Thrombosis Research 129 (2012) 407–417

Contents lists available at SciVerse ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Fondaparinux – data on efficacy and safety in special situations

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ARTICLE INFO

Article history:
Received 9 September 2011
Received in revised form 27 October 2011
Accepted 28 October 2011
Available online 30 November 2011

Keywords:
Fondaparinux
impaired renal function
pregnancy
children
heparin-induced thrombocytopenia
drug concentration

ABSTRACT

New anticoagulants promise to have better efficacy, more safety and/or a better manageability than traditional anticoagulants. However, knowledge is limited regarding special situations such as renal insufficiency, obesity, pregnancy, long-term therapy, heparin-induced thrombocytopenia, treatment in patients with mechanical heart valves, use for children, and in patients with a high risk of thromboembolic complications. These situations have rarely or even never been the objective of randomised controlled trials. The purpose of the present article is to summarize and discuss available data on efficacy and safety in these special situations for one of the first new anticoagulants, the indirect factor-Xa inhibitor fondaparinux. Furthermore, we discuss safety in licensed indications and management of bleeding complications and comment on measuring of drug concentration in plasma.

Contents

Abbreviations: ACS, acute coronary syndrome; anti-Xa, anti-factor Xa activity; APS, antiphospholipid syndrome; BID, twice a day; BMI, body mass index; DVT, deep vein thrombosis; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; FEIBA, factor eight inhibitor bypassing activity; FFP, fresh frozen plasma; GFR, glomerular filtration rate; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MDRD, Modification of Diet in Renal Disease formula; OD, once daily; PCC, prothrombin complex concentrate; PE, pulmonary embolism; PF4, platelet factor 4; rFVIIa, recombinant factor VIIa; s.c., subcutaneously; SRA, serotonin release assay; SVT, superficial vein thrombosis; Swissmedic, Swiss Agency for Therapeutic Products; UFH, unfractionated heparin; VKA, vitamin K antagonists; VTE, venous thromboembolism.

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doi:10.1016/j.thromres.2011.10.037

Introduction

Despite recent advances in anticoagulation therapy there are regularly situations in clinical practice, which are not covered by current guidelines [1–4]. These include renal insufficiency, obesity, pregnancy, use for children, heparin-induced thrombocytopenia, and long-term therapy e.g. in patients with mechanical heart valves and in patients with a high risk of thromboembolic complications, particularly if vitamin K antagonists (VKA) and/or heparin derivatives are inappropriate. These situations have rarely or even never been the objective of randomised controlled trials. Problems with VKA therapy can include bleeding complications, inability to achieve the target international normalised ratio (INR), venous thromboembolism in spite of adequate anticoagulation or rare situations such as the presence of a factor IX propeptid mutation. Furthermore, there are non-bleeding side effects such as hair loss, fatigue, or elevations of hepatic enzymes. Possible problems with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) are heparin-induced thrombocytopenia (HIT), hypersensitive skin reactions or failure of absorption. New anticoagulants promise to have better efficacy, more safety and/or a better manageability than traditional anticoagulants. However, knowledge is limited regarding special situations.

The purpose of the present article is to summarize and discuss available data on efficacy and safety in these special situations for one of the first new anticoagulants, the indirect factor-Xa inhibitor fondaparinux. Furthermore, we discuss safety in licensed indications and management of bleeding complications and comment on measuring of drug concentration in plasma.

Mechanism of action and pharmacokinetics

Fondaparinux is a pentasaccharide which strongly binds to antithrombin and enhances the inactivation of factor Xa without interaction with factor II or platelets [5]. It has a markedly increased affinity for antithrombin and improved inhibition of thrombin generation in comparison with UFH [6]. Furthermore, in an animal model it shows a stronger anticoagulation effect in arterial thrombosis [7]. Fondaparinux has a high bioavailability (107%; 90% CI 102 – 112%) two hours after subcutaneous (s.c.) administration and an elimination half-life of 17 to 21 hours [8,9]. This enables once-daily dosing. Unmetabolized excretion through the kidneys warrants caution in patients with impaired renal function. Very low intra- and intersubject variability [9] makes drug monitoring and dose adjustments in most cases unnecessary. There were no relevant drug interactions in corresponding investigations and in phase III clinical trials [10–12]. Data on pharmacokinetics are summarized in Table 1.

