European Review for Medical and Pharmacological Sciences 2011; 15: 950-959

Update on low molecular weight heparins at the beginning of third millennium. Focus on reviparin

R. DEL BONO, G. MARTINI, R. VOLPI

Haemostasis and Thrombosis Centre, University-Hospital Institute of "Spedali Civili di Brescia", Brescia (Italy)

Abstract. – *Background:* **This review provides an outline of the main pharmacological and clinical features of low molecular weight heparins (LMWHs) and a wider description of reviparin. The basic pharmacological properties of LMWHs are compared with those of unfractionated heparin, showing clear advantages of the former, mainly as for pharmacokinetic profile.**

Design: **Consequently LMWHs are characterized by a more predictable behaviour. A key issue is the lack of "bioequivalence": LMWHs are in fact distinct chemical entities, with typical pharmacological and clinical profile for each agent. Therefore, they are not reciprocally interchangeable. The efficacy and safety of reviparin, a second generation LMWH, has been evaluated in many clinical trials as both thrombosis prevention and treatment. Reviparin use is documented in general and orthopaedic surgery. In patients undergoing abdominal surgery reviparin resulted more effective and better tolerated than unfractionated heparin (UFH). In total hip replacement patients, reviparin compared favourably with enoxaparin, showing the same efficacy but better safety. In patients who undergone total hip replacement, also the long-term, out of hospital prevention of deep vein thrombosis (DVT) has been proven.**

Conclusions: **The comparison with acenocoumarol demonstrated that reviparin was more effective in preventing DVT recurrences and far better tolerated than oral anticoagulant treatment. Reviparin was also effective and well tolerated in immobilised patients following leg injury with plaster casts or braces applications. Positive results were also obtained in the treatment of venous thromboembolism in well-designed studies on large patient populations. In this indication reviparin compared favourably with iv UFH. As for the use in cardiology patient, reviparin is at present the only approved LMWH for the prevention of acute thrombotic events in patients undergoing percutaneous transluminal coronary angioplasty.**

Key Words:

Low molecular weight heparin (LMWH), Reviparin, Review, Pharmacology, Clinical efficacy.

Outline of Low Molecular Weight Heparin Pharmacology

Low molecular weight heparins (LMWHs), marketed first in Europe from the second half of '80, represented a new therapeutic measure, not only alternative and more practical, but also often more effective than standard heparin in many clinical fields[1-3].

As known, the search on LMWHs (obtained by unfractionated heparin (UFH) through different chemical or enzymatic methods) has been prompted by some basic observations:

- markedly lower activity of LMWHs on factor IIa than on factor Xa of the coagulation cascade[4,5];
- higher risk/benefit ratio of LMWHs versus UFH in animal models[6,7];
- strongly better clinical pharmacokinetic profile of LMWHs versus UFH[8-13].

The pharmacological differences between various LMWHs are largely explained by different methods of production and by varying proportions in chains of different length: short, medium and long chains[1].

LMWHs, showing a mean molecular weight of 4,000-5,000 d (range 2,000-9,000 d), are characterised by a reverse anti-IIa/anti-Xa ratio and also by a reduced interaction with blood cells and plasma proteins[2]. This implies a more predictable behaviour versus UFH and a lower risk of heparin-induced thrombocytopenia[2,14-16].

As for clinical pharmacokinetics, LMWHs exhibit a bioavailability by subcutaneous (sc) route close to 100%, a peak plasma level following sc administration at 3-5 h, a predictable dose-response profile and an elimination half-life of 3-6 h[2-16].

It is easily understandable, therefore, the interest stimulated among clinicians and researchers by this new class of molecules, that has been developed in many indications as prophylactic and therapeutic measures[2].

Corresponding Author: Roberto Del Bono, MD; e-mail: roberto.delbono@tin.it

Role of LMWHs in Clinical Practice

It is definitely acquired that clinicians should base their therapeutic decisions on the best available medical evidence as, for example, that provided by randomised controlled clinical trials[17].

A strong support is also given by Guidelines worked out by the most reliable Medical Associations as, for instance, the American College of Chest Physicians[18].

According to the recommendations of the most recent international guidelines, LMWHs are now properly indicated in prophylaxis and therapy of deep vein thrombosis (DVT) in the medical conditions listed in Table I.

In each of the above mentioned conditions, the decision of adopting a prophylaxis with LMWH as well as the application protocol (doses, time of administration, possible association with other measures, etc) will depend on the thrombotic risk of each single patient and on the balance with the haemorrhagic risk, as provided in detail in the Guidelines already quoted[18-21].

In fact, specific Guidelines and different Consensus Conferences reported in detail the patient characteristics requiring routine DVT prophylaxis and other categories, where special preventive measure and possible precautions are needed[19].

Table I. Clinical use of LMWHs[18-21].

