Low-molecular-weight heparin for thromboprophylaxis

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Purpose of review

Venous thromboembolism represents a potentially threatening complication in surgical and medical patients. Thromboprophylaxis showed a significant reduction of venous thromboembolic events, and low-molecular-weight heparins have been considered the standardized prophylactic regimen for a long time. The purpose of this review is to provide updated evidence on the use of low-molecular-weight heparins for prevention of venous thromboembolism after the publication of the latest American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on antithrombotic and thrombolytic therapy.

Recent findings

Low-molecular-weight heparins, used as comparator or investigational drug, have been investigated in several studies not included in the analysis of the latest American College of Chest Physicians Guidelines on Antithrombotic and Thrombolytic Therapy. Data gathered from studies published from December 2007 up to May 2009 dealing with surgical and medical patients have been collected and discussed.

Summary

Low-molecular-weight heparins are expanding their application, but progressively they will be replaced by other new antithrombotics for the prophylaxis of venous thromboembolism. Surgical patients undergo a more concerted approach to thromboprophylaxis than medical patients. Future research should aim at improving prophylaxis in the latter setting in order to significantly reduce the rate of venous thromboembolic events.

Keywords

low-molecular-weight heparin, thromboprophylaxis, venous thromboembolism

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Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism, is acknowledged as a serious complication in hospitalized medical and surgical patients associated with increased morbidity and mortality, particularly fatal pulmonary embolism [1–3,4•].

The incidence of first-time VTE in the general population is age-related, being very low (0.005%) in adolescence, mainly occurring in the presence of typical risk factors (cancer, pregnancy, hormonal treatments and congenital thrombophilic states) and progressively increasing up to 0.5–2.5% per year in patients aged 70–80 years and older [2,5–9]. This is a crucial point, as the elderly population is also exposed to concomitant and additive risk factors (hospitalization, partial or total immobilization, malignancy, cardiac or respiratory failure, stroke, major orthopaedic surgery and so on) [10].

Without thromboprophylaxis, the incidence of DVT ranges from 10–20% in medical patients to 60–80% in patients with spinal cord injuries (SCI) (Table 1), and VTE-related mortality in the acute phase is about 12% (in-hospital case-fatality rate) [2,5,11•]. The well established scientific evidence that primary thromboprophylaxis significantly reduces VTE events represents a strong rationale for recommending effective thromboprophylaxis [5].

In VTE prevention, low-molecular-weight heparins (LMWHs) clearly are both effective and well tolerated alternatives to the standardized prophylactic regimen with unfractionated heparin (UFH) because of their greater bioavailability, longer half-lives, more predictable dose response, improved safety profile, lower incidence of heparin-induced thrombocytopenia and absence of laboratory monitoring.

The purpose of this review is to provide updated evidence on the use of LMWHs for VTE prevention following the publication of the latest American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines on antithrombotic and thrombolytic therapy (8th ACCP) [5].

Table 1 Incidence of deep-vein thrombosis in hospitalized patients without thromboprophylaxis

Category of patients	DVT prevalence (%)
Minor orthopaedic surgery	1–18
Medical patients	10–20
General surgery	15–40
Major gynaecologic surgery	15–40
Major urologic surgery	15–40
Neurosurgery	15–40
Stroke	20–50
Major orthopaedic surgery	40–60
Major trauma	40–80
Spinal cord injury	60–80
Critical care patients	10–80

Rates based on objective diagnostic screening for asymptomatic DVT. DVT, deep-vein thrombosis. Adapted with permission from Geerts *et al.* [5].

Methods

We searched MEDLINE, EMBASE and Google Scholar for studies published between December 2007 and May 2009 using the keywords 'thromboprophylaxis', 'low-molecular-weight heparin for thromboprophylaxis' or 'LMWH for thromboprophylaxis'. Only articles or abstracts written in English, German, Spanish or French were considered; we also cross-checked the references of relevant articles to find additional studies. Data of all retrieved articles were tabulated, but only the most relevant studies were included in the text.

Surgical patients

Prevention of peri and postoperative VTE complications remains a topic of clinical care in patients undergoing surgery. Without appropriate prophylaxis, up to 80% of these patients will develop a DVT, and subsequently up to 30% pulmonary embolism, which can be fatal in up to 7.5% [12–17].

General surgery

The 8th ACCP endorses LMWH prophylaxis during the hospital stay in these patients, except for those undergoing low-risk surgery or those at high bleeding risk, and suggests that it should be prolonged for up to 28 days after discharge in selected patients [5].

Two recent meta-analyses [18•,19•] of patients undergoing major abdominal surgery (approximately 70% with cancer) support the latter indication, showing a marked benefit with a postdischarge prolonged prophylaxis (up to 31 days). In the first [18•], a statistically significant reduction of objectively documented VTE was observed in patients receiving prolonged prophylaxis as compared with patients allocated to in-hospital prophylaxis only [5.9 versus 13.6%, relative risk (RR) 0.44, 95% confidence interval (CI) 0.28–0.7]), without an increased bleeding risk (3.85 versus 3.48%, RR 1.12, 95% CI 0.61–2.06). In the second [19•], a similarly higher efficacy was documented in the prolonged prophylaxis patients [6.1 versus 14.3%, Peto odds ratio (OR) 0.41, 95% CI 0.26–0.63, $P < 0.0005$]. A recent trial [20•], not included in the meta-analyses, compared extended with conventional duration in 308 patients undergoing bariatric surgery, observing a significant reduction of VTE events with prolonged prophylaxis, without an increased bleeding risk (Table 2).