Safety of fondaparinux in recommended indications

Recommended indications of fondaparinux are summarized in Table 2. Fondaparinux 2.5 mg is recommended for the prevention of VTE in major orthopaedic surgery, major abdominal surgery and medical patients [2]. In phase III clinical trials, it did show superior efficacy or non-inferiority compared to enoxaparin, UFH or physical measures alone [13–17]. Although prevention trials did show a slight increase in major bleeding events, this was counterbalanced by a consistent pattern in reduced mortality [18]. Although statistically not significant, the effect of reduced mortality was internally consistent, as it was seen in nearly all subgroups and externally consistent as it was observed in all trials. In addition, most of the bleeding complications occurred if fondaparinux was given within 6 hours after surgery [13,19]. If administered at a correct interval after interventions (6 to 8 hours), ACCP guidelines consider prophylaxis with fondaparinux 2.5 mg as safe as a prophylactic dose of LMWH or UFH [20]. To enhance feasibility of postoperative application, a delayed initiation of fondaparinux treatment (morning after surgery) was tested and proved to have comparable efficacy in preventing thrombembolic complications [21]. Another important safety concern is when continuous neuraxial or deep peripheral nerve catheters are used postoperatively. In phase III clinical trials type of anaesthesia was left to the discretion of the anaesthesiologist and 30 – 65% of the patients received regional anaesthesia [22]. No case of spinal or epidural haematoma was observed, however [15,17,23–26]. A prospective cohort study investigated efficacy of fondaparinux treatment if application was discontinued for 48 hours to allow removal of neuraxial or peripheral nerve catheter (n = 1431). Catheter was removed 36 hours after last application and 12 hours before next application with a comparable efficacy and safety in patients with and without a catheter (and discontinuation of fondaparinux) [27].

A recent study of fondaparinux 2.5 mg vs. placebo for treatment of superficial vein thrombosis (SVT) showed efficacy in terms of prevention of deep vein thrombosis (DVT) respective pulmonary embolism (PE) without any increase in major bleeding [28].

Fondaparinux 7.5 mg is recommended as initial treatment of DVT and PE because of its comparable efficacy to LMWH (DVT) or UFH (PE) [3,29,30]. In both phase III studies, bleeding complications were similar to the comparator. For that reason, ACCP guidelines consider therapeutic doses of fondaparinux (7.5 mg, respectively 10 mg in case of body weight >100 kg and 5 mg if <50 kg) comparable safe to therapeutic doses of UFH/LMWH [20].

Fondaparinux 2.5 mg is recommended for the treatment of acute coronary syndrome (ACS) by ACCP, ACC-AHA and ESC [12,31–33]. Phase III clinical trials showed efficacy comparable or superior to LMWH/UFH in respect of myocardial infarction as well as a significant reduction in mortality at most of the points in time [34,35]. Furthermore, a reduction in major bleeding events was observed compared to enoxaparin, most markedly in the case of non-ST elevation ACS at day 9 (Hazard ratio 0.52; 95% CI 0.44 – 0.61). Therefore, fondaparinux is particularly recommended for patients at high risk of bleeding complications such as the elderly, women, patients with renal impairments and those with anaemia [32,33]. Because of a trend towards higher mortality in a subgroup of patients, fondaparinux only carries a 1B recommendation and is not recommended in cases of primary angioplasty [36].

Table 1
Mechanism of action and pharmacokinetics of fondaparinux.

Mechanism of action	Binding to antithrombin with high affinity. Inactivation of factor Xa
Bioavailability	100%, two hours after s.c. application
Elimination half-life	17 to 21 hours(young healthy volunteers - elderly)
Elimination	Excreted unmetabolized in urine (80%)
Metabolism	Not demonstrated
Within-subject variability	Low (4.4 – 5.5%)
Inter-subject variability	Low (11.6 – 17.5%)
Interaction with digoxin	None
Interaction with aspirin	None
Batch-to-batch variability	None

Table 2
Recommended indications of fondaparinux.

Indication	Dose mg	Recommendation	Approved by	Major phase III clinical trials
Prevention of VTE	2.5 OD	ACCP [2]: Grade 1A recommended in elective hip or knee arthroplasty and hip fracture surgery Grade 1A recommended in inpatients with acute medical illness Grade 1A recommended in major abdominal surgery, major gynaecologic surgery, major urologic surgery	FDA°, EMA, Swissmedic	PENTAMAKS (knee replacement): Bauer KA et al. 2001 [23] PENTHIFRA(hip fracture): Eriksson BI et al. 2001 [24] EPHESUS (hip replacement): Lassen MR et al. 2002 [25] PENTATHLON (hip replacement): Turpie AG et al. 2002 [26] ARTEMIS (acute medical illness): Cohen AT et al. 2006 [16] APOLLO (major abdominal surgery): Turpie AG et al. 2005 [17] PEGASUS (major abdominal surgery): Agnelli G et al. 2005 [15]
Treatment of VTE	7.5 OD**	ACCP* [3]: 1A recommended in DVT and PE	FDA, EMA, Swissmedic	MATISSE-PE: Büller HR et al. 2003 [30] MATISSE-DVT: Büller HR et al. 2004 [29]
Treatment of SVT	2.5 OD		EMA	CALISTO: Decousus HP et al. 2010 [28]
Acute coronary syndrome	2.5 OD	ACCP* [115,116]: Grade 1A recommended (without primary angioplasty) ACC-AHA†[12]: Level A recommended (conservative strategy), Level B (primary angioplasty) ESC# non-ST elevation ACS [32,33]: Grade 1 A recommended ESC# STEMI## [32]: Grade 1 B recommended (without primary angioplasty)	EMA, Swissmedic	OASIS-5 (non-ST elevation ACS): Yusuf S et al. 2006 [35], OASIS-6 (STEMI): Yusuf S et al. 2006 [34] OASIS-8 (Heparin dose in non-ST elevation ACS initially treated with Fondaparinux): Steg PG et al. 2010 [117]