Prophylaxis	
Orthopaedic surgery	Hip replacement
	Knee replacement
	Arthroscopic surgery
	Hip fracture
	Elective spine surgery
Neurosurgery	
Surgery	Major general surgery
	Gynaecologic surgery
	Vascular surgery
	Urologic surgery
	Laparoscopic surgery
	Bariatric surgery
	Thoracic surgery
	Coronary Artery Bypass Graft (CABG)
Traumatic conditions	Trauma
	Spinal injury
	Burns
Non surgical patients	
Oncology patients	
Intensive care patients	
Therapy	
Deep vein thrombosis (DVT)	
Pulmonary embolism (PE)	

Differentiation of LMWHs

Due to the various depolimerization techniques adopted to obtain different LMWHs, the resulting products show molecular and structural differences and, consequently, different profiles: it is important, therefore, to start underlying that the several LMWHS on the market are not reciprocally interchangeable on weight basis or anti-Xa activity[22-24].

In fact, it is now definitely acquired that:

1. The various LMWHs are distinct entities;
2. They exhibit typical pharmacokinetic and pharmacodynamic features for any single agent;
3. Each drug shows a definite efficacy and safety profile;
4. The "bioequivalence" does not exist;
5. Therefore, LMWHs are not reciprocally interchangeable[1,25-28].

The major Regulatory Authorities, particularly Food and Drug Administration (FDA) and European Medicines Agency (EMEA), clearly stated that LMWHs are distinct pharmacological agents, each showing a unique therapeutic profile in different clinical conditions[23].

For instance, in surgical patients at high risk of venous thromboembolism (VTE), reviparin, the most recently marketed LMWH, resulted as effective as enoxaparin but with a far better safety profile[29].

Safety of LMWHs: Some Critical Issues

In spite of the great amount of clinical studies, some aspects concerning safety and optimal use of LMWHs still need deeper evaluations[25]. For instance, even if their safety at therapeutic doses has been evaluated in proper clinical trials, some doubts on specific issue still remain[25].

Patients at High Haemorrhagic Risk/Renal Failure

As in these cases the main problem is represented by bleeding events, one relevant question is if the fixed dose, not adjusted on activated partial thromboplastin time (aPTT) values, could be considered safe in patients at documented haemorrhagic risk as elderly, obese, pregnant and renal failure patients[25].

In patients with severe renal failure (creatinine clearance < 30 ml/min), needing a therapeutic

dose, UFH should certainly be considered a safer option.

All above mentioned patients are usually excluded from clinical trials and the most part of data on these cases is provided by pharmacokinetic or pharmacodynamic studies. Consequently, little information is available – unfortunately – on the possible precautions to be adopted in patients with chronic real failure showing higher blood anticoagulation, due to a reduced elimination rate[25,30].

A growing number of major bleeding events, sometimes fatal, has been reported in patients with reduced renal clearance and it is clear that the lack of dose adjustment remains one of the unsolved issues in these cases[30].

More exactly, it has been noticed that the accumulation of anti-Xa activity is an effect of varying intensity depending on the LMWH used[25].

Risk of Spinal/Epidural Hematoma in Neuraxial Anaesthesia in Surgical Patients Under Anticoagulant Therapy

Regional neuraxial anaesthesia is a highly effective procedure, allowing optimal conditions both intra- and post-operatively (anaesthesia, analgesia and muscle ralaxation) and, therefore, widely adopted[31,32].

As well known, in neuraxial anaesthesia, spinal hematoma is a rare complication, but also, unfortunately, potentially devastating[31,32].

One of the major challenges in VTE prophylaxis with LMWHs in surgery under neuraxial anaesthesia is surely represented by the risk of spinal/epidural hematoma[31-35].

Even if this complication is rarely observed, the severity of its sequelae needs an extreme care in adopting perioperatively antithrombotic prophylaxis with LMWHs in surgical patients undergoing neuraxial anaesthesia[32,35].

Focus on Reviparin

The reasons for focusing on reviparin are mainly based on the fact that the markedly favourable profile of this LMWH has been too often underestimated up to now. It should also to take into due account that reviparin is the only approved LMWH for the prevention of acute thrombotic events in patients undergoing percutaneous transluminal coronary angioplasty (PTCA)[36].

It is, therefore, useful at this time an assessment of the benefits provided by reviparin, clearly resulting from both, pharmacological and clinical data.

Pharmacological Profile

Reviparin, a second generation LMWH, is characterised by an interesting pharmacological and clinical profile[37-39].

A summary of the main pharmacological properties is given in Table II.

In clinical practice reviparin resulted markedly effective and well tolerated in many indications. Clinical studies demonstrated that reviparin can maximise the antithrombotic activity minimising at the same time the haemorrhagic risk[37].

Clinical Efficacy

1-VTE Prophylaxis

Abdominal Surgery[39]

In a European multicentre trial (15 Centres), double-blind, randomised, controlled versus UFH, 1,351 patients scheduled to abdominal surgery were randomly assigned to reviparin (n=672) or UFH (n=679). The end points were incidence of DVT, pulmonary embolism (PE), and haemorrhagic complications (including wound hematomas). 655 patients received sc reviparin 1,750 anti-Xa IU od and 677 received sc UFH 5.000 IU bid. The first dose was administered 2 h before intervention and the second 8 h after the end of intervention. 648 patients in reviparin group and 663 in the UFH group were evaluable for clinical activity.