Another four clinical studies were published in this setting after the 8th ACCP; of them three (all randomized open studies) dealt with bariatric surgery [21–23] and one (a cohort study) with vascular surgery [24] (Table 2). All three studies of bariatric patients [21–23] essentially investigated the tolerability/safety of two high-dose prophylactic regimens (with enoxaparin) administered during hospitalization [22,23] or also for 10 days after discharge [21]. No studies included a control group.

The last study [24], a prospective cohort of patients undergoing major vascular surgery, reports a high incidence of VTE despite active prophylaxis with UFH or LMWH (Table 2).

Gynaecologic surgery and pregnancy

The 8th ACCP recommends VTE prophylaxis until discharge in patients undergoing major gynaecologic surgery (MGS); moreover, limited to elderly women ($\geq$60 years) with malignancy or with a history of VTE, extended prophylaxis (LMWH and UFH) for up to 4 weeks following discharge is suggested [5]. In a recent study [25], 311 consecutive patients undergoing MGS for cancer were assigned to a combination of sequential compression devices as well as UFH or LMWH (dalteparin or enoxaparin) and were compared with a historical cohort of 294 patients, in which sequential compression devices were used as the sole prophylactic strategy. The combined prophylactic protocol was shown to be significantly more efficacious than the compression devices alone in reducing VTE (1.9 versus 6.5%, adjusted OR 0.33, 95% CI 0.12–0.88).

The usefulness of LMWH on pregnancy-related outcomes has been clearly evaluated by two recent systematic reviews [26,27], but randomized trials investigating the optimal use of LMWH during pregnancy are still lacking. We found seven studies dealing with the use of LMWH in pregnant patients [28,29••,30–33,34•], including two randomized studies (Table 3). In the first randomized controlled trial (RCT) [34•], enoxaparin along with folic acid significantly reduced the frequency of early (OR 0.44, 95% CI 0.15–1.2) and late (OR 0.49, 95% CI 0.06–3.18) miscarriage as compared with folic acid alone in 340 women with unexplained spontaneous recurrent miscarriage. However, no differences were

Table 2 Update on low-molecular-weight heparin thromboprophylaxis in patients undergoing major surgery

Reference	Study design	Indication	Method of VTE diagnosis	Interventions (patients, *n*)	MEO	MSO	Comments
Raftopoulos *et al.* [20•]	C	BS	DUS, CT–angiography	Short LMWH[*]; ($n=132$) Extended LMWH[*] ($n=176$)	4.5%[°] 0%[°]	5.3%[#] 0.56%[#]	–
Borgkren-Okonek *et al.* [21]	RO	BS	DUS, CT–angiography	Enoxaparin 40 mg; ($BMI \leq 50\ kg/m^2$); ($n=124$)[†] Enoxaparin 60 mg; ($BMI > 50\ kg/m^2$); ($n=99$)[†]	0.45%[†]	1.79%[†]	Targeted prophylactic anti-Xa levels were achieved by 74% of the patients after the third enoxaparin dose
Simone *et al.* [22]	RO	BS	Not considered	Enoxaparin 40 mg b.i.d.; ($n=24$)[‡] Enoxaparin 60 mg b.i.d.; ($n=16$)[‡]	A-Xa 1, 0.173 U/ml; A-Xa 3, 0.21 U/ml[¶] A-Xa 1, 0.261 U/ml; A-Xa 3, 0.43 U/ml[¶]	4.1%[¶] 0%[¶]	–
Rowan *et al.* [23]	RO	BS	Not considered	Enoxaparin 30 mg b.i.d.; ($n=19$)[‡] Enoxaparin 40 mg b.i.d.; ($n=33$)[‡]	A-Xa 1, 0.06 U/ml; A-Xa 3, 0.08 U/ml[∫] A-Xa 1, 0.14 U/ml; A-Xa 3, 0.15 U/ml[∫]	Not reported	–
de Maistre *et al.* [24]	C	VS	DUS, CT–angiography	Enoxaparin 40 mg o.d. or UFH 5000 IU b.i.d.[§]	8.1%	Not reported in detail	Among perioperative data, delay to prophylaxis was related to bleeding complications ($P=0.05$) and blood transfusion ($P=0.02$)

b.i.d., twice daily; BS, bariatric surgery; C, cohort study; CT, computed tomography; DUS, Doppler ultrasonography; Hb, haemoglobin; LMWH, low-molecular-weight heparins; MEO, major efficacy outcomes; MSO, major safety outcomes; o.d., once daily; RO, randomized open clinical trial; UFH, unfractioned heparin; VS, vascular surgery; VTE, venous thromboembolism.

[*] Short course: enoxaparin 30 mg b.i.d., starting 12 h before surgery and continued until discharge; extended course: enoxaparin 30 mg b.i.d., starting 12 h before surgery and continued until discharge followed by enoxaparin 40 mg o.d. for 10 days.

[°] VTE incidence during the first 30 days after surgery; $P=0.006$.

[#] $P=0.02$; the significant difference was only due to transfusion of blood products, whereas re-exploration rate for bleeding, mean Hb difference and frequency of Hb difference more than 2 g/dl were similar in the two groups.

[†] Enoxaparin was administered b.i.d. during hospitalization and o.d. for 10 days after discharge; MEO, one nonfatal event; MSO, four nonfatal events (requiring transfusion).

[‡] Prophylaxis was administered only during hospitalization.