STEMI = ST-segment elevation myocardial infarction. * American College of Chest Physicians. † American College of Cardiology/American Heart Association. # European Society of Cardiology. **respectively 10 mg in case of body weight >100 kg and 5 mg if <50 kg. ° except in patients with acute medical illness.

Generally, clinical trials didn't reveal any relevant side effects beside bleedings, in particular no increase in liver enzymes and no excess of cardiovascular events. The allergenic potential is much lower than for low-molecular weight heparins [37].

Long term therapy

Duration of therapy with the prophylactic dose of fondaparinux (2.5 mg) in phase III trials was between 6 days in case of ACS [35], 25 to 31 days during prolonged prophylaxis after hip fracture surgery [38] and 45 days for the treatment of SVT [28]. A therapeutic dosage of fondaparinux (7.5 mg) was given for 6 or 7 days for the treatment of DVT and PE prior to the start of VKA [29,30]. With the exception of renal impairments, phase III trials did not report any accumulation or additional adverse events in the course of therapy. However, no formal measurement of drug concentration was conducted and possible accumulation comparable to LMWH may be a major concern. Table 3 summarizes available publications on treatment with fondaparinux for longer than 15 days. Two randomized controlled trials reported about fondaparinux treatment (2.5 mg) over 25–31 or 45 days (n = 1829) [28,39]. In another cohort study 26 patients where treated with a therapeutic dose of fondaparinux (7.5 mg) for 90 days [40]. Several cohort studies, one case control study and a number of case reports exist regarding the treatment of pregnant women or children with prophylactic doses of fondaparinux [41–54]. The duration of treatment in most of these cases was between several weeks and 8 months. A recently published cohort study reported about 24 children treated with therapeutic doses of fondaparinux (0.1 mg/kg once daily - OD) for up to 19 days because of DVT or HIT [54]. One case is reported regarding a 30-month-treatment with 10 mg fondaparinux in an obese patient with a mechanical heart valve (BMI 36 kg/m^2) [55]. All of the investigations on long-term treatment stated no bleeding events or non-significant differences to the comparator (enoxaparin/placebo). Furthermore, no accumulation is reported and no additional adverse events.

In conclusion, based on the data mentioned above and our own clinical experience we would use fondaparinux for long-term therapy in prophylactic and therapeutic dosages in cases where VKA and LMWH are not appropriate. For safety reasons, we monitor drug concentration in patients on long-term application of fondaparinux.

Mechanical heart valve

Two experimental investigations and two case reports suggest the use of fondaparinux to prevent thrombembolic complications in patients with a mechanical heart valve (Table 4). The rate of thrombosis was tested in an in-vitro “thrombosis tester” and an experimental ex-vivo rabbit model with similar rates compared to UFH and LMWH [56,57]. A report exists on a pregnant woman with a mechanical aortal and mitral valve who was treated with fondaparinux 7.5 mg for 20 weeks as well as a report on a 63-year-old man with a mechanical aortal valve who was treated for 30 months with fondaparinux 10 mg [55,58]. In both patients, no thrombembolic complications and no bleeding events were noticed.

Although clinical data are very limited, we consider treatment with fondaparinux as a reasonable option in patients with a mechanical heart valve if VKA and LMWH are not appropriate. In our practice, we use a therapeutical dosage (7.5 mg OD s.c., respectively 10 mg in case of body weight >100 kg and 5 mg if <50 kg).

Impaired renal function

Fondaparinux is eliminated almost completely through the kidneys without previous metabolism [9]. In the case of impaired renal function, caution is advised regarding possible drug accumulation. Most phase III trials excluded patient with a serum creatinine >177 μmol/L (2 mg per decilitre). Clinical trials on the treatment of ACS (OASIS 5, OASIS 6) [34,35] permitted the inclusion of patients with a serum creatinine <265 μmol/L (3 mg per decilitre). The safety of fondaparinux in relation to renal function was tested in a subgroup analysis of the OASIS 5 trial (Table 5) [59]. Fondaparinux 2.5 mg consistently showed significantly fewer major bleeding events than enoxaparin in patients with and without a glomerular filtration rate lower than 58 ml/min.

