

Update on the clinical use of the low-molecular-weight heparin, parnaparin

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Abstract: Parnaparin is a low-molecular-weight heparin that has widely shown its efficacy and safety in prevention of venous thromboembolism, in the treatment of chronic venous disorders, and in the treatment of venous and arterial (stable and unstable angina, acute ST-segment elevation myocardial infarction) thrombosis. Parnaparin at the respective dosages of 3200, 4250, 6400, or 12800 IUaXa for a period ranging from 3 to 5 days to 6 months, is usually administered subcutaneously by means of once-daily regimen and is better tolerated than unfractionated heparin at the injection site. In the variety of commercially available low-molecular-weight heparins, parnaparin represents a useful therapeutic option, even though little evidence is available comparing the superiority or the equivalent efficacy and safety of parnaparin to that of the unfractionated heparin or placebo. This review summarizes the available literature on the use of parnaparin in different settings of cardiovascular diseases, including papers published during the past year and ongoing studies.

Keywords: low-molecular-weight heparin, heparin, parnaparin, acute coronary syndromes, venous thromboembolism

Introduction

Anticoagulant therapy, such as heparin, has been used for at least 40 years in the management of chronic venous disorders and plays an important role in the prevention and treatment of venous and arterial thrombosis.¹ Low-molecular-weight heparins (LMWHs) have been extensively investigated in a large number of randomized clinical trials. Where shown to be safe and effective they have been used as drugs for the prevention and treatment of venous thromboembolism (VTE), and for the treatment of acute coronary syndromes (ACS) and peripheral arterial occlusive disease (PAOD), and for the management of chronic venous disorders (CVD), including chronic venous insufficiency (secondary to post-thrombotic syndrome or varicose disease), and varicophlebitis or thrombophlebitis of nonvaricose veins.

Among other LMWHs, parnaparin (parnaparin sodium; FluxumTM)¹ has been successfully employed for the prevention and the treatment of VTE and CVD, while its use in the management of ACS and PAOD has been less extensively investigated.²⁻⁴

The present review focuses on the pharmacological properties and clinical uses of parnaparin, especially in the management of venous thromboembolism, chronic venous disease, PAOD, and coronary artery disease.

Note on dosage

Dosages of parnaparin reported in this review (3200, 4250, 6400 and 12800 IUaXa) were calculated according to the European Pharmacopoea Standard of LMWHs, and

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are equivalent to those reported in clinical papers published between the early 1980s and the mid 1990s (7500, 10000, 15000 and 30000 aXaU, respectively), which in turn were based on the 4th International Standard of Unfractionated Heparin (UFH).

Pharmacology of parnaparin

Pharmacodynamics

Parnaparin is a LMWH with a mean molecular weight of approximately 4.5 kDa, obtained with a specific fragmentation procedure that warrants the homogeneity of each fragment in terms of molecular weight and length, in order to optimize and maintain an anti-Xa/anti-IIa ratio of >4 .^{3,5} The pharmacodynamics of subcutaneous parnaparin were investigated in studies *in vitro*, in healthy volunteers; and in patients with peripheral vascular diseases, acute coronary syndromes and undergoing surgery.

By *in vitro* studies, parnaparin was shown to possess the following properties:

- inhibition of the thrombin activatable fibrinolytic inhibitor (TAFI) less potently than UFH (with inhibition of 50% of relative concentrations [IC50] of 0.6 to 0.8 vs 0.01 U/mL, respectively), similarly to dalteparin and tinzaparin, and more potently than enoxaparin (IC50 > 1.0 U/mL);⁶
- active control of the anticoagulant effect in the presence of activated platelets, greater than UFH and independent of the concomitant intake of aspirin;⁷
- inhibition of aggregate formation of platelets/polymorphonuclear leukocytes and of the expression of tissue factor and L-selectin in leukocytes; prevention of leukocyte degranulation and of fibrinogen binding to platelets more potently than UFH and enoxaparin.^{8,9}

Studies in healthy volunteers showed that parnaparin inhibits factor Xa (antithrombotic effect) more efficiently than factor IIa (anticoagulant effect), resulting in a greater anti-Xa/anti-IIa activity ratio than UFH.^{10–12} The inhibition of factor Xa occurs intensively and rapidly (anti-Xa activity about 0.2, 0.5 and 0.9 aXaU/mL, approximately 2 to 4 hours after administration of parnaparin 3200, 6400 and 12800 IUaXa, respectively), is dose-dependent, and persists for many hours after administration of a single bolus of subcutaneous parnaparin (ranging from 6 to 12 hours after administration of parnaparin 3200 or 6400 IUaXa, with demonstrable anti-Xa activity still occurring at 20 hours with the parnaparin 6400 IUaXa dose; in contrast, the anti-IIa activity was undetectable at 4, 8 and 12 hours postadministration).¹¹