[¶] MEO: anti-Xa concentrations were determined 4 h after the first (A-Xa 1) and the third (A-Xa 3) doses of enoxaparin; the anti-Xa range for prophylaxis is defined as 0.18–0.44 U/ml; after the third enoxaparin dose, 44% of the patients in the 40-mg group versus 0% of the patients in the 60-mg group had subtherapeutic anti-Xa levels, and 0% of the patients in the 40-mg group versus 57% of the patients in the 60-mg group had overtherapeutic levels ($P=0.02$). MSO: $P=$NS.

[∫] Anti-Xa concentrations were determined 4 h after the first (A-Xa 1) and the third (A-Xa 3) dose of enoxaparin. The anti-Xa range for prophylaxis is defined as 0.18–0.44 U/ml. No overtherapeutic anti-Xa levels were observed. Adequate anti-Xa levels at the first enoxaparin dose were obtained in 0% of the patients in the 30-mg group versus 30.8% in the 40-mg group ($P=0.01$); and at the third dose in 9.1 and 41.7% ($P=0.155$), respectively.

[§] UFH was administered in patients with renal insufficiency or older than 80 years; all patients were prescribed concomitant compression bandages or stockings and were invited to pursue early mobilization; MEO, one superficial-vein thrombosis, 14 asymptomatic DVT (two proximal, 12 distal), and two pulmonary embolism.

Table 3 Update on low-molecular-weight heparin thromboprophylaxis in patients undergoing gynaecological surgery, and pregnant patients

Reference	Study design	Indication	Interventions (patients, *n*)	Method of VTE diagnosis	MEO	MSO	Comments
Fox *et al.* [30]	R	Pregnancy*	Dalteparin 100 IU/kg × q.d. ($n=60$)* Enoxaparin 1 mg/kg × q.d. ($n=22$)*	Not considered	Anti-Xa levels:* 59% in range; 26% in subrange; 15% in suprarange	2.6%*; 3.9%*	−ve correlation with maternal age, BMI, gestational age; +ve correlation with the percentage of the minimal weight-based dose
Ni Ainle *et al.* [28]	R	Pregnancy°	Tinzaparin 175 IU o.d. ($n=37$)	Not reported	New DVT, 2.7%; DVT recurrence, 0%	MB, 0%; mb, 21.6%	Tinzaparin was well tolerated, no HIT, symptomatic osteoporosis, foetal malformations
Warren *et al.* [31]	R	Pregnancy#	UFH or LMWH ($n=25$) ASA or no treatment ($n=28$)	Not considered	84%† 82%†	Not reported	No significant difference in preeclampsia, SGA, foetus abruption, preterm birth, foetal death, early pregnancy loss between the two groups
Ramidi *et al.* [32]	C	Pregnancy§	Enoxaparin 30 mg b.i.d. + metformin 1.5–2.55 g/day ($n=21$), group A Enoxaparin 30 mg b.i.d. ($n=7$), group B	Not considered	SAB rate 17%; live births 83%‡ SAB rate, 0%; live births, 100%‡	Not reported	No adverse maternal–foetal side effects
Grandone *et al.* [33]	R	Pregnancy¶	Enoxaparin 40 mg o.d. ($n=7$) No treatment ($n=25$)	Not reported	87.5%^ 28.4%^	Not reported	Enoxaparin improved pregnancy outcomes
Badawy *et al.* [34•]	RO	Pregnancy**	Enoxaparin 20 mg o.d. + folic acid 0.5 mg o.d. ($n=170$)**	Not reported	Early PL, 4.1%; late PL, 1.1%	17.6%**	VTE incidence, 1.17; HIT incidence, 3.5%; no differences in preeclampsia, placental abruption, caesarean delivery, intrapartum bleeding
			Folic acid 0.5 mg o.d. ($n=170$)**		Early PL, 8.8%; late PL, 2.3%	13.5%**	VTE incidence, 2.35; HIT incidence, 0%; no differences in preeclampsia, placental abruption, caesarean delivery, intrapartum bleeding
Qublan *H et al.* [29••]	RDB	Pregnancy∫	Enoxaparin 40 mg o.d. ($n=42$) Placebo; ($n=41$)	Not considered	Implantation, 20.9%; Pregnancy 31.1%; Live-births 23.8% Implantation 6.1%; pregnancy, 9.6%; live births, 2.8%	not reported	No difference in treatment complications
Einstein *et al.* [25]	C	Cancer	Benign neoplasm: SCD + UFH 5000 IU b.i.d., or dalteparin 5000 IU or enoxaparin 40 mg o.d. until discharge ($n=74$) Malignant neoplasm: SCD + UFH 5000 IU t.i.d., or dalteparin 5000 IU or enoxaparin 40 mg o.d. for further 2 weeks after discharge ($n=237$) SCD alone ($n=294$)	DUS, CT–angiography, V/Q scan	1.9%¶¶ (DVT 0.6%, PE 1.3%) 6.5%¶¶ (DVT, 2.4%; PE, 4.8%)	14.9% 16.1%	No difference in major bleedings or HIT