Table II. Main pharmacological properties of reviparin[37-40].

- Obtained by nitrous acid depolimerization followed by chromatografic purification
- Mean molecular weight (MMW): 3,900 d
- Narrow range of MMW: 3,500-4,500 d
- More than 90% of chains shows a MMW of 2,700-3,600 d
- Polydispersion index of 1.13
- Bioavailability > 90%
- Half life by sc route: 3.3 h
- Plasma levels 5 times higher than UFH
- Plasma levels 3 times more prolonged than UFH
- Anti-IIa/anti-Xa ratio ≥ 3.6
- No influence on blood coagulation tests

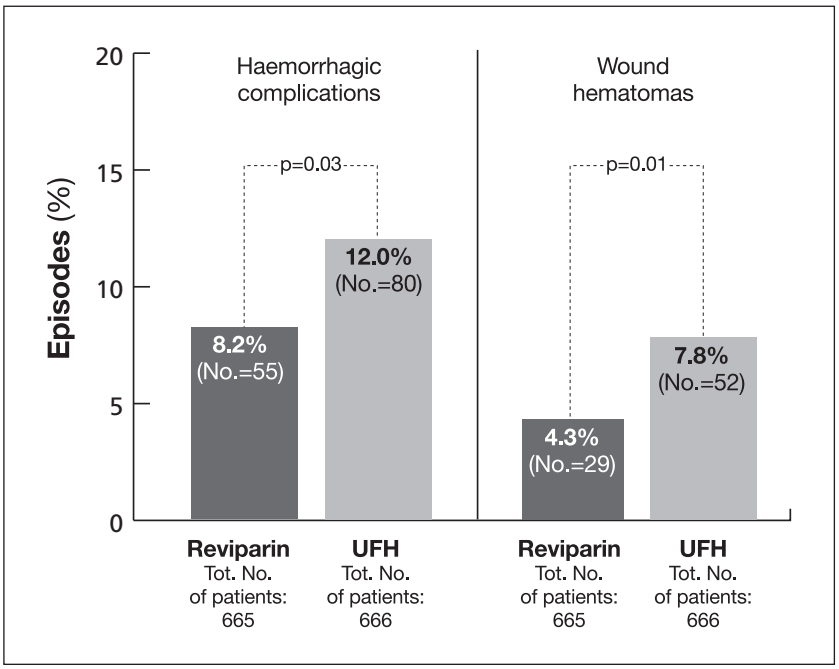

Figure 1. Safety of reviparin 1,750 anti-Xa IU od as compared with UFH 5,000 IU bid in patients who undergone abdominal surgery. Histograms report the percentage of patients with complications (from Kakkar VV, et al, mod)[39].

While as for the antithrombotic efficacy the two treatments appeared practically equivalent, on the contrary the safety resulted significantly in favour of reviparin, with only 55 patients who developed haemorrhagic complications versus 80 cases observed in the UFH group (p=0.03) (Figure 1).

In addition, it is to be noted that statistically significant differences were recorded for almost all safety end points, not only the total haemorrhagic complications but also wound hematomas, all wound complications, thoracic and abdominal haemorrhages and those in extra-operatory sites, as well as complications in the site of injection.

This study allows to conclude that reviparin, even a very low dose (such as 1,750 anti-Xa IU), is able to effectively reduce the thrombotic risk, with a safety profile far more favourable than UFH.

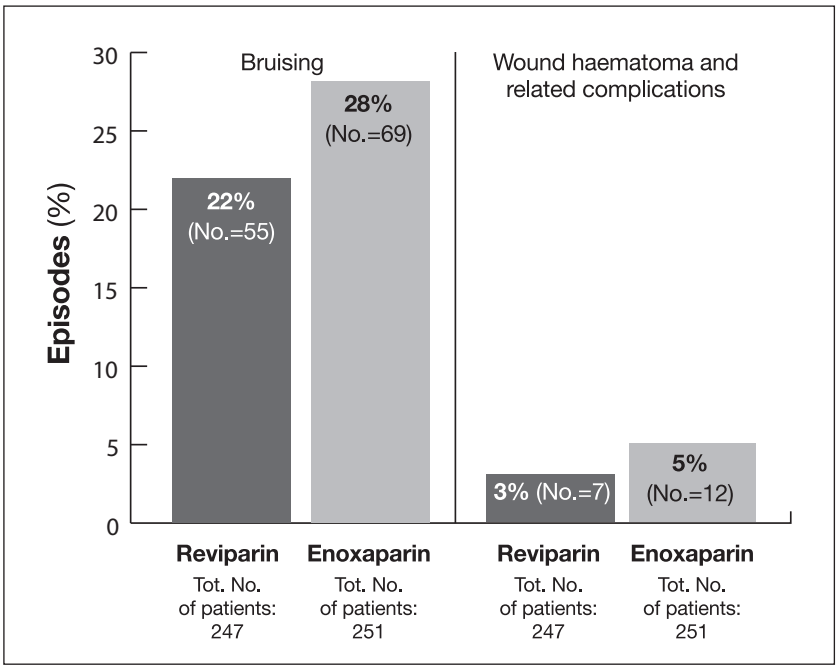

Figure 2. Prevalence of bleeding complications: percentage of patients with brusing or wound haematoma during the treatment period with reviparin 4,200 anti-Xa IU and enoxaparin 4,000 anti-Xa IU (from Planès A, et al, mod.)[29].