Clinical studies conducted in patients undergoing bariatric surgery reported that the obesity (BMI ≥ 45 kg/m²)

does not influence parnaparin anti-Xa activity.¹³ When fixed-dose parnaparin is employed as thromboprophylaxis in obese patients, a strong negative correlation between total body weight and anti-factor Xa levels is observed. These findings suggest that weight-based prophylactic dosing might be preferable to fixed-dosing for obese patients, and especially those with severe obesity (BMI 52.4 kg/m²).¹⁴ A similar anti-factor Xa activity inhibitory effect, greater than UFH, is reported both in patients undergoing surgery^{15–17} and in patients with a peripheral arterial occlusive disease (PAOD).¹⁸ Moreover, in PAOD and surgical patients, as in patients with acute myocardial infarction (MI), parnaparin has been shown to have a weak effect on activated partial thromboplastin time (aPTT) (only the highest dose of 12,800 IU aXa caused a peak value reaching the lower limit of clinical significance),^{10,11} to decrease fibrin formation in a proportional dose-dependent manner,^{18–20} and to reduce whole blood viscosity.^{20,21}

Finally, in patients with unstable angina (UA) or acute ST-segment elevation myocardial infarction (STEMI), parnaparin was able to reduce platelet count to a lesser extent than UFH.^{22,23}

Pharmacokinetics

As with other LMWHs, the assessment of the main pharmacokinetic properties after administration of a single dose of parnaparin have been made indirectly *ex vivo* by measuring anti-Xa activity, considered to be the main antithrombotic mechanism.

In healthy volunteers the peak inhibition of factor Xa (E_{max}) after subcutaneous administration of parnaparin is dose-dependent (0.27 IU/mL after administration of 3200 IUaXa, 0.58 IU/mL with 6400 IUaXa).^{10–12} After intravenous administration E_{max} is approximately 5-fold greater than after subcutaneous administration of the same dose (eg, mean E_{max} 1.35 IU/mL after iv administration of 3200 IUaXa).^{10,12} Parnaparin peak anti-Xa activity (t_{max}) occurs rapidly after administration, approximately 3 hours and 5 minutes when the subcutaneous or intravenous route are used, respectively, regardless of dose.^{10,12} Independently of the injection site (abdomen, gluteal region, deltoid), the bioavailability of the drug was $>90\%$.^{24,25} No signs of drug accumulation after repeated once-daily subcutaneous administration for 7 days were detected.²⁶

Parnaparin is metabolized in the liver and kidneys and, as with other LMWHs, is cleared principally by the renal route;³ however, the effects of renal or hepatic impairment on its pharmacokinetics have not been reported. In general,

the clearance of the anti-Xa effect of LMWHs is strongly related to the creatinine clearance (CrCl), the cutoff value to avoid accumulation being a CrCl ≥ 30 mL/min, and renal insufficiency is associated with an increased risk of bleeding complications when therapeutic doses of LMWHs are used. Conversely, the administration of prophylactic doses is not reported to confer an higher bleeding risk.²⁷ Therefore, it is likely that prophylactic doses of parnaparin may be safely administered in patients with severe renal insufficiency; however, if therapeutic doses are needed, weight-adjusted low-doses of parnaparin or UFH (which is not cleared through the kidneys) should be used.^{3,27}

Search strategy

We started with a Medline search, using the keyword “parnaparin” [All Fields], with the limit “human”, which yielded 23 papers published between 1993 and 2007, of which 5 were reviews. We also crosschecked the references of all relevant articles and reviews in order to retrieve more evidence. Finally, we asked Alfa Wasserman (Bologna, Italy) to provide us with all the documentation inherent to the clinical development of parnaparin.

Overview of therapeutic efficacy

Clinical experience with subcutaneous parnaparin in various clinical situations is summarized in Tables 1 to 5.

Prevention of venous thromboembolic disease (Table 1)

Subcutaneous parnaparin, administered once or twice daily at 3200 or 6400 IUaXa, was compared with placebo^{28,29} or subcutaneous UFH^{14–16,30–38} in 14 randomized or parallel group studies conducted in adult patients undergoing (major) general,^{15,28,29,32,34–37} orthopedic,^{16,30,33} cardiac,³¹ urologic³⁸ and vascular surgery.¹⁴ Parnaparin was also evaluated in 8 cohort studies^{22,39–45} of patients undergoing (major) general,³⁹ vascular,^{40,41} urologic,^{42,43} gynecologic,⁴⁴ minor orthopedic⁴⁵ and bariatric²² surgery, in all of which it was administered once daily at 3200 or 6400 IUaXa, but in one⁴⁵ at 4250 IUaXa.