C, cohort study; CI, confidence interval; mb, minor bleedings; DUS, Doppler ultrasonography; DVT, deep-vein thrombosis; HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; MB, major bleeding; MEO, major efficacy outcomes; MSO, major safety outcomes; PE, pulmonary embolism; PL, pregnancy loss; q.d., daily; R, retrospective study; RDB, randomized, double-blind clinical

trial; RO, randomized open clinical trial; SAB, spontaneous abortion; SCD, sequential compression devices; SGA, small-for-gestational-age infants; UFH, unfractionated heparin; VTE, venous thromboembolism; V/Q, ventilation/perfusion.
* Pregnant women with thrombophilia or previous VTE; five patients switched medications during pregnancy; targeted prophylactic range of peak plasma anti-Xa level of 0.2–0.4 U/ml at 4 h after injection: VTE incidence 0%; bleeding rate 2.6% between 12 and 28 weeks and 3.9% after 28 weeks of pregnancy.
° The study aimed to evaluate efficacy and safety of tinzaparin in pregnant women who had received antenatal therapeutic doses of tinzaparin for VTE treatment, in substitution of warfarin therapy commenced prior to the pregnancy, or because of high-risk pregnancy.
Asymptomatic pregnant women with inherited thrombophilia.
† Live births rate, VTE incidence 0%.
§ Pregnant women with recurrent pregnancy loss and spontaneous abortion, and with (group A) or without (group B) polycystic ovary syndrome.
‡ As compared with previous untreated pregnancies in the same patients in which spontaneous abortion rate was 75% (group A) and 53% (group B), and live births rate was 18% (group A) and 40% (group B), respectively.
¶ Pregnant patients with inherited antithrombin-III, protein C, protein S deficiency.
Fisher exact test: $P = 0.002$; VTE incidence 0% in treated and 2.1% in untreated women; risk of foetal loss in untreated women 3.1 times higher than in treated ones (95% CI 1.7–3.5).
** Pregnant women with idiopathic recurrent pregnancy loss; enoxaparin was administered from the time of confirmation of foetal viability until 34 weeks' gestation; folic acid was continued until 13 weeks of gestation; MSO were all mild first trimester bleedings, not requiring blood transfusion.
∫ Patients with recurrent in-vitro fertilization–embryo transfer (IVF-ET) failure. Enoxaparin was given from the day of embryo transfer until delivery or foetal demise.
¶¶ Adjusted odds ratio 0.33; 95% CI 0.12–0.88.

detected between the two groups in terms of pregnancy complications, caesarean delivery or bleeding. In the second RCT [29••], 83 women with a history of three or more previous in-vitro fertilization embryo transfer (IVF-ET) failures and at least one thrombophilic defect were allocated to enoxaparin or placebo (Table 3). Women given enoxaparin had a significantly higher rate of implantation ($P < 0.001$), pregnancy ($P = <0.05$) and live births ($P = <0.05$) than those in the placebo group, whereas the abortion rate was significantly higher ($P < 0.05$) in the latter group.

Neurosurgery

Neurosurgical patients are considered at high risk of developing postoperative VTE, particularly elderly patients and those with cancer or prolonged interventions. The 8th ACCP [5] recommendations include intermittent pneumatic compression (IPC) as first-line option and postoperative LMWH or low-dose UFH as acceptable alternatives [5,35,36]. In general, neurosurgeons are reluctant to administer pharmacological thromboprophylaxis due to the high risk of intracranial bleeding. In a recent meta-analysis [37], including 30 studies (7779 patients), LMWH showed a significantly higher efficacy in preventing DVT as compared with graduated compression stockings (GCS) (pooled RR 0.60, 95% CI 0.44–0.81) and only a positive trend as compared with IPC (pooled RR 0.79, 95% CI 0.30–2.12), without increasing the rate of intracranial haemorrhage (RR 1.97, 95% CI 0.64–6.09).

Patients with blunt traumatic brain injury present a moderately increased risk (20–40%) [38–40] of developing VTE complication without thromboprophylaxis, the risk being higher in the presence of multiple trauma [40]. A recent study by Norwood *et al.* [41], including 525 patients with blunt trauma brain injury, showed that early prophylaxis with LMWH [enoxaparin 30 mg twice daily (b.i.d.) administered within 48 h of admission, and continued to discharge] is associated with a low frequency of intracranial haemorrhage (1.1%). These results are consistent with the findings of previous similar studies [42–46].

In patients with spontaneous intracerebral haemorrhage, VTE complications are still not adequately estimated due to the lack of evidence. The American Heart Association and the American Stroke Council recommend IPC or GCS in this setting and suggest the use of LMWH or UFH only in patients without active bleeding [47]. Recently, Kiphuth *et al.* [48] retrospectively analysed the course of 97 patients with spontaneous intracerebral haemorrhage in whom an early (within 36 h of admission) prophylaxis with LMWH (enoxaparin or dalteparin) was given, using haematoma growth on computed tomography as the main outcome. None of the patients had a

Table 4 Venous thromboembolism incidence after major orthopaedic surgery without thromboprophylaxis

	DVT (%)		Pulmonary embolism (%)	
Procedures	Total	Proximal	Total	Fatal
Total hip replacement	42–57	18–36	0.9–28	0.1–2.0
Total knee replacement	41–85	5–22	1.5–10	0.1–1.7
Hip fracture surgery	46–60	23–30	3–11	0.3–7.5

DVT rates based on mandatory venography in prospective RCTs published between 1980 and 2002 in which patients received no prophylaxis or placebo. Pulmonary embolism rates derived from studies that may have used thromboprophylaxis. DVT, deep-vein thrombosis; RCTs, randomized-controlled trials. Adapted from Geerts *et al.* [5].

significant (>33%) haematoma growth, and only two patients experienced a moderate enlargement (20.9 and 22.4%, respectively), leading to the conclusion that the early application of subcutaneous LMWH for VTE prevention in this setting seems to be well tolerated [48].