Orthopaedic Surgery[29]

A prospective, double-blind, randomised, multicentre trial (17 Centres) was carried out in patients undergoing total hip replacement, with the objective of comparing reviparin and enoxaparin.

498 patients were selected, 247 randomised to reviparin 4,200 anti-Xa IU and 251 to enoxaparin 4,000 anti-Xa IU. The first dose was administered 10-12 h before intervention and a daily administration was maintained until discharge. Presence of DVT was revealed by phlebography.

As for the safety, only 3 major bleeding events were recorded (1 in the reviparin group and 2 in the enoxaparin group) and 1 minor bleeding (in the enoxaparin group).

Peri- and postoperative blood loss, as well as transfusion requirements, were not different between the two groups. However, reviparin was associated to a trend toward a lower risk of complications in the injection site, in addition to higher levels of haemoglobin and blood red cells.

This study basically confirms the high antithrombotic efficacy of reviparin, comparable to that of enoxaparin, as well as the favourable safety profile, superior to that of enoxaparin: these results indicate reviparin as a LMWH characterized by an optimal risk/benefit ratio.

To be mentioned also the antithrombotic efficacy showed by reviparin in other orthopaedic patients, at lower DVT risk than total hip replacement, such as the patients undergoing *knee arthroscopy*[41].

In a study conducted on 260 patients, reviparin reduced the thromboembolic risk by 80% as compared with the control group, not receiving active treatment[41]. The study underlines, therefore, the need of an effective prophylaxis even in moderate risk conditions, as arthroscopic surgery.

Long-term, After Discharge Prophylaxis in Orthopaedic Patients[42]

Patients undergoing hip replacement are at high thromboembolic risk, that affects not only the hospitalisation period (by the way quite short at present), but can persist for longtime.

In fact, according to recommendations provided by International Guidelines, in patients undergoing hip or knee replacement or hip fracture surgery, the "minimal" duration of 10-day prophylaxis should be extended up to 35 days after intervention[19].

In the past, many hospital protocols already scheduled a long term at home prophylaxis that, until the LMWHs came, was carried out (by the way not in Italy) through oral anticoagulants. The main problem of these drugs, undoubtedly effective, is the need of a systematic and regular monitoring of blood coagulation for dose adjustment, in order to reduce the bleeding risk[19].

It is easily understandable, therefore, that LMWHs appeared as a useful tool for prolonging at home the antithrombotic prophylaxis after surgery, provided the patients could comply with a sc daily injection.

Reviparin, at fixed daily doses by sc route, has been evaluated in a large multicentre randomised study versus acenocoumarol for 6 weeks after elective hip replacement[42].

The SACRE study (Study Comparing Oral Anticoagulants with Reviparin) enrolled 1.322 patients undergoing total hip replacement, who received sc reviparin 4,200 anti-Xa IU od (first dose 12 h before intervention and second dose 6-12 h postoperatively), followed by 1 dose/day for 3 ± 1 days. At this time, in absence of any signs or symptoms of DVT or PE, patients were randomised to prolong reviparin prophylaxis or to start acenocoumarol treatment for 6 weeks from intervention. 644 out of 1.289 evaluable patients received reviparin and 645 acenocoumarol.

Between the two groups, global differences (considering all parameters of efficacy, safety, mortality) were always statistically significant:

- intent-to-treat analysis: 4.6% difference, CI 2.0-7.2% (p=0.001)
- per protocol analysis: 6.1% difference, CI 2.9-9.4% (p=0.001).

Similarly, also treatment failures resulted significantly lower with reviparin as compared with acenocoumarol in both analyses, as reported in Table III.

In addition, another evaluation was performed, precisely a regression analysis of composite endpoint (thromboembolic events/major bleedings/deaths), that showed a trend significantly favouring reviparin (p=0.001) (Figure 3).

The safety of reviparin was excellent, with highly significant differences (p=0.001) as for both, major and clinically relevant bleedings (Figure 4).

In conclusion, this study confirms that reviparin allows a long-term at home prophylaxis after high-risk surgery with marked efficacy and safety.

Table III. Treatment failures under reviparin or acenocoumarol in patients undergoing hip replacement, treated for 6 weeks after intervention (from M.M. Samama et al., mod.)[42].

	Intent-to-treat analysis		Per protocol analysis	
Failures	Reviparin (n=643)	Acenocoumarol (n=636)	Reviparin (n=501)	Acenocoumarol (n=448)
Nr	24	53	21	46
%	3.7%	8.3%	4.2%	10.3%
p	0.001		0.001	

Immobilization Following Trauma[43]

An interesting study (prospective, double-blind controlled versus placebo) was carried out to evaluate efficacy and safety of reviparin in patients immobilized by plaster casts or brace for at least 5 weeks, following lower limb fracture or Achilles' tendon rupture. Incidence of thromboembolic events was estimated through phlebography, performed within a week after the plaster cast or brace was removed or even before, in case of symptoms suggesting a DVT.