Data of thromboembolism prevention trials (n = 13085) were analysed in a retrospective analysis (Table 5) [18]. It was demonstrated that reduced creatinine clearance is a predictor of major bleeding in

Table 3
Studies of fondaparinux in long-term therapy > 15 days, including pregnancy** and children population***.

Study/year	Clinical situation	Design	No of patients	Age	Dose	Anti Xa level	Duration of treatment	Outcomes
			Overall/ female	years	mg	μg/ml		Efficacy/Safety
Eriksson BI et al. 2003 [38]	VTE prophylaxis after hip fracture surgery	RCT	656/466	79 (23–96)*	2.5 OD	NR	25-31 days	RRR vs. Placebo 96%/ n.s.
Decousus H et al. 2010 [28]	Treatment of SVT	RCT	3002/ 974	57°	2.5 OD	NR	45 days	RRR vs. Placebo 85%/ n.s.
Shetty R et al. 2007 [40]	Treatment of DVT/PE	Cohort	26/14	50°	7.5† OD	NR	90 days	No recurrent VTE/No major bleedings
Knol HM et al. 2010**[46]	VTE prophylaxis in pregnancy	Cohort	10/12	30 (26–34)*	2.5 BID	NR	1-36 weeks†	No foetal loss, no VTE/No major bleedings
Young G 2011***[54]	Treatment of DVT/DVT+HIT	Cohort	24/14	1-18	0.1 mg/ kg OD	0.68 (±0.21)°	2-19 days	Drug concentrations similar to adults/Major bleedings: 1, Minor bleedings: 1
Singelyn FJ et al. 2007 [27]	VTE prophylaxis in major orthopaedic surgery	Cohort	5704/ 3775	66 (±12)°	2.5 OD	NR	35 days (1–105)*	VTE: 1% Major bleedings: 0.8%
Winger EE et al. 2009**[52]	VTE prophylaxis in pregnancy	Case control	29/29	37.1 (±4.3)°	2.5 OD	NR	≥78 days	Similar to enoxaparin/No major bleedings
Grabowski EF 2007***[44]	Atrial thrombosis, HIT	Case series	6/6	1-18	Not specified	0.5–1.2§§	2 – 18 months	No recurrent VTE/No bleeding events
Nagler M et al. 2011 [55]	VTE prophylaxis in mechanical heart valve	Case report	1/0	63	10 OD	1.01 (0.95-1.13)*	30 months	No VTE/No bleedings
Lian EC 2003 [47]	Treatment of PE in APS and HIT	Case report	1/0	36	2.5 OD/5 OD‡	NR	8 months	No VTE/No bleedings
Young G 2004***[53]	Catheter thrombus, HIT	Case report	1/1	2 months	0.15 mg/ kg OD	0.20-1.79§§	6 months	No recurrent VTE/No bleeding
Harenberg J 2007**[45]	VTE prophylaxis in pregnancy, APS	Case report	1/1	31	2.5 OD	0.34-0.57§§	35 weeks	No VTE, foetal growth retardation due to plancentar insuffiency/No bleeding
Gerhard A 2007**[43]	VTE prophylaxis in pregnancy	Case report	2/2	30, 35	2.5 OD	0.15-0.34§§	28/ 13 weeks	No VTE, no foetal loss/No bleedings
Mazzolai L 2006**[49]	VTE prophylaxis in pregnancy	Case report	1/1	39	2.5 OD	0.35-0.43§§	21.5 weeks	No VTE, no foetal loss/No bleedings
Mondorf W et al. 2011**[58]	Pregnancy Hypersensitive skin reactions to LMWH	Case report	1/1	40	7.5 OD	NR	20 weeks	No VTE/No bleedings
Dempfle CE 2004**[42]	VTE prophylaxis in pregnancy	Case report	3/3§	Not specified	2.5 OD	0.11-0.40§§	4-14 weeks	No VTE, no foetal loss/No bleedings
Boshkov LK 2004***[41]	Catheter thrombus	Case report	1/1	4 months	0.15 mg/ kg OD	0.33-0.77§§	12 weeks	No recurrent VTE/No bleeding
Mason AR*** 2008 [48]	Chronic haemodialysis patient	Case report	1/1	2 months	0.12 mg/ kg OD	0.39-0.5§§	12 weeks	No recurrent VTE/No bleeding
Wijesiriwardana A 2006**[51]	VTE prophylaxis in pregnancy	Case report	1/1	20	2.5 OD	NR	3 weeks	No VTE, no foetal loss/No bleedings
Sharathkumar AA*** et al. 2007 [50]		Case report	1/1	15	0.0125 - 0.05 mg/ kg	0.65-0.8§§	21 days	Treatment of PE

RRR = relative risk reduction. n.s. = not significant. * Median (range). ° Mean (±SD). 5 mg for patients <50 kg 10 mg for patients > 100 kg. † Therapy started in 1st to 3rd trimester of pregnancy. ‡ on alternate days. § Two more patients recieved fondaparinux for 1 to 9 days. NR, not reported. §§ range.

patients treated with fondaparinux as well as in those treated with the comparator (low molecular weight heparin or placebo). However, fondaparinux treatment was consistently associated with a trend towards reduced mortality.