Of the studies using a randomized design, 2^{28,29} were double-blind placebo-controlled studies, 1³⁸ was single-blind and the other 7^{14,15,30,31,34,35,37} were open, due to different administration schedules. Randomized studies were conducted over 4,³¹ 7,^{14,15,28,29,34,35,37,38} or up to 14³⁰ days; in all parallel group studies, prophylactic treatment with parnaparin lasted for 7^{16,32,33,36} days, and in cohort studies for 7,^{39,42–44} 8,⁴¹ 9,⁴⁰ 10⁴⁵ and 30²² days. Prophylactic therapy was generally

initiated 2 hours before low- to medium-risk thromboembolic surgery, and 12 hours before high-risk surgery. In a cohort study of patients undergoing minor orthopedic procedures, parnaparin was initiated 3 to 9 hours postoperatively.⁴⁵

The efficacy endpoints were: frequency of DVT, investigated with venography, ultrasonography (continuous-wave Doppler, compression ultrasound, color-coded Doppler ultrasound), fibrinogen uptake test or plethysmography (impedance, strain-gauge); and the frequency of pulmonary embolism (PE), which was assessed with ventilation/perfusion lung scan or chest X-ray, if suspected on clinical grounds (Table 1).

In general, although the methodological quality of the trials published before 1990 was modest, subcutaneous parnaparin demonstrated to be effective in the prevention of DVT and PE (Table 1). Specifically, subcutaneous parnaparin was at least as effective as UFH in preventing DVT across all clinical trials; and in two large studies in patients undergoing general surgery (n = 610, and n = 173, respectively),^{32,35} the incidence of DVT in the parnaparin (3200 or 6400 IUaXa once-daily) group was statistically significantly lower than in the UFH (5000 IU 2- or 3-times daily) group (3.2% vs 6.3%, $P < 0.05$; and 1.1% vs 7.1%, $P = 0.038$, respectively).

The low number of events recorded did not allow meaningful statistical comparisons for the frequency of PE.

Treatment of deep-vein thrombosis (Table 2)

Subcutaneous parnaparin, administered once or twice daily at 6400 or 12,800 IUaXa, was compared with intravenous⁴⁶ or subcutaneous^{47,48} UFH, or with nadroparin⁴⁹ in 4 randomized trials of adult patients with objectively proven DVT. In all studies parnaparin was at least as effective as the comparator in preventing recurrent extending DVT and PE, with a similar safety profile. The short duration of patient observation (at most 6 months), combined with the choice of noninvasive tests to assess the endpoints (frequency of recurrent/extending DVT, and frequency of PE) is very likely responsible for the low frequency of events observed.

Chronic venous disease (Table 3)

The efficacy of parnaparin in the treatment of postphlebotic syndrome or chronic venous insufficiency of the lower limbs was compared with that of UFH in 5 randomized trials.^{51–55} Treatment duration ranged from 30 to 90 days. These small-sample (number of patients included = 46 to 92)

Table 1 Clinical experience with parnaparin for prophylaxis of venous thromboembolism