Out of 440 enrolled patients, 217 were randomized to sc reviparin 1,750 anti-Xa IU/day and 223 patients to placebo.

The results, expressed as DVT incidence in 317 evaluable patients, are reported in Figure 5.

These results clearly show that reviparin provided a significant reduction of the thrombotic risk versus placebo: DVT 9% vs 19%; PE 0 vs 2 cases in placebo group.

Even the frequency of major bleeding events was comparable between the 2 treatments: 2 patients under reviparin and 1 patient under placebo.

Finally, another extremely important aspect must be stressed: the compliance. As in this study the observed compliance was excellent, we can foresee the possibility of a long-term prophylaxis with reviparin by sc route.

2-VTE treatment

COLUMBUS Study

As well known, before LMWHs became available, PE treatment was based on continuous iv infusion of UFH at doses adjusted on aPTT values. The iv administration of 5-10 days, performed in hospitalised patients, was followed by at least 3 months of home therapy with oral anticoagulants.

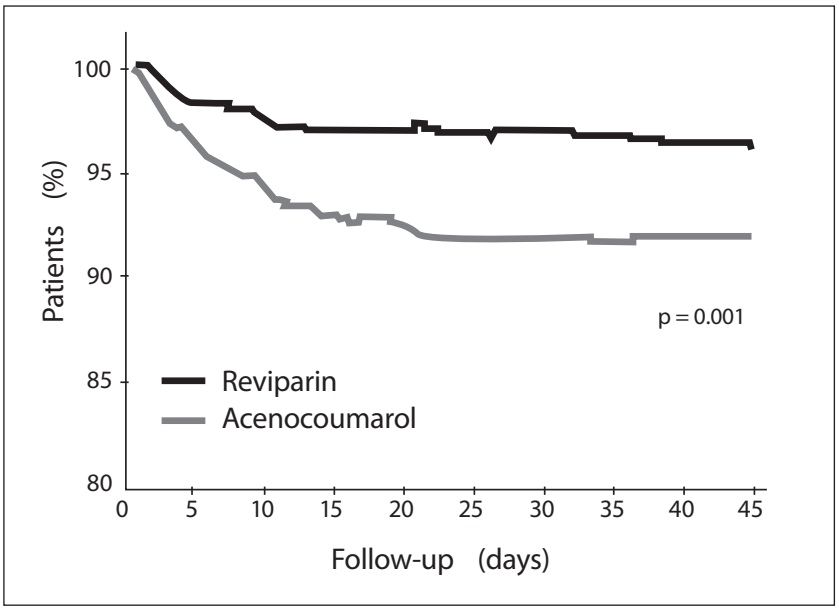

Figure 3. Trend of the composite endpoint: thromboembolic events/major bleedings/deaths (from Samama MM, et al, mod.)[42].

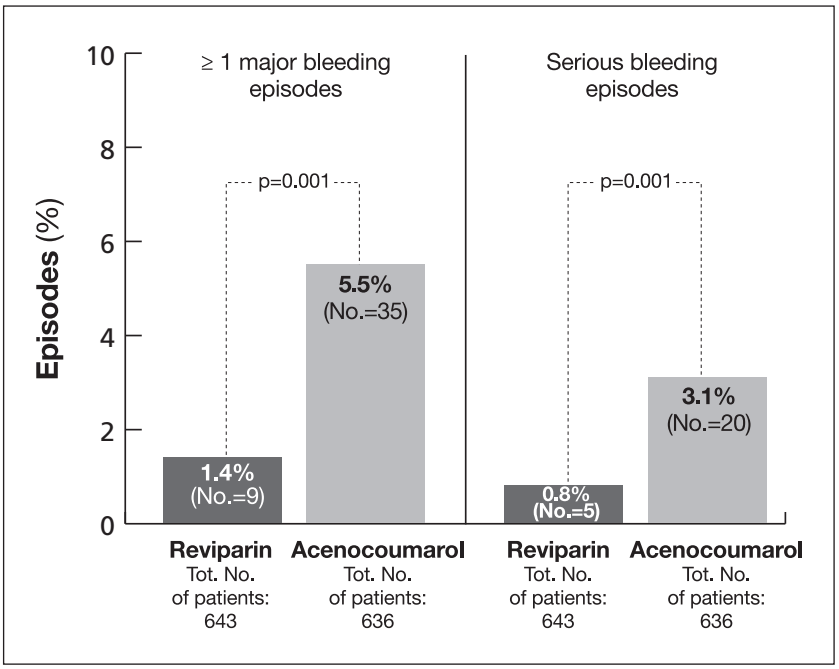

Figure 4. Safety of reviparin 4,200 anti-Xa IU/day and acenocoumarol in patients who undergone total hip replacement and treated for 6 weeks after intervention. Histograms represent the percentage of patients reporting at least 1 of the events included in the composite endpoint (intent-to-treat analysis) (from Samama MM, et al, mod.)[42].