Another subgroup analysis was focused on patients with impaired renal function in four phase-II dose finding trials on thromboembolism prevention during orthopaedic surgery [60]. In patients with a creatinine clearance between 20 and 50 ml/min, the reduced dose of 1.5 mg

Table 4
Studies of fondaparinux in VTE prophylaxis of mechanical heart valve.

Study/year	Clinical situation	Design	No of patients	Age	Dose	Anti Xa level	Duration of treatment	Outcomes
			Overall/ female	years	mg	μg/ml		Efficacy/Safety
Nagler M et al. 2011 [55]	Factor IX propeptide mutation Hypersensitive skin reactions to LMWH	Case report	1/0	63	10 OD	1.01 (0.95-1.13)	30 months	No VTE/No bleedings
Mondorf W et al. 2011 [58]	Pregnancy Hypersensitive skin reactions to LMWH	Case report	1/1	40	7.5 OD	NR	20 weeks	No VTE/No bleedings
Schlitt A et al. 2003 [56]	-	Ex-vivo animal model (rabbit)	-	-	-	-	-	Comparable to UFH
Schlitt A et al. 2006 [57]	-	In-vitro model	-	-	-	-	-	Comparable to UFH/ LMWH

NR, not reported.

Table 5
Studies of fondaparinux use in impaired renal function and haemodialysis.

Study/year	Clinical situation	Degree of renal impairment	Design	No of patients	Age	Dose	Anti Xa level	Duration of treatment	Outcomes
				Overall/female	Years	mg	μg/ml		Efficacy/Safety
Eikelboom JW et al. 2009 [18]	VTE prophylaxis in major orthopaedic surgery, abdominal surgery and high-risk medical patients	Not specified	Meta analysis	13085	70° (17–101)	2.5 OD	NR	5-9 days	Decreased GFR (62.4 vs. 74.8 ml/min°) is associated with increased major bleeding in fondaparinux and comparator-treated patients ($p<0.0001$)
Fox KA et al. 2007 [59]	Treatment of ACS	GFR <58 ml/min‡	RCT subgroup analysis	19979/7649‡	66.6 (±10.9)*	2.5 OD	NR	6 days*	VTE and death: comparable to enoxaparin† in patients with and without GFR <58 ml/min‡ Major bleeding events: HR 0.52 in favour of fondaparinux† in patients with and without GFR <58 ml/min‡
Turpie A et al. 2009 [60]	VTE prophylaxis in total knee and hip replacement	GFR >20 and <50 ml/min	RCT (n = 3) subgroup analysis	69#	60.9*, 70.5*, 67°	1.5 OD	0.33 (0.21-0.50)*	5-10 days	VTE: reduced vs. placebo, comparable to LMWH Major bleeding events: comparable to LMWH and placebo
Delavenne X et al. 2010	VTE prophylaxis in major orthopaedic surgery	GFR_{MDRD} <60 ml/min	Cohort§	809'	74.1 (±13)*	2.5/1.5 OD	0.5 (0.19-1.16)*	8 days*	Fondaparinux clearance decreased by 25% if GFR <60 ml/min and by 43% if GFR <30 ml/min
Sombolos KI et al. 2008 [63]	Prophylaxis during haemodialysis	Chronic haemodialysis patients	Cohort	16	Not specified	2.5 single dose	0.12-0.58°°	Single dose	Increased clot formation in high-flux polysulfone dialysers compared to low-flux polsulfone dialyzers
Kalicki RM et al. 2007 [62]	Prophylaxis during haemodialysis	Chronic haemodialysis patients	Cohort	12	57.7 (±18.6)*	0.05 mg/kg°°°	0.61 (±0.14)* – 0.89 (±0.24)*	9 sessions	Comparable clot formation to UFH, mild bioaccumulation. Minor bleeding events.
Sharathkumar AA et al. 2007 [50]	Treatment of PE	Chronic haemodialysis patient	Case report	1	15	0.0125 - 0.05 mg/kg§§	0.66-2.05°°	21 days	Minor bleeding events made dose adjustments necessary