Author	Year	Setting	Design	End-point assessment	Patients ^a	Parnaparin (IUaXa) sc	Comparator	Treatment duration	Follow-up	Deep-vein thrombosis ^b	Pulmonary embolism ^b	Bleeding ⁱ
Verardi et al ³²	1988	Major general surgery	PG	RFUT, CWD, SGP, V	610 (308/302)	3200 or 6400 od	UFH 5000 IU bid or tid sc	7 days	none	3.2/6.3 (<0.05)	0.32/1.0 (>0.05)	0.97/3.6 (0.032)
Gossetti et al ⁴⁰	1988	Vascular surgery	C	RFUT, CWD, US	40	6400 od	–	9 days	none	2.5	NR	NR
Gruttadauria et al ³⁶	1988	General surgery	PG	RFUT, CWD	179 (89/90)	3200 od	UFH 5000 IU bid	7 days	none	2.2/4.4 (0.68)	NR	3.4/12.2 (0.048)
Bonomo et al ³⁹	1988	General surgery	C	IPG, V	78	3200 od	–	7 days	none	2.3	NR	2.3
Chiapuzzo et al ¹⁶	1988	Major orthopedic surgery	PG	RFUT, CWD	140 (70/70)	3200 od	UFH 5000 IU tid sc	7 days	none	7.1/10.0 (0.66)	0/0	4.2/7.1 (0.6)
Catania et al ³⁵	1988	General surgery	R, O	CWD, CXr	173 (88/85)	3200 od	UFH 5000 IU tid sc	7 days	none	1.1/7.1 (0.038)	0/1.2 (0.25)	0/0
Mascali et al ³³	1988	Major orthopedic surgery	PG	DUS	136 (68/68)	3200 bid	UFH 5000 IU tid sc	7 days	none	1.5/2.4 (1.00)	NR	2.9/13.4 (0.55)
Speziale et al ¹⁴	1988	Vascular surgery	R, O	RFUT	92 (46/46)	6400 od	UFH 5000 IU bid	7 days	none	6.5/8.6 (0.86)	NR	8.7/17.4 (0.29)
Valle et al ²⁸	1988	General surgery	R, DB	CWD	100 (50/50)	3200 od	Placebo	7 days	none	0.0/6.0 (0.24)	NR	2.0/6.0 (0.61)
Pellegrino et al ⁴²	1988	Urologic surgery	C	CE, V	87	3200 or 6400 od	–	7 days	none	2.3	0	2.3
Cortellini et al ⁴³	1988	Urologic surgery	C	IPG	80	3200 or 6400 od	–	7 days	none	6.2	NR	5.0
Salcuni et al ³⁷	1988	Major general surgery	R, O	Phy, CWD, CXr	141 (73/68)	3200 od	UFH 5000 IU tid sc	7 days	none	4.1/10.3 (0.15)	1.4/2.9 (0.61)	8.2/7.3 (0.88)
Forzano et al ⁹	1988	General surgery	R, DB	CWD	100 (50/50)	3200 od	Placebo	7 days	none	2.0/12.0 (0.11)	NR	NR
Pini et al ³⁰	1989	Hip fracture surgery	R, O	RFUT, SGP, V	49 (25/24)	3200 bid	UFH 5000 IU tid sc	14 days, or discharge	none	20.0/29.2 (0.5)	0.0/12.5 (0.11)	12.0/8.3 (1.0)
Tartaglia et al ⁴⁴	1989	Gynecological surgery	C	CE, CWD, CXr	92	3200 od or 6400 od	–	7 days	none	3.3	0.0	NR
Corrado et al ³⁸	1988	Urologic surgery	R, SB	RFUT, CWD, IPG	58 (29/29)	6400 od	UFH 5000 IU bid sc	7 days	none	0.0/0.0	0.0/0.0	0.0/0.0
Verardi et al ³⁴	1989	Major general surgery	R, O	RFUT, CWD	88 (44/44)	6400 od	UFH 5000 IU bid sc	7 days	none	2.3/6.8 (0.62)	NR	0.0/0.0
Garcea et al ¹⁵	1992	Major general surgery	R, O	RFUT, US, V, CXr, LS	90 (45/45)	3200 od	UFH 5000 IU tid sc	7 days	none	0.0/2.2 (1.0)	0.0/0.0	0.0/11.1 (0.056)
Gossetti et al ⁴¹	1992	Major vascular surgery	C	RFUT, US	65	3200 od	–	8 days	none	1.5	NR	1.5

Beghi et al ³¹	1993	Cardiac surgery	R, O	CWD, ECD	39 (20/19)	3200 od	UFH 5000 IU tid sc	4 days	none	0.0/0.0	NR	NR
Montebugnoli et al ⁴⁵	2005	Minor orthopedic surgery	C	CUS	509	3200 or 4250 od	-	10 days	none	0.0	0.0	1.6
Forestieri et al ²²	2007	Bariatric surgery	C	ECD, LS	10	6400 od ^c	-	30 days	none	0.0	10.0	NR

^atotal number (parnaparin group/comparator group); ^bfrequency of outcome events in the parnaparin group/in the comparator group (p value); ^cplus intermittent pneumatic compression (during hospitalization) and stockings (up to 30 days).

Abbreviations: PG, parallel-group, nonrandomized; C, cohort study; R, randomized; O, open; SB, single blind; DB, double blind; CE, clinical evaluation; RFUT, radio-labeled fibrinogen uptake test; SGF, strain-gauge plethysmography; IPG, impedance plethysmography; V, venography; CWD, continuous wave Doppler sonography; US, ultrasonography; DUS, Doppler ultrasonography; ECD, echo-color Doppler ultrasonography; CXr, chest X-ray; LS, lung scan; sc, subcutaneously; od, once daily; bid, twice daily; tid, three times daily; NR, not reported.

trials failed to show any statistically significant difference in terms of efficacy between parnaparin and UFH; although both parnaparin and UFH were generally effective in improving clinical and instrumental outcomes evaluated at baseline and at the end of treatment.^{51,53–55} In one double-blind study,⁵² parnaparin (6400 IUaXa) proved to be statistically significantly better than UFH and than a lower parnaparin dose (3200 IUaXa) in reducing the intensity of symptoms (evaluated on a clinical scale), the ankle diameter, and in increasing venous outflow (as assessed by strain-gauge plethysmography).

Peripheral arterial occlusive disease (Table 4)

Subcutaneous parnaparin (6400 IUaXa once-daily) was compared with placebo in 6 small (number of patients = 33 to 36) randomized trials^{56–61} or with UFH in one nonrandomized study,¹³ performed over 6^{56–61} or 7¹³ months. All randomized studies, except one⁵⁸ were double-blinded, and conducted in patients with stage II disease (Leriche-Fontaine classification). Endpoints included the evaluation of pain-free walking distance (by treadmill) or time of rest and peak calf blood flow (by strain-gauge plethysmography), and of the ankle-brachial index (ratio between ankle and brachial artery pressures, normal ratio being >0.9).