The better pharmacokinetics and the more predictable activity provided by LMWHs appeared as critical factors in stimulating the search and development of effective and easy to handle protocols, adopting these new drugs at fixed doses defined only on the body weight.

The encouraging results, initially obtained in DVT patients, induced to widen the potential population, including also PE patients.

In the COLUMBUS Study[44], 1,021 patients with symptomatic DVT (associated to PE in nearly 1/3 of cases) were randomised to reviparin treatment at fixed doses, adjusted on the body weight or to iv UFH. Reviparin doses were: 3,500 anti-Xa IU bid for body weight <45 kg; 4,200 anti-Xa IU bid for body weight of 46-60 kg and 6,300 anti-Xa IU bid for body weight > 60 kg. UFH was administered in hospital as a iv

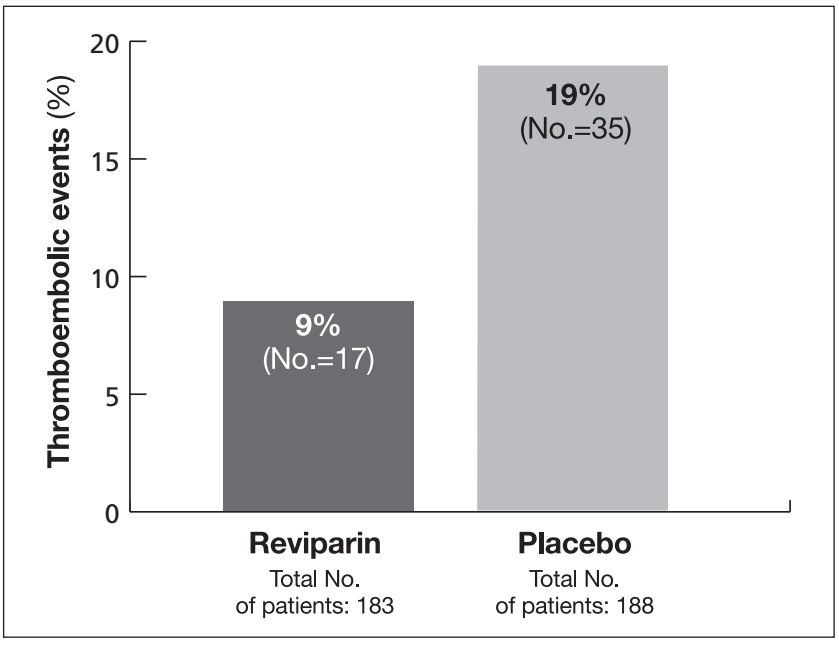

Figure 5. Incidence of total thromboembolic events in patients immobilized for trauma and treated with reviparin 1,750 anti-Xa IU/day or placebo (from Lassen MR, et al, mod.)[43].

bolus of 5,000 IU followed by continuous iv infusion of 1,250 IU/h and dose adjustments on aPTT values. Starting from the first or second day of therapy, heparin infusion was associated also to an oral anticoagulant, whose administration was maintained for 12 weeks.

Both treatments resulted comparable, showing the same efficacy (incidence of thromboembolic recurrences) and tolerability (major bleedings) as reported in Table IV.

In conclusion, the COLUMBUS Study demonstrated that reviparin at sc fixed dose is as effective as UFH at iv adjusted doses, not only in DVT patients but also in PE patients and in those with a story of VTE.

CORTES Study

It is important to stress that reviparin in the CORTES Study resulted more effective than UFH in the treatment of VTE. This discrepancy can be explained by the longer interval between symptoms appearance and start of pharmacological treatment in the COLUMBUS Study as compared with CORTES Study[45]. Anyway, reviparin represents today a valuable alternative to UFH, providing the benefits of a sc administration without the need of systematic laboratory monitoring of blood coagulation values[44-46].

As in all heparins, the presence in the specimen of the activation of platelets during collection can lead to a false low heparin assay in the specimen. A care, thus, should be taken to collect a high quality specimen assuring that has a very low platelet count. Moreover, if plasma from a heparinized sample sits on cells, the PF4, a natural inhibitory of heparin, released from platelets, may neutralize the heparin, resulting in a false decrease of aPTT.

Table IV. Efficacy and safety of reviparin in the treatment of VTE. Results of the COLUMBUS Study (44, mod.).

	Reviparin (n = 510)	UFH (n = 511)
VTE recurrences		
Whole study	27 (5.3%)	25 (4.9%)
0-14 days	16	8
15-42 days	2	15
43-84 days	7	3
Major bleedings		
Whole study	16 (3.1%)	12 (2.3%)
0-14 days	5	1
15-42 days	10	1
43-84 days	37	8

Role of Reviparin in Cardiological Indications

As previously reported (see section "Focus on reviparin") reviparin is presently the only LMWH approved for the prevention of acute thromboembolic events in patients undergoing PTCA[36].

It must be stressed that several widening of cardiological use are expected following the positive evidence observed in many clinical trials.

Some of them are already concluded, while other studies are still ongoing, in acute coronary syndromes, and in myocardial infarction, with or without ST-segment elevation[47-49].