* Mean (±SD). ° Median (range). †Dosage of enoxaparin 1 mg per kilogram of body weight OD and BID in patients with and without GFR <58 ml/min respectively. ‡ n = 5141 patients with GFR <58 ml/min, patients with a serum creatinine level ≥3 mg per decilitre (265 μmol/L) were excluded. HR = Hazard ratio. # patients with a creatinin clearence ≥20 and ≤50 ml/min, 38 of them treated with fondaparinux. §Pharmokokinetic study. 'n = 166 with GFR_{MDRD} <60 ml/min. 7 patients with a GFR >30 ml/min and <60 ml/min were treated with fondaparinux 1.5 mg. NR, not reported. °° range. °°° extra-corporeal applied during haemodialysis session. §§ OD to every other day.

fondaparinux was administered (n = 38) compared with enoxaparin 30 mg or placebo. At least a comparable safety regarding major bleeding events was observed. In addition, a pharmacokinetic model was developed. This study and a cohort study confirmed a trend towards accumulation of fondaparinux with decreasing renal function. Fondaparinux clearance was decreased by 25% in patients with a GFR less than 60 ml/min (MDRD) and by 43% in patients with a GFR less than 30 ml/min. A comparable exposure to the drug was demonstrated for fondaparinux 1.5 mg in patients with moderate renal impairment (GFR > 30 and <60 ml/min) as compared with 2.5 mg fondaparinux in patients with normal renal function derived from a pharmacokinetic simulation [61].

There are two cohort studies and one case report about fondaparinux treatment in chronic haemodialysis patients (Table 5) [50,62,63]. The treatment with fondaparinux was effective (with the exception of high-flux polysulfone dialysers), but was associated with a certain degree of accumulation, which precludes long-term treatment.

In conclusion, the available data suggest that fondaparinux 2.5 mg is safe in patients with moderate renal impairment (GFR > 30 ml/min) although a certain amount of accumulation may occur. In our practice, we use fondaparinux without dose reduction and monitor drug concentration. In case of accumulation (drug concentration above 0.5 μg/ml, see paragraph below) we reduce dosage to 1.5 mg OD. Our approach is different from the manufacturer's recommendation to reduce the dosage in all patients with a creatinine clearance below 50 ml/min because this recommendation is mainly based on the pharmacokinetic simulation mentioned above. Only few data exist for patients with a GFR of less than 30 ml/min. Therefore, other than for short-term treatment, we avoid fondaparinux in patients with a GFR of less than 30 ml/min and in haemodialysis patients. No data exist on treatment with fondaparinux 7.5 mg in patients with serum creatinine > 177 μmol/L; for that reason, treatment with fondaparinux in these patients should be avoided.

Obesity

Because of high bioavailability, small intra- and intersubject variability and a distribution volume limited to blood volume, fondaparinux is assumed to have good tolerability in the case of obesity [9]. All phase III clinical trials included patients irrespective of body weight. Some thromboembolism prevention trials specifically report on the ratio of obese patients, for example 53% of the patients with body-mass index (BMI) above 30 kg/m2 in PENTAMAKS trial [23] and 25% in PENTHIFRA trial [38]. No dose adjustments were performed. Eikelboom et. al. used individual data from all prevention trials (n = 13085) to analyze risk factors for major bleeding and mortality. In this investigation, obesity did not contribute to major bleeding or mortality [18]. Phase III clinical trials on the treatment of ACS and myocardial infarction did not specifically identify the proportion of obese patients [34,35]. Recommendations on dose adjustments are not available for this scenario, nor are reports about subgroup analyses.

Regimens in thromboembolism treatment trials include dose adjustments dependent on body weight. 10 mg instead of 7.5 mg is recommended in case of body weight > 100 kg and 5 mg for a body weight <50 kg [29,30]. A subgroup analysis compared recurrent thromboembolism and major bleeding in patients with and without a body weight > 100 kg (n = 496) or, respectively, a BMI > 30 kg/m^2 (n = 1216). Efficacy and safety outcomes were similar in both groups [64]. Anti Xa levels in obese patients are not given in the studies mentioned above.

In our practice we use fondaparinux without any restrictions in obese patients. For treatment of DVT and PE dose adjustment to 10 mg OD s.c. is indicated in case of body weight > 100 kg. In patients with prophylactic indication of fondaparinux 2.5 mg we measure drug concentration in very obese patients (> 120 kg) because of a lack of data and consider dose adjustment to 5 mg if drug concentration is below 0.1 μg/ml.