In 4 of these studies^{56,58–60} parnaparin significantly improved pain-free walking distance or time, ankle-brachial index, or both, as compared to placebo. In the remaining 3 studies,^{13,57,61} in which only within-group analysis was available, baseline values for pain-free walking distance, blood flow, or ankle-brachial index were significantly increased at the end of the treatment period in the parnaparin group⁵⁷ or in both parnaparin and the UFH¹³ or placebo⁶¹ groups, respectively.

Acute coronary syndromes (Table 5)

Parnaparin was compared with placebo in a small (n = 29), randomized, double-blind study of patients with stable angina,⁶² and with UFH in 2 large-sample randomized nonblinded trials of patients with unstable angina²¹ and STEMI.²³

The two larger trials^{21,23} used composite efficacy hard endpoints, including death, while the smaller used only substitute endpoints.⁶² In the two larger trials, parnaparin yielded a statistically significant reduction in the frequency of the primary efficacy endpoint versus UFH,^{21,23} while in the smaller trial a statistically significant improvement in the primary efficacy endpoint was observed only in the

Table 2 Clinical experience with parnaparin for the treatment of deep-vein thrombosis

Author	Year	Design	End-point assessment	Patients ^a	Parnaparin (IUaXa) sc	Comparator	Treatment duration	Follow-up	Deep-vein thrombosis ^b	Pulmonary embolism ^b	Bleeding ^b
Notarbartolo et al ⁴⁶	1988	R, O	SGP	90 (30, 30/30)	6400 od or 12800 od 6400 od	UFH 30000 IU iv od warfarin	10 days 60 days	NR	0.0/0.0	NR	0/3.1 (0.034)
Zinicola et al ⁵⁰	1989	C	DS, LS	47	12800 od 6400 od	-	10 days 50 days	NR	0 ^c	0	NR
Teoldi et al ⁴⁷	1993	R, SB	SGP, CE	40 (20/20)	6400 bid 6400 od	UFH 5000 IU sc tid UFH 5000 IU sc bid	15 days 30 days	NR	0.0/5.0 (1.0)	0.0/0.0	0.0/0.0
Bellosta et al ⁴⁹	2007	R, O	ECD	91 (51/40)	6400 bid for 1 month, then 6400 od	Nadroparin 11400 (<70 kg) or 15000 (>70 kg) sc od	3 or 6 ^d months	NR	1.9/10.0 (0.16) ^e	1.9/0.0 (1.0)	1.9/0.0 (1.0)
Vashist et al ⁴⁸	2006	R, O	ECD	100 (50/50)	6400 od plus VKI	UFH 10000 IU sc tid plus VKI	3 months	NR	0.0/0.0	0.0/2.0 (1.0)	0.0/0.0

^atotal number (parnaparin group/comparator group); ^bfrequency of outcome events in the parnaparin group/in the comparator group (P value); ^c1 superficial thrombophlebitis; ^din the case of unprovoked DVT; ^ethe figures reported refer to DVT extension, as assessed by ECD.

Abbreviations: R, randomized; O, open; C, cohort study; SB, single blind; CE, clinical evaluation; DS, doppler sonography; SGP, strain-gauge plethysmography; ECD, echo-color doppler ultrasonography; LS, lung scan; sc, subcutaneously; iv, intravenously; od, once daily; bid, twice daily; tid, three times daily; NR, not reported; VKI, vitamin K inhibitor.

parnaparin group (no between-group comparisons available) versus placebo.⁶²

Clinical update

Based on our search strategy, we were able to retrieve 1 full paper,⁶³ and 2 congress abstracts^{64,65} dealing with clinical uses of parnaparin which were published during 2008. The first, a small-sample (n = 10) open-label study,⁶³ evaluated the efficacy of 3 different oral dosages (70, 140 and 210 mg once daily) of parnaparin in the treatment of mild-to-moderate relapse of left-sided ulcerative colitis, over 8 weeks. The endpoints were standardized clinical and endoscopic activity of the disease. At the end of the treatment, 7 patients (70%) were in clinical remission, only 1 achieving endoscopic healing, and standardized clinical scores were statistically significantly improved from baseline. The second, a randomized open multicenter dose-finding study of patients (n = 66) with severe obesity (BMI > 36) undergoing bariatric surgery, evaluated the effect of 2 parnaparin doses (4250 IUaXa or 6400 IUaXa, administered once daily for 9 ± 2 days) on anti-Xa levels, evaluated the day before operation, and at 4 and at 6 days after operation. The authors observed that with the administration of 4250 IUaXa the anti-Xa levels were within the expected activity range in 98.3% of the cases, while with 6400 IUaXa the anti-Xa activity was above the specified prophylactic range in 62.3 of the cases.⁶⁴ The third study reported the results of a multicenter, randomized, double-blind, controlled trial comparing the efficacy and safety of aspirin (100 mg/daily for 3 months) versus parnaparin (12,800 IUaXa for 7 days followed by 6400 IUaXa for a total of 3 months) for treatment of retinal vein occlusion (RVO). The primary efficacy endpoint of the study was the incidence of functional worsening of the eye with RVO at 6 months, objectively assessed by fluorescein angiography, visual acuity and visual field. The endpoint was adjudicated in 20.7% of patients treated with parnaparin (n = 28) and in 59.4% of patients treated with aspirin (n = 30) (P = 0.002). Recurrent RVO was diagnosed in 3 patients, all treated with aspirin (P = ns). Bleeding rates were similar between the two groups. Due to the small sample size of patients, the authors concluded that these promising results need to be confirmed in a larger clinical trial.⁶⁵