References

1) Fareed J, Hoppensteadt DA, Bick RL. An update on heparins at the beginning of the new millennium. Semin Thromb Hemost 2000; 26(suppl 1): 5-21.
2) Hirsh J, Raschke R. Heparin and low-molecular-weight heparin. The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004; 126: 188S-203S.
3) Hoppenstaedt D, Walenga J, Fareed J, Bick RL. Heparin, lowmolecular- weight heparins, and heparin pentasaccharide. Basic and clinical differentiation. Hematol Oncol North Am 2003; 17: 313-341.
4) Harenberg J. Pharmacology of low molecular weight heparins. Semin Thromb Hemost 1990; 16: 12-18.
5) Johnson EA, Kirkwood, Stirling Y, Perez-Requejo JL, Ingram GI, Bangham DR, Brozovi, M. Four heparin preparations. Anti-Xa potentiating effect of heparin after subcutaneous administration. Thromb Haemost 1976; 26: 586-591.
6) Carter CJ, Kelton JG, Hirsh J, Cerskus A, Santos AV, Gent M. The relationship between the hemorrhagic and antithrombotic properties of low molecular weight heparins in rabbits. Blood 1982; 59: 1239-1245.
7) Bergqvist D, Nilsson B, Hedner U, Pedersen PC, Ostergaard PB. The effect of heparin fragments of different molecular weights on experimental thrombosis and haemostasis. Thromb Res 1985; 38: 589-601.
8) Frydman A, Bara L, Le Roux Y, Woler M, Chauliac F, Samama MM. The antithrombotic activity and pharmacokinetics of enoxaparin, a low molecular weight heparin, given in single subcutaneous doses of 20 mg up to 80 mg. J Clin Pharmacol 1988; 26: 609-618.
9) Briant L, Caranobe C, Saivin S, Sié P, Bayrou B, Houin G, Boneu B. Unfractionated heparin and CY216. Pharmacokinetics and bioavailabilities of the anti- factor Xa and IIa. Effects of intravenous and subcutaneous injections in rabbits. Thromb Haemost 1989; 61: 384-353.

10) Bratt G, Tornebhom E, Widlund L, Lockner D. Low-molecular-weight heparin (KABI 2165, Fragmin). Pharmacokinetics after intravenous and subcutaneous administration in human volunteers. Thromb Res 1986; 42: 613-620.

11) Matzsch T, Bergqvist D, Hedner U, Ostergaard P. Effect of an enzymatically depolymerized heparin as compared with conventional heparin in human volunteers. Thromb Res 1987; 57: 97-101.

12) Bara L, Samama MM. Pharmacokinetics of low-molecular-weight heparins. Acta Chir Scand 1988; 543: 65-72.

13) Bradbrook ID, Magnani HN, Moelker HC, Morrison PJ, Robinson J, Rogers HJ, Spector RG, Van Dinther T, Wijnand H. Org 10172. A low molecular-weight heparinoid anticoagulant with a long half life in man. Br J Clin Pharmacol 1987; 255: 10081-10090.

14) Hirsh J, Levine MN. Low-molecular-weight heparin. Blood 1992; 79: 1-17.

15) Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997; 37: 688-698.

16) Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, Kelton JG. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparins or unfractionated heparin. N Engl J Med 1995; 332: 1330-1335.

17) Handeland GF, Abildgaard U, Holm HA, Arnesen KE. Dose adjusted heparin treatment of deep venous thrombosis: a comparison of unfractionated and low-molecular-weight heparin. Eur J Clin Pharmacol 1990; 39: 107- 112.

18) Eikelboom JW, Karthikeyan G, Fagel N, Hirsh J. American Association of Orthopedic Surgeons and American College of Chest Physicians Guidelines for venous thromboembolism prevention in hip and knee arthroplasty. Chest 2009; 135: 513-520.

19) Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. The American College of Chest Physicians. Prevention of venous thromboembolism. American College of Chest Physicians Evidence- Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133: 381S- 453S.

20) Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. The American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease. American College of Chest Physicians Evidence- Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133: 454S-545S.

21) Bates SM, Greer IA, Pabinger J, Sofaer S, Hirsh J, The American College of Chest Physicians. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(suppl 6): 844S-886S.

22) Mousa SA. Comparative efficacy of different low-molecular-weight heparins (LMWHs) and drug interactions with LMWH. Semin Thromb Hemost 2000; 26(suppl 1): 39-46.

23) Fareed J, Leong WI, Hoppenstaedt D, Jeske WP, Walenga J, Wahi R, Bick RL. Generic low molecular weight heparins. Some practical considerations. Semin Thromb Hemost 2004; 30: 703-713.

24) Fareed J, Walenga J. Why differentiate low molecular weight heparins for venous thromboembolism? Thromb J 2007; 5: 1-3.

25) Gouin-Thibault I, Pautas E, Siguret V. Safety profile of different lowmolecular- weight heparins used at therapeutic doses. Drug Saf 2005; 28: 333-349.

26) Nenci GG. Low molecular weight heparins. Are they interchangeable? No. J Thromb Hemost 2003; 1: 12-13.