Orthopaedic surgery

This topic has been divided into five sections due to the numerous articles published in the past 18 months dealing with orthopaedic patients in different settings.

Major orthopaedic surgery

Patients undergoing major orthopaedic surgery (MOS), including total hip replacement (THR), total knee replacement (TKR) and hip fracture surgery (HFS), are at high risk of VTE, the risk being increased in the presence of one or more concomitant risk factors (Table 4) [5,10,49].

LMWHs have been widely investigated in patients undergoing MOS, and their efficacy, as compared with low-dose unfractionated heparin (LDUH) or warfarin, is well documented, especially following THR and TKR [5], apparently with an acceptable safety profile (overall bleeding complications of approximately 2%) [5,50]. Currently, LMWHs are considered the standard regimen in MOS to which all new antithrombotic agents have to relate for phase II, III and IV studies. The continuous expanding number of patients undergoing MOS, and requiring adequate thromboprophylaxis, encouraged the pharmaceutical industry to develop new drugs. At present, some new antithrombotic agents have been investigated or are still under evaluation in numerous RCTs analysing their efficacy and safety in VTE prevention following MOS.

Idraparinux, a long-acting derivative of fondaparinux administered once weekly, has raised some concerns about an excess bleeding risk, particularly in the absence of a specific antidote. Currently, a biotinylated variant of idraparinux (SSR12517E), in which the anticoagulant effect can be rapidly reversed by intravenous administration of avidin, is under investigation in some RCTs [51].

We found nine RCTs testing new oral [rivaroxaban, (Xarelto; Bayer, Leverkusen, Germany and Johnson & Johnson, New Brunswick, New Jersey, USA), apixaban, and dabigatran (Pradaxa; Boehringer Ingelheim, Ingelheim, Germany)] or parenteral [SR123781A (Sanofi-Aventis, Paris, France), a new oligosaccharide with a mixed antifactor Xa (aXa)/anti-IIa activity] anticoagulant versus LMWH [enoxaparin 40 mg once daily (o.d.) or 30 mg b.i.d.] (Table 5). Also, one open RCT testing a new mechanical compression device in association with LMWH was found.

Oral dabigatran 150 or 220 mg o.d. has been investigated in three RCTs, including patients undergoing THR [52] or TKR [53••,54••]. In summary, dabigatran was shown to be as effective as the European enoxaparin regimen following THR or TKR [52,53••], whereas when the North American enoxaparin regimen for TKR was used, the noninferiority criterion with respect to enoxaparin was not met [54••]. The safety profile was similar in all three studies, with a rare incidence of major bleedings.

Oral rivaroxaban 10 mg o.d. was investigated in four RCTs (Regulation of Coagulation in Major Orthopedic Surgery Reducing the Risk of DVT and Pulmonary Embolism, RECORD Program) in patients undergoing THR [55••,56••] and TKR [57••,58••]. When data from all four studies were pooled, rivaroxaban showed a statistically significant superiority with respect to the comparator enoxaparin, without a statistically significant difference in major bleeding between the study groups (Table 5). However, when major bleeding by their definition was added to clinically relevant nonmajor bleeding, there was a significant difference favouring enoxaparin.

On the basis of the results of the respective drug development programmes, both rivaroxaban and dabigatran have been submitted to the European Medicines Agency (EMEA); in April 2008, dabigatran was approved by the EMEA and introduced in the market, whereas rivaroxaban's approval is still ongoing.

Oral apixaban has been investigated in a dose-ranging phase II double-blind study [59], in which 1238 patients undergoing TKR were randomized to receive one of six doses of apixaban, or to enoxaparin 30 mg b.i.d., or to warfarin [international normalized ratio (INR) 1.8–3.0].

Table 5 Update on low-molecular-weight heparin thromboprophylaxis in patients undergoing major orthopaedic surgery

Reference	Study design	Indication	Interventions[e]	MEO (%)[a]	MSO (%)[b]
RE-NOVATE [52]	RDB	THR	Enoxaparin 40 mg o.d.	6.7	1.6
			Dabigatran 150 mg o.d.	8.6	1.3
			Dabigatran 220 mg o.d.	6.0	2.0
RE-MODEL [53••]	RDB	TKR	Enoxaparin 40 mg o.d.	37.7	1.3
			Dabigatran 150 mg o.d.	40.5	1.3
			Dabigatran 220 mg o.d.	36.4	1.5
RE-MOBILIZE [54••]	RDB	TKR	Enoxaparin 30 mg b.i.d.	25.3	1.4
			Dabigatran 150 mg o.d.	33.7[c]	0.6
			Dabigatran 220 mg o.d.	31.1	0.6
RECORD1 [55••]	RDB	THR	Enoxaparin 40 mg o.d.	3.7	0.1
			Rivaroxaban 10 mg o.d.	1.1	0.3
RECORD2 [56••]	RDB	THR	Placebo[d]	9.3	<0.1
			Rivaroxaban 10 mg o.d.	2.0	<0.1
RECORD3 [57••]	RDB	TKR	Enoxaparin 40 mg o.d.	18.9	0.5
			Rivaroxaban 10 mg o.d.	9.6	0.6
RECORD4 [58••]	RDB	TKR	Enoxaparin 30 mg b.i.d.	10.1	0.3
			Rivaroxaban 10 mg o.d.	6.9	0.7
APROPOS [59]	RDB	TKR	Enoxaparin 30 mg b.i.d.	17	0
			Warfarin (INR 1.8–3.0)	29.9	0
			Apixaban 2.5/5/10 mg b.i.d. or 5/10/20 mg o.d.	4.8–12.6	0–3.3
DRIVE [60]	RDB	THR	Enoxaparin 40 mg o.d.	8.7	0.6
			SR123781A 0.25/0.5/1.0/2.0/4.0 mg o.d.	21.2–4.4	0.6–5.8

