* 66: 408-414, 2013.
16. Partsch H, Kechavarz B, Mostbeck A, Köhn H and Lipp C: Frequency of pulmonary embolism in patients who have iliofemoral deep vein thrombosis and are treated with once- or twice-daily low-molecular-weight heparin. *J Vasc Surg* 24: 774-82, 1996.
17. Siegbahn A, Y-Hassan S, Boberg J, Bylund H, Neerstrand HS, Ostergaard P and Hedner U: Subcutaneous treatment of deep venous thrombosis with low molecular weight heparin. A dose finding study with LMWH-Novo. *Thromb Res* 55: 767-78, 1989.

18. Holmoström M, Berglund MC, Granquist S, Bratt G, Törnebohm E and Lockner D: Fragmin once or twice daily subcutaneously in the treatment of deep venous thrombosis of the leg. *Thromb Res* 67: 49-55, 1992.
19. Charbonnier BA, Fiessinger JN, Banga JD, Wenzel E, d'Azemar P and Sagnard L: Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. FRAXODI group. *Thromb Haemost* 79: 897-901, 1998.
20. Narin C, Reyhanoglu H, Tülek B, Onoglu R, Ege E, Sarigül A, Yeniterzi M and Durmaz I: Comparison of different dose regimens of enoxaparin in deep vein thrombosis therapy in pregnancy. *Adv Ther* 25: 585-594, 2008.
21. Trujillo-Santos J, Bergmann JF, Bortoluzzi C, López-Reyes R, Giorgi-Pierfranceschi M, López-Sáez JB, Ferrazzi P, Bascuñana J, Surinach JM and Monreal M: Once versus twice daily enoxaparin for the initial treatment of acute venous thromboembolism. *J Thromb Haemost* 15: 429-438, 2017.
22. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, Elias D, Grigg A, Musset D, Rodgers GM, *et al*: Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment venous thromboembolic disease. *Ann Intern Med* 134: 191-202, 2001.
23. Merli H, Shetty R, Niles CM, Gerhard-Herman M, Vallurupalli N, Baroletti S, McKean SC, Sonis J, Parasuraman S, Kosowsky JM and Goldhaber SZ: Once daily enoxaparin for outpatient treatment of acute venous thromboembolism: A case-control study. *Clin Appl Thromb* 16: 21-25, 2010.
24. King AC, Ma MQ, Chisholm G and Toale KM: Once daily versus twice daily enoxaparin for acute pulmonary embolism in cancer patients. *J Oncol Pharm Pract* 22: 265-270, 2016.
25. Tazi Mezalek Z, Nejari C, Essadouni L, Samkaoui M, Serraj K, Ammouri W, Kanjaa N, Belkhadir Z, Housni B, Awab M, *et al*: Evaluation and management of thromboprophylaxis in Moroccan hospitals at national level: The Avail-MoNa study. *J Thromb Thrombolysis* 46: 113-119, 2018.
26. Merli GJ and Groce JB: Pharmacological and clinical differences between low-molecular-weight heparins: Implications for prescribing practice and therapeutic interchange. *P T* 35: 95-105, 2010.
27. Diaz AH, Rodgers GM and Gilreath JA: Enoxaparin once daily vs. twice daily dosing for the treatment of venous thromboembolism in cancer patients: A literature summary. *J Oncol Pharm Pract* 18: 264-70, 2012.
28. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, Ginsberg J, Turpie AG, Demers C and Kovacs M: A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 334: 677-681, 1996.
29. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG and Büller HR: Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: A retrospective analysis. *J Clin Oncol* 18: 3078-3083, 2000.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.