Pregnancy

In an ex-vivo model, no placental transfer of fondaparinux was noted [65]. Minor placentar passage could be shown using chromogenic assay of anti-factor Xa activity (anti-Xa) and activated-partial thromboplastin time (aPTT) of umbilical blood in four women treated with fondaparinux 2.5 mg during pregnancy [42]. However, the concentration of fondaparinux was very low and no adverse events to these four mothers or their babies were reported. A number of reports exist on successful prophylaxis with fondaparinux in pregnancy (Table 3). A retrospective analysis compared 29 pregnancies treated with fondaparinux 2.5 mg and 98 pregnancies treated with enoxaparin 30 mg twice daily (BID). No difference was found in pregnancy success rates, gestational age, birth weight or miscarriage, nor any major bleeding complications [52]. A recently published prospective cohort analysis reports on 12 pregnancies with application of fondaparinux 2.5 mg because of thrombembolic disorders. The pregnancy success rate was 100%, there were no thrombembolic complications, no congenital abnormalities, no bleedings of the newborn and no excess of bleeding in the mothers [46]. In addition, there are reports on twelve more cases of safe and successful treatments in pregnancy [43,45,49,51,58,66]. These reports on safety are particularly relevant because most of the cases were long term treatment of several months.

In our clinical practice, we consider fondaparinux as a safe and effective option for anticoagulation in pregnancy if LMWH is not appropriate. We use fondaparinux 2.5 mg OD s.c. for TE prophylaxis. We use fondaparinux 7.5 mg for treatment of DVT and PE as well as for prophylaxis in high-risk situations (mechanical heart valve, antiphospholipid syndrome) if LMWH is contraindicated, but these situations are rare. We recommend stopping fondaparinux 24 hours before delivery or at the time of the first contractions. First postpartal application is earliest after 6 hours or after 12 hours after removal of a continuous neuroaxial catheter, respectively. In case of a long interval between prepartal and postpartal applications and a high-risk situation we recommend 'bridging' with UFH (100 U / kg bodyweight in 24 h).

Children

As with most drugs, clinical trials for treatment in children are rare. In accordance with data on pharmacokinetics mentioned above, there is no expectation of special problems in children. In a recently published cohort study, 24 children were successful treated with fondaparinux because of DVT/HIT. With a dosage of 0.1 mg/kg body weight OD, drug concentrations similar to adults were achieved, and one major and one minor bleeding event were recognized (Table 3) [54]. Additionally, a small number of case reports on successful treatment are available [41,44,48,50,53]. Dosages between 0.1 and 0.15 mg per kg body weight OD were chosen according to measured drug concentration and clinical situation. Only minor bleeding complication were noticed.

In conclusion, we consider treatment with fondaparinux as a valuable option for children if LMWH and VKA are inappropriate. In our practice we start treatment of DVT or LE with a dosage between 0.1 and 0.15 mg per kg body weight OD s.c. and adjust dosage if drug concentration is below 0.6 or above 1.5 μg/ml.

Cancer patients

There are no controlled trials that specifically evaluate the safety and efficacy of fondaparinux for prophylaxis or treatment of DVT/PE exclusively in patients with cancer. However, such patients are included in thromboembolism treatment trials, and there are some case reports. The phase III MATISSE-DVT trial included 237 patients (10.7%) with

active cancer and the MATISSE-PE 475 patients (10.8%). A post-hoc subgroup analysis of these cancer patients did not produce conclusive results. The three-month recurrence rate in case of DVT was 12.7% in the fondaparinux group compared to 5.4% in the enoxaparin group. The 95% confidence interval of absolute difference (7.3%) was very wide (0.1-14.5). In the case of PE, patients treated with fondaparinux had a lower recurrence rate (8.9%) compared to patients treated with UFH (17.2%). Bleeding and overall survival was similar in both groups and both trials [67]. A recent review of the Cochrane collaboration did not show any significant difference regarding efficacy and safety compared to LMWH/UFH [68]. Patients with active cancer were investigated in another retrospective analysis comparing fondaparinux, UFH and LMWH treatment for thromboembolism prevention in medical patients. This analysis is limited because only 9 patients were treated with fondaparinux; however, no thromboembolism events and no bleeding events were reported [69]. A high proportion of cancer patients (about 70%) were included in a phase III trial (PEGASUS) on the prevention of thromboembolism in major abdominal surgery with good efficacy and safety [15]. A recently published article reports on good efficacy and the safety of fondaparinux in a cohort of 231 patients in a real-life setting, including 23 with active malignancy [70].

In conclusion, the available data suggest that fondaparinux is of equivalent safety and efficacy (thrombembolic and bleeding complications respectively) in patients with cancer if compared with UFH/LMWH or with non-cancer patients. In our practice we use fondaparinux without any restrictions in cancer patients and use the same dosages and application intervals as in non-cancer patients.

Thrombophilic patients

Only few data exist on the efficacy and safety in patients with thrombophilia. The MATISSE-DVT study included 121 patients (5.5%) with a 'known prothrombotic state' and the MATISSE-PE study 99 patients (4.5%). The nature of the known prothrombotic state was not specified. The proportion of these patients was the same in the treatment and control groups (UFH/enoxaparin). A subgroup analysis is not available. A remarkably high proportion of thrombophilic patients were included in a prospective cohort study by Shetty et al. [40]. Over three months, 29 patients with symptomatic DVT or PE and unable to take warfarin and 13 patients (43%) with antiphospholipid syndrome (APS), heterozygote factor V Leiden mutation, hyperhomocysteinemia, protein C deficiency or prothrombin gene mutation received a therapeutic dose of fondaparinux. There were no recurrent thrombembolic complications and only one minor bleeding event during the treatment period [40].