No clinical studies using parnaparin during 2009 were retrieved, but we are aware of an ongoing phase 3 Italian multicenter randomized clinical trial (STEFLUX trial, all active recruiting centers located in Italy) on the treatment of superficial thrombophlebitis. The study compares the efficacy and safety of 3 different doses of parnaparin (8500 IUaXa subcutaneous, once daily for

Table 3 Clinical experience with parnaparin for the management of chronic venous disease

Author	Year	Target disease	Design	End-point definition	End-point Assessment	Patients ^a	Parnaparin (IUaXa) sc	Comparator	Treatment duration	Follow-up	Efficacy	Safety ^b
Verardi et al ⁵¹	1988	PTS	R, O	Intensity of symptoms (scale 0–3), calf/ankle diameter	CE, DS (only if recurrent DVT)	77 (39/38)	30,000/day for 10 days, 15,000/day for up to 50 days	UFH 20,000 IU/day iv for 10 days UFH 12,500 IU sc for up to 50 days	10 to 50 days	None	c	7.0/8.0 (1.0)
Samazzari et al ⁵²	1989	CVI	R, DB	Intensity of symptoms (scale 0–3), ankle diameter; venous outflow	CE, SGP	92 (30, 30/30)	3200 od or 6400 od	UFH 5,000 IU sc tid	30 days	None	Statistically significant improvement with Parnaparin 6400 IUaXa od compared to the other two groups	0.0, 0.0/6.7 (0.49)
Catania et al ⁵³	1993	PTS	R, SB	Intensity of symptoms (scale 0–3), venous outflow	CE, SGP, DS	46 (24/22)	4250 od	UFH 5,000 IU sc bid	90 days	None	c	None reported
Canova et al ⁵⁴	1993	PTS	R, SB	Intensity of symptoms (scale 0–3), venous outflow	CE, SGP, US	57 (27/30)	4250 od	UFH 5,000 IU sc tid	90 days	None	c	None reported
Della Marchina et al ⁵⁵	1993	CVI	R, SB	Intensity of symptoms (scale 0–3)	CE, SGP, US	70 (35/35)	4250 od	UFH 5,000 IU sc tid	90 days	None	c	8.6/17.1 (0.48)

^atotal number (parnaparin group/comparator group); ^bfrequency of outcome events in the parnaparin group/in the comparator group (P value); ^cequivalent to comparator.**Abbreviations:** PTS, post-thrombotic syndrome, CVI, chronic venous insufficiency; R, randomized; O, open; DB, double blind; SB, single blind; CE, clinical evaluation; DS, doppler sonography; SGP, strain-gauge plethysmography; US, ultrasonography; sc, subcutaneously; od, once daily; bid, twice daily; tid, three times daily; iv, intravenously.

Table 4 Clinical experience with parnaparin for the management of peripheral arterial occlusive disease

Author	Year	Target disease	Design	End-point definition	End-point Assessment	Patients ^a	Parnaparin (IUaXa) sc	Comparator	Treatment duration	Follow-up	Efficacy	Safety ^b
Di Stefano et al ¹³	1988	PAOD	PG	Symptoms, PFWD, resting blood flow	CE (scale 0–3), TDM, DS	55 (27/28)	6400 od	UFH 5000 IU sc bid	7 months	None	Only within-group analysis (both improved)	Almost 100% of patients in both groups
Palmieri et al ⁶¹	1988	PAOD Fontaine 2	R, DB	ABI, pain-free walking time, peak blood flow	DS, SGR, TDM	55 (28/27)	6400 od	placebo	6 months	None	Only within-group analysis (ABI improved in both groups; pain free walking time, peak blood flow improved only by parnaparin)	4.0/2.0 (0.34)
Tesi et al ⁵⁹	1989	PAOD Fontaine 2	R, DB	ABI, PFWD	DS, TDM	20 (10/10)	6400 od	placebo	6 months	None	Parnaparin improved both ABI ($P < 0.05$) and PFWD ($P = 0.03$) as compared to placebo	None reported
Mannarino et al ⁵⁶	1991	PAOD Fontaine 2	R, DB	ABI, PFWD	DS, SGR, TDM	44 (22/22)	6400 od	placebo	6 months	None	Parnaparin improved PFWD ($P < 0.05$) as compared to placebo	None reported
Serrao et al ⁶⁰	1991	PAOD Fontaine 2–3	R, DB	Intensity of symptoms (scale 0–3), ABI, pain-free walking time	CE	40 (20/20)	6400 od	placebo	6 months	None	All outcomes significantly improved by Parnaparin as compared to placebo	5.0/1.7 (0.65)
Simoni et al ⁵⁸	1992	PAOD Fontaine 2	R, O	ABI, PFWD, resting and peak blood flow	DS, SGR, TDM	66 (33/33)	6400 od	placebo	6 months	None	Parnaparin significantly ($P < 0.05$) improved PFWD (+28.9%), ABI and peak flow compared to placebo	2.8/0.7 (0.49)
Calabrò et al ⁵⁷	1993	PAOD Fontaine 2	R, DB	ABI, PFWD, total walking distance, resting and peak blood flow	SGR, TD	36 (18/18)	6400 od	placebo	6 months	None	Only within-group analysis (PFWD and resting blood flow improved in the parnaparin group only)	None reported