b.i.d., twice daily; CT, computed tomography; MEO, major efficacy outcomes; MSO, major safety outcomes; o.d., once daily; RDB, randomized double-blind clinical trial; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.
[a] Composite of death from all causes and total VTE as assessed with venography, CT–angiography, ventilation/perfusion lung scan or pulmonary angiography; unless stated otherwise, noninferiority criteria were met for the dabigatran regimens compared with the control enoxaparin regimen.
[b] Major bleeding according standardized criteria.
[c] Noninferiority criterion not met.
[d] Following an initial 12-day period with enoxaparin 40 mg/day.
[e] All studies double-blind, with independent outcomes adjudication committee.Adapted from Bouneamoux [51].

VTE incidence ranged from 5 to 13% in the six apixaban subgroups, without a significant dose-dependent effect, as compared with 17% in the enoxaparin and with 29.9% in the warfarin arms. A significant dose-related increase of bleeding was observed in the six apixaban subgroups. These results were used to develop a phase III study programme with apixaban, 2.5 mg b.i.d., for VTE prevention following THR (ADVANCE 2 versus enoxaparin 40 mg o.d.) and TKR (ADVANCE 1 versus enoxaparin 30 mg b.i.d. or ADVANCE 3 versus enoxaparin 40 mg o.d.) that is still ongoing [60].

The new parenteral drug SR123781A is the first synthetic oligosaccharide with a mixed profile of antithrombin-dependent aXa and IIa activities. It has been investigated in a double-blind, double-dummy, dose-ranging study [61•], in which 1023 patients undergoing THR were randomly assigned to receive 0.25, 0.5, 1.0, 2.0 and 4.0 mg of SR123781A or a calibrator enoxaparin 40 mg o.d. regimen, both administered subcutaneously. A significant dose–response effect in reducing VTE was obtained for SR123781A, with a significant RR reduction in VTE of 67 and 79% with 2.0 and 4.0 mg, respectively, with a comparable safety profile for the 2.0 mg dose group (0.6% incidence of major bleedings in both enoxaparin and SR123781A arms). On the basis of these findings, SR123781A doses ranging from 1.5 to 2.5 mg seemed to provide an acceptable risk-to-benefit ratio for VTE prevention following MOS, worthy of further studies in properly designed phase III trials.

In the open RCT [62], 320 patients undergoing THR or TKR were randomized to receive enoxaparin alone 30 mg b.i.d. or an association of enoxaparin (same regimen) and a new portable continuous enhanced circulation therapy (CECT; Medical Compression Systems, Or Akiva, Israel) compression device. The study showed an absolute risk reduction of DVT (but not of symptomatic pulmonary embolism) of 12.9% ($P = 0.018$) in TKR patients receiving combined enoxaparin and CECT, whereas in THR patients this association did not significantly change the VTE incidence.

Knee arthroscopy

The 8th ACCP did not endorse routine thromboprophylaxis after knee arthroscopy due to the scarce evidence coming from adequate studies in this setting (grade 2A recommendation), other than for high-risk patients or with complicated procedure, in which LMWH prophylaxis is recommended (grade 1B) [5]. A recent meta-analysis by Ramos *et al.* [63] confirmed this statement. The results of the recently published Knee Arthroscopy Nadroparin Thromboprophylaxis (KANT) study [64••], not included in that meta-analysis, challenge this point of view, reporting a 2.3% absolute risk reduction (95% CI 0.7–4.0, $P = 0.005$; adjusted OR 0.27, 95% CI 0.11–0.69)

of VTE complication in patients receiving a 7-day LMWH course (nadroparin 3800 IU aXa o.d.) as compared with a 7-day GCS course, without a significant increase of bleeding events (0.9 versus 0.3% major and clinically relevant bleeding, respectively; absolute difference −0.6%, 95% CI −1.5 to 0.2, P = NS). Given the huge and increasing number of arthroscopic procedures performed worldwide (over 4 000 000 per year), that small but significant advantage in terms of efficacy could potentially translate into meaningful improvement in the general population. After the publication of the KANT trial, some authors supported, even with some good criticism, this new approach [65–67], especially for patients having more extensive procedures.

Lower leg immobilization

Isolated lower extremity injuries include below-knee fractures, ligament and cartilage injuries of the ankle, rupture of the Achilles tendon and wide soft-tissue injuries. Without thromboprophylaxis, the incidence of VTE, as assessed by venography, ranges from 10 to 45% [5] and from 4 to 17% when compression ultrasound is used [68,69]. The use of pharmacological thromboprophylaxis in this setting is strongly debated; accordingly, available guidelines issued controversial and conflicting recommendations [5,70,71]. Two new meta-analyses [72•,73•] analysed six RCTs, for a total of 1456 and 1490 patients, respectively, concluding that LMWH thromboprophylaxis following lower leg immobilization is both effective (RR 0.58, 95% CI 0.39–0.86, $P = 0.006$; OR 0.49, 95% CI 0.34–0.72, respectively) and well tolerated (RR 1.22, 95% CI 0.61–2.46, $P = 0.57$) as compared with placebo or no prophylaxis. On the contrary, a recent double-blind RCT conducted in 238 patients undergoing operative fixation of isolated fractures below the knee failed to show a statistically significant difference in the incidence of DVT between patients administered LMWH or placebo for 14 days (8.7 versus 12.6%, $P = 0.22$) [74•]. Currently, a multicenter randomized clinical trial comparing fondaparinux versus nadroparin in this setting (FONDACAST trial) is ongoing.