27) Merli GJ, Groce JB. Pharmacological and clinical differences between low molecular weight heparins: implications for prescribing practice and therapeutic interchange. P T 2010; 35: 95-105.

28) Maddinieni J, Walenga J, Jeske WP, Hoppenstead DA, Fareed J, Wahi R, Bick RL. Product individuality of commercially available low-molecular-weight heparins and their generic versions: therapeutic implications. Clin Appl Thromb Hemost 2006; 12: 267-276.

29) Planes A, Vochelle N, Fagola M, Belland M. The Reviparin Study Group. Comparison of two low- molecular-weight heparins for the prevention of postoperative venous thromboembolism after elective hip surgery. Blood Coagul Fibrinol 1998; 9: 499-505.

30) Vega J, Martinez G, Goecke H. Low-molecular-weight heparins in patients with chronic renal disease. Rev Med Chil 2010; 138: 487-495.

31) Allen DJ, Chae-Kim SH, Trousdale DM. Risks and complications of neuraxial anesthesia and the use of anticoagulation in the surgical patient. BUMC (Bayolor Univ Med Center) Proc 2002; 15: 369-373.

32) Moraca RJ, Sheldon DG, Thirlby RC. The role of epidural anesthesia and analgesia in surgical practice. Ann Surg 2003; 238: 663-673.

33) Sternlo JE, Hybbinette CH. Spinal subdural bleeding after attempate epidural and subsequent spinal anesthesia in a patient on thromboprophylaxis with low molecular weight heparin. Acta Anesthesiol Scand 1995; 39: 557-559.

34) Han IS, Chung EY, Hahn Y-J. Spinal epidural hematoma after epidural anesthesia in a patient receiving enoxaparin–A case report. Kor J Anesthesiol 2010; 59: 119-122.

35) Horlocker TT. Low-molecular-weight heparin and neuraxial anesthesia. Thromb Res 2001; 10: V141-V154.

36) Reviparina. Riassunto delle caratteristiche del prodotto–Scheda tecnica. Abbott, Maggio 2011.

37) Gore M, Kelkar P, Rege N, Ross C. Reviparin sodium clivarine: a review of its therapeutic use. J Ind Med Ass 2004; 102: 589-592.

38) Breddin HK. Reviparin sodium–a new low-molecular-weight heparin. Expert Opin Pharmacother 2002; 3: 173-182.

39) Kakkar VV, Boeckl O, Boneu B, Bordenave L, Brehm OA, Brucke P, Coccheri S, Cohen AT, Galland F, Haas S, Jarrige J, Koppenhagen K, LeQuerrec A, Parraguette E, Prandoni P, Roder JD, Roos M, Rushemeyer C, Slewert JR, Vinazzer H, Wenzel E. Efficacy and safety of a low-molecular-weight heparin and standard unfractionated heparin for prophylaxis of postoperative venous thromboembolism. World J Surg 1997; 21: 2-9.

40) Kakkar VV, Cohen AT, Mohamed MS. Patients at risk of venous thromboembolism. Clinical results with reviparin. Thromb Res 1996; 81(Suppl 2): S39-S45.

41) Wirth T, Schneider B, Misselwitz F, Lomb M, Tuylu H, Egbring R, Griss P. Prevention of venous thromboembolism after knee arthroscopy with low-molecular-weight heparin (reviparin). Results of a randomized controlled trial. J Arthroscopy 2001; 17: 393-399.

42) Samama MM, Vray M, Barrè J, Fiessinger JN, Rosencher N, Lecompte T, Potron G, Basile J, Hull R, Desmichels D. Extended venous thromboembolism prophylaxis after total hip replacement. Arch Intern Med 2002; 162: 2191-2196.

43) Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep vein thrombosis after leg injury requiring immobilization. N Engl J Med 2002; 347: 726-730.

44) Low molecular weight heparin in the treatment of patients with venous thromboembolism. The COLUMBUS Investigators. N Engl J Med 1997; 337: 657-662.

45) Breddin HK, Hach-Wunderle V, Nakov R, Kakkar W; CORTES Investigators. Clivarin: assessment of regression of thrombosis efficacy and safety. Effects of a low-molecularweight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. N Engl J Med 2001; 344: 626-631.

46) Wellington K, McClellan K, Jarvis B. Reviparin. A review of its efficacy in the prevention and treatment of venous thromboembolism. Drugs 2001; 61: 1185-1209.

47) Rubboli A. Efficacy and safety of low-molecular-weight heparins as an adjunct to thrombolysis in acute ST-elevation myocardial infarction. Curr Cardiol Rev 2008; 4: 63-71.

48) Rubboli A, Ottani F, Capecchi A, Brancaleoni R, Galvani M, Swahn E. Low-molecular-weight heparins in conjunction with thrombolysis for ST-elevation acute myocardial infarction. A critical review of the literature. Cardiology 2007; 107: 132-139.

49) Jusu S, Mehta SR, Xie C, Ahmed RJ, Xavier D, Pais P, Zhu J, Liu J; The CREATE Trial Group Investigators. Effects of reviparin, a lowmolecular- weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. JAMA 2005; 293: 427-435.