^atotal number (parnaparin group/comparator group). ^bFrequency of outcome events in the parnaparin group/in the comparator group (P value).**Abbreviations:** PAOD, peripheral arterial occlusive disease; ABI, ankle-brachial index; PFWD, pain-free walking distance; PG, parallel-group, nonrandomized; R, randomized; O, open; DB, double blind; CE, clinical evaluation; DS, doppler sonography; SGR, strain-gauge plethysmography; TDM, treadmill; sc, subcutaneously; od, once daily; bid, twice daily.

Table 5 Clinical experience with parnaparin for the management of acute coronary syndromes

Author	Year	Target disease	Design	Patients ^a	Parnaparin (IUaXa) sc	Comparator	Treatment duration	Follow-up	Efficacy ^b	Major bleeding ^b
Melandri et al ⁶²	1993	SA	R, DB	29 (15/14)	6400 od	placebo	3 months		Only within-group analysis (time to ST segment depression, peak ST segment depression, time to onset of moderate angina (all after treadmill testing), Canadian Cardiovascular Society class for angina	NR
PRIME CARE investigators ²¹	2005	UA	R, O	897 (446/451)	6400 od	UFH bolus 5000 IU iv followed by 800–1000 IU/h for 48 h, then 5000 IU 4 × daily sc for 5 d	7 days	30 days	7.3/11.4 (RR 0.64; 95%CI 0.42–0.97, P = 0.034) 21.8/12.1 (RR 0.56; 95% CI 0.39–0.79, P = 0.0008)	0.4/0.4 (P = 1.0)
Wang et al ¹³	2006	STEMI	R, O	186 (96/90)	4250 bid	UFH bolus 100 IU/kg iv followed by 1000 IU/h for 3 d, then 7500 IU bid sc for 4 d	7 days	45 days	27.1/42.2 (P = 0.03) ^c	2.1/4.4 (P = 0.43)

^atotal number (parnaparin group/comparator group); ^bFrequency of outcome events in the parnaparin group/in the comparator group (P value); ^cAssessed at 45 days.

Abbreviations: SA, stable angina; UA, unstable angina; R, randomized; O, open; DB, double blind; sc, subcutaneously; iv, intravenously; od, once daily; bid, twice daily; tid, three times daily; NR, not reported; h, hour; d, days.

10 days followed by placebo for 20 days versus 8500 IUaXa subcutaneous, once daily for 10 days, followed by 6400 IUaXa subcutaneous, once daily for 20 days; versus 4250 IUaXa subcutaneous, once daily for 30 days), and the planned sample size exceeds 1000 patients.

Tolerability and management

In all clinical trials in which parnaparin was investigated, a general good tolerability was reported. As with the other commercially available LMWHs, the most important side effect was bleeding, usually classified as major (heavy blood loss, such as clinically overt hemorrhage associated with hemoglobin drop of at least 2 g/L or requiring the transfusion of 2 or more units of packed red-blood cells; or bleeding at life-threatening sites, such as retroperitoneal or intracranial events; or bleeding requiring re-intervention) or minor (including, for example, bleeding at the injection site).^{21,23} Studies of thromboprophylaxis after major surgery reported of an incidence of hemorrhagic complications ranging from 1% to 4%, whereas in studies dealing with parnaparin use in unstable angina, a 3% incidence of minor bleeding and only 1 major bleeding were observed.^{15,21,28,32} In a study considering patients with STEMI, bleedings events occurred in 3% of patients receiving parnaparin.²³ After minor orthopedic surgery, bleeding complications were reported in <2% of the 509 patients investigated, most of which were minor bleedings (injection site hematomas).⁴⁵

In studies evaluating the use of parnaparin in peripheral vascular diseases or chronic venous disorders, minor bleeding complications and/or pain occurred less in patients allocated to subcutaneous parnaparin than in those randomized to subcutaneous UFH.^{13,32,55,66}