Spinal cord injuries

In absence of thromboprophylaxis, patients with acute SCI experience the highest VTE incidence among all hospitalized groups (asymptomatic VTE occurs in up to 100%, whereas DVT and pulmonary embolism are clinically evident in up 10 and 3%, respectively) [5,75–77]. Notably, the associated fatal pulmonary embolism rate has not decreased in the past 25 years. Even if not strong, there is evidence that LMWHs significantly reduce the incidence of VTE in SCI patients [78–86]. For this reason, they represent, alone or in association with IPC, the recommended prophylactic option in these patients, as reported in various guidelines [5,87,88]. A recent retrospective cohort study [88] challenged this view, reporting a similar incidence of VTE in patients given LMWH (dalteparin, 5000 IU o.d.) or LDUH.

Podiatric surgery

Patients undergoing podiatric surgery (including below-knee, ankle and foot surgical procedures) are at hypothetical low risk of developing VTE complications because these procedures do not involve the proximal veins, and only rarely the calf veins. Consequently, the risk/benefit ratio of systematic thromboprophylaxis in this group of patients is still uncertain. The incidence of DVT following podiatric surgery ranges from 0.22 to 4.0% and that of pulmonary embolism from 0 to 0.15% [89–92]. A recent retrospective study by Felcher *et al.* [93•] reported an overall postprocedural incidence of symptomatic VTE of 0.3%, the risk being higher in the presence of risk factors such as a history of VTE, hormone therapy and obesity. On this basis, the authors concluded that podiatric patients, unless with a concomitant risk factor, should not routinely be offered LMWH prophylaxis and should only be encouraged to mobilize early. This view is shared by other authors who also emphasize the importance of keeping a high index of suspicion about signs and symptoms of VTE in these patients [94].

Medical patients

The 8th ACCP recommends LMWH thromboprophylaxis for acutely ill medical patients admitted to hospital with congestive heart failure or severe respiratory disease or who are confined to bed and have one or more additional risk factors such as active cancer, previous VTE, sepsis, acute neurologic disease or inflammatory bowel disease [5]. Several studies investigated the extent to which this specific issue of the guidelines is implemented in the daily hospital routine [95••,96] or in selected populations such as patients with acute stroke [97], with heart failure [98••] or with renal failure [99]. The two larger studies [95••,98••], including about 70 000 patients each, clearly demonstrated that LMWH prophylaxis is definitely underused in medical wards, as only 31–40% of the patients qualifying for thromboprophylaxis did indeed receive it, whereas in the smaller studies, the lowest proportion of prophylaxis was observed in Chinese patients with acute stroke (3.4%) [97], and the highest was reported by an Italian survey (61.4%) [99]. A similarly low pattern of prescription (35%) was observed in a prospective multicentre cohort study [100•] conducted in 2895 general practice patients, in which a reduction in mobility longer than 48 h was expected due to an acute medical condition. Interestingly, slightly more than half of the patients receiving LMWH thromboprophylaxis in one of these studies [100•] had moderate to severe renal failure; surprisingly, differences neither in the rate of prescription nor in the dosage of LMWH were observed between patients with or without renal failure.

Several strategies to enhance the adherence with the appropriate thromboprophylaxis level have been devised by the 8th ACCP, including the use of computer reminders [5]. Two recent observational studies [4•,11•] reported very high prescription rates (65–100%) through the use of electronic alert systems. The large sample study by Lecumberri *et al.* [4•], conducted in Spain on more than 19 000 medical and surgical patients, demonstrated a statistically significantly higher prescription rate in medical patients after the implementation of such a system (49.2 versus 64.4%, $P < 0.01$, in the pre and postintervention phases, respectively), paralleled by a significant reduction in terms of reduction of VTE events (OR 0.36, 95% CI 0.12–0.98).

Stroke

The 8th ACCP recommends LMWH or LDUH for VTE prevention in patients with acute stroke and restricted mobility [101]. A recent meta-analysis supports the concept of a higher efficacy of LMWH, observing a significant reduction of any VTE (OR 0.54, 95% CI 0.41–0.70, $P < 0.001$), of proximal DVT (OR 0.53, 95% CI 0.37–0.75, $P < 0.001$) and of pulmonary embolism (OR 0.26, 95% CI 0.07–0.95, $P < 0.042$) with LMWH as compared with UFH. Significantly, this superior efficacy is not paid at the price of a higher major bleeding risk, either intracerebral (OR 0.70, 95% CI 0.26–1.84, $P = 0.466$) or extracerebral (OR 1.31, 95% CI 0.63–2.71, $P = 0.467$) [102•].

Advanced age

A nonrandomized, cross-sectional, multicentre study [103] evaluated LMWH for prophylaxis in 1603 patients aged at least 65 years with restricted mobility. The primary study endpoint was the incidence of proximal DVT as assessed by complete compression ultrasonography. Although the incidence of proximal DVT did not differ between patients given or not given LMWH (4 versus 5.7%, $P = 0.16$), the adjusted OR for proximal DVT was reduced in patients given LMWH (OR 0.56, 95% CI 0.33–0.95, $P = 0.03$), although only in those receiving high-dose LMWH [103].