Heparin-induced thrombocytopenia (HIT) is another well known complication of heparin, its incidence being approximately 0.8%, with LMWH, about 3-fold lower than with UFH.^{67,68} HIT is caused by heparin-dependent antibodies (usually immunoglobulin G) binding a conformationally modified epitope on platelet factor 4 (PF4), its modified structure being subsequently recognized as a foreign protein by the immunocompetent cells of the patients. HIT was not observed in any of the clinical trials of parnaparin discussed in this review. Nonetheless, patients receiving either a prophylactic or a therapeutic course of parnaparin are recommended to carefully monitor their platelet count during the first 2 weeks of exposure to the drug, especially those with a recent history of heparin exposure, who are at higher risk of developing HIT.⁵

Parnaparin is administered at different dosage according to the type and the severity of the disease. Doses and administration of parnaparin in different clinical settings are shown in Table 6. Caution should be used in patients with renal or hepatic insufficiency, arterial hypertension, or any organ lesion subject to bleeding.⁵

Place in therapy and conclusion

In VTE prevention, parnaparin administered subcutaneously (3200 UIaXa) once daily for 7 days showed to be more effective than placebo (0% versus 6%, respectively) and at least as effective as UFH, in patients undergoing abdominal, vascular, orthopedic (major and minor) or cardiac surgery.

Compared to UFH, the equivalent efficacy of parnaparin given once daily for up to 3 months has been demonstrated in the treatment of CVD (above all chronic venous insufficiency secondary to a post-thrombotic syndrome), superficial thrombophlebitis and DVT.

Table 6 Dosage and administration of parnaparin in different clinical settings

Setting	Dose, UIaXa	Route and frequency
Treatment of CVD, SVT, VPH	3200 to 6400	sbc, od for 20–30 d
DVT prevention in general nonhigh risk surgery	3200	sbc, od 2 h before surgery, then for at least 7 d
DVT prevention in general high risk surgery, or orthopedic surgery	4250	sbc, od 12 h before surgery 12 h after surgery, at least for 10
DVT treatment	12800 6400 4250–6400	iv slow, for 3–5 d sbc, tid for at least 7–10 d sbc, od for 10–20 d
Unstable angina	6400	sbc, od for 7 d
STEMI	4250	sbc, tid for 7 d
PAOD	6400	sbc, od for 6 m

Abbreviations: CVD, chronic venous diseases; SVT, superficial vein thrombophlebitis; VPH, varicophlebitis; DVT, deep vein thrombosis; STEMI, ST-segment elevation myocardial infarction; PAOD, peripheral arterial occlusive disease; sbc, subcutaneous; od, once-daily; tid, twice-daily; d, days; m, months.

In patients with stable angina a 3-month course of therapy with parnaparin provides a significant improvement in the exercise time on treadmill test compared with baseline, but not in patients receiving placebo. Recently, in patients with unstable angina or STEMI, once-daily subcutaneous parnaparin has been shown to be able to significantly reduce the primary efficacy composite endpoint of death, acute MI or need for emergency myocardial revascularization (including coronary artery bypass grafting or angioplasty) in the first 7 days or 45 days after the start of treatment, respectively, compared to UFH (7% vs 11%, $P = 0.034$; 27% vs 42%, $P = 0.03$, respectively).

Subcutaneous parnaparin has been compared with placebo or UFH in patients with stage II PAOD (Leriche-Fontaine Classification). Compared with both placebo or UFH, parnaparin was able to significantly improve all the endpoints investigated, such as pain-free walking time and pain-free walking distance, peak blood flow in the calf and the ankle-brachial index.

Tolerability of parnaparin has been generally reported across all studies. The risk of bleeding complications arising from parnaparin compared with UFH seems similar for the major bleeds, whereas the incidence of minor bleeds is lower with parnaparin.

No cases of HIT are reported with parnaparin use. However, a platelet count should be taken every 3 days for the first 2 weeks of treatment in all patients receiving parnaparin.

As with other LMWHs, and in contrast to UFH, parnaparin enables patients with most peripheral vascular diseases to be treated at home or as an outpatient because treatment is easy to manage, has good tolerability, equivalent efficacy and safety.

Further applications of parnaparin have been recently investigated in different settings (ulcerative colitis, RVO, severe obese patients undergoing bariatric surgery), even though its promising results on efficacy need to be confirmed in larger clinical trials.

In conclusion, parnaparin is a safe, effective, well tolerated LMWH widely investigated and used in the prevention and treatment of VTE, and in the management of CVD and of coronary artery disease. As with other LMWHs, parnaparin can be administered subcutaneously, once daily, with a better local tolerability than UFH, and the available data indicate that parnaparin could be the optimal choice among all the commercially available LMWHs.

Disclosures

The authors declare no conflicts of interest.

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