Cancer

Patients with cancer are at high risk of developing VTE *per se* [104•], and prophylaxis against VTE is warranted if they are exposed to additional risk factors associated with surgical procedures or with medical illnesses [5].

Conversely, there is no such indication for the prevention of upper limb DVT in cancer patients with indwelling central venous catheters (CVC) [5,105]. Two recent meta-analyses [104•,106•], not included in the 8th ACCP, corroborate the concept endorsed by the guidelines. The first [104•] included eight RCTs that evaluated the incidence of CVC-related thrombosis, bleeding and thrombocytopenia in patients given heparin (unfractionated or LMWH) versus placebo or no treatment. The authors, using a random effects model, found no statistically significant differences in terms of the outcomes considered (catheter-related thrombosis: RR 0.46, 95% CI 0.18–1.20, $P = 0.18$; bleeding: RR 1.29, 95% CI 0.85–1.95, $P = 0.23$; thrombocytopenia: RR 0.85, 95% CI 0.49–1.46, $P = 0.55$). The second [106•], whose results are quite similar to the former, included nine RCTs and evaluated the efficacy and safety of heparin (unfractionated or LMWH) versus placebo or no intervention on the incidence of mortality (RR 0.74, 95% CI 0.40–1.36), CVC-related thrombosis (RR 0.43, 95% CI 0.18–1.06), infection (RR 0.91, 95% CI 0.36–2.28), major bleeding (RR 0.68, 95% CI 0.10–4.78) and thrombocytopenia (RR 0.85, 95% CI 0.49–1.46). Of note, some authors claim that subgroups of cancer patients, such as those with distant metastases, more than one CVC insertion attempts, previous CVC insertions, CVC tip misplacement, left insertion and chest radiotherapy, may benefit (up to 50% CVC-related thrombosis reduction) from the prophylactic administration of LMWH [107,108].

The 8th ACCP also recommended against routine prophylaxis for primary prevention of VTE in cancer patients receiving chemotherapy or hormonal therapy [5]. Two recent trials [109,110•] provide further evidence in this setting. The first [109] evaluated the use of LMWH (enoxaparin, nadroparin or dalteparin) for symptomatic VTE prevention in patients with relapsed multiple myeloma treated with lenalidomide and dexamethasone. LMWH was administered at least for the first three cycles of chemotherapy. Only one (2.2%) of 45 patients developed symptomatic VTE, whereas none experienced bleeding complications, although there was no comparator. The second [110•] is an open-label, multicentre RCT comparing a LMWH (enoxaparin) versus no treatment for VTE prophylaxis during chemotherapy in patients with locally advanced or metastasized pancreatic cancer. The declared sample size is 40 patients. A planned safety interim analysis was performed after 152 patients were enrolled, and no differences in terms of overall and major bleeding events were observed between the two study groups (five versus six patients); also, no heparin-induced thrombocytopenia was observed.

Critical care

The 8th ACCP recommends routine thromboprophylaxis in most patients admitted to intensive care units, except those at high risk for bleeding. A recent systematic review [111] challenges this statement by stating that the wealth of evidence available is insufficient to recommend that LMWH be used for thromboprophylaxis or used in preference to UFH. The frequency of VTE in patients receiving LMWH ranged from 5.1 to 15.5%, bleeding complications ranged from 7.2 to 23.1% and mortality ranged from 1.4 to 7.4%.

Renal impairment

The issue of LMWH bioaccumulation in critically ill patients with severe renal insufficiency was explored in a multicentre cohort study [112•] in which these patients were administered LMWH (dalteparin) for a median duration of 7 days. The authors found no association between excessive anticoagulant effect due to drug bioaccumulation, and that LMWH prophylaxis is unlikely to contribute to bleeding. This concept is detailed in another similar trial [113•] based on the same patient population, in which the only independent risk factors for major bleeding were aspirin use (hazard ratio 6.30, 95% CI 1.35–29.4) and a spontaneously high INR (hazard ratio for 0.5-unit increase 1.68, 95% CI 1.07–2.66). A recent systematic review [111], including three studies that evaluated potential bioaccumulation of LMWH (dalteparin) in patients with severe renal insufficiency, found little or no evidence of bioaccumulation.

Conclusion

UFH have been progressively replaced by LMWHs for thromboprophylactic indications. In surgical patients, LMWHs are increasingly expanding their applications (knee arthroscopic or podiatric surgery, IVF-ET, vascular surgery and so on), and at the same time, surgeons are more prone to recommend thromboprophylaxis for their patients. LMWHs currently represent the standard regimen with which all new antithrombotics involved in registration or clinical trials (phase II or phase III) have to relate, particularly in MOS, which is considered the first testing ground for these drugs. In the past 12–18 months, some new compounds have been shown to be at least as effective (dabigatran) or superior (rivaroxaban) in VTE prevention in MOS patients, and other are currently under investigation. Therefore, it is likely that they will gradually replace LMWHs in the near future.

However, in medical patients, despite the clear scientific evidence about their efficacy and safety in VTE prevention, LMWHs are at present universally underused, and a number of clinical trials are now ongoing assessing LMWHs or new drugs in this setting. In order to improve VTE thromboprophylaxis in these patients, better approaches to risk assessment and wider use of effective thromboprophylaxis are required.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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