There are several more case reports on the successful treatment with fondaparinux for high risk patients such as those with antiphospholipid antibody syndrome (APS), antithrombin deficiency et cetera [47,71–74].

In conclusion, fondaparinux appears to be safe and effective in thrombophilic patients. However, fondaparinux is not formally investigated in this patient group and the data are limited. In our practice, we use fondaparinux if LMWH and VKA are not appropriate and use the same dosages and application intervals as in non-thrombophilic patients.

Heparin-induced thrombocytopenia (HIT)

Can fondaparinux cause HIT and is fondaparinux capable of treating HIT efficiently? Fondaparinux is assumed to be less immunogenic regarding the development of platelet-activating antibodies recognizing complexes of platelet factor 4 (PF4) bound to heparin (or polysaccharides). Pentasaccharide fondaparinux is shorter than the 10 to 12 saccharides thought to be necessary for a strong immunologic reaction of HIT antibodies with PF4-saccharid complexes [75]. Furthermore, LMWH has already been shown to be less immunogenic than the larger UFH [76], and fondaparinux is much shorter than LMWH. Warkentin et al. tested sera of 2726 patients randomized to fondaparinux or enoxaparin in trials on the prevention of VTE in major orthopaedic surgery (PENTAMAKS, PENTATHLON). Antibodies against PF4/heparin were found in 71 of 2726 patients (3.2%) with a similar frequency in the fondaparinux and enoxaparin group. Antibodies reacted in vitro with comparable intensity against PF4/UFH and PF4/LMWH, but none of the sera reacted against PF4/fondaparinux. Thrombocytopenia or thrombosis did not develop [77]. This indicates that no relevant immunologic interaction occurred between PF4/heparin antibodies and PF4/fondaparinux. Development of antibodies against PF4/heparin was confirmed in another investigation by Pouplard [78]. In another, blinded, trial, Savi et. al. sent sera of 39 clinically and serologically confirmed HIT cases and 15 control cases to three specialized laboratories which carried out heparin-induced platelet agglutination assay (HIPA), serotonin release assay (SRA) and platelet aggregation assay. They found a high proportion of positive test results in HIT sera tested with UFH (66.7 – 91.7%) and a low proportion of positive test results in the control sera (0.0 – 9.1%). Tests with fondaparinux revealed no positive test results in the control cases (0%) and a low proportion in the HIT sera (0.0 – 5.9%). Furthermore, flow cytometry analysis did not reveal any sign of platelet activation in HIT sera tested with fondaparinux [79]. The authors conclude that fondaparinux is not able to activate platelets in presence of HIT sera. Several other investigations could not detect interaction between PF4/heparin antibodies and PF4/fondaparinux complexes in vitro, either [80–82]. Furthermore, over the course of large phase III clinical trials, there was no development of clinical HIT despite the overall total of 49673 patients and despite the high risk situation such as major orthopaedic surgery. These findings are confirmed by two case control studies, several case reports and one case series about the successful treatment of HIT with fondaparinux [66,72,83–90]. In contrast to these findings, there are few case reports on a possible association of fondaparinux with HIT; however, common to most of them is the possibility of other explanations [91,92]. In one case, the evidence of HIT is a drop in thrombocytopenia one day after a single application of fondaparinux in a patient with active metastasized cancer, whipple procedure and HIT with multiple thrombembolic complications. The investigators in this case did not repeat the blood count nor exclude other reasons for thrombocytopenia including in vitro platelet clumping nor demonstrate any cross reaction of the antibodies with fondaparinux [93]. However, a possible explanation of the thrombocytopenia could be delayed-onset HIT. There are two other reports with similar questions [94,95]. Warkentin reported on a patient with thrombocytopenia, DVT, bilateral adrenal infarction and positive result in the SRA in the course of bilateral knee replacement. The patient is reported not to have received any heparin, not even in central venous catheters. However, it was impossible to establish a cross reaction of antibodies with fondaparinux as the serotonin release was 90% without the addition of any drug and 96% in case of heparin [96]. It is reported elsewhere that SRA was negative in the presence of fondaparinux in this case [91]. There is one recently published case report in which the authors reported a cross-reaction of PF4/heparin antibodies with fondaparinux in a patient with HIT [97]. However, even if the above cases represent fondaparinux-associated HIT, the incidence would be very low, based on the total of treated patients in phase III trials <0.004 to 0.008 percent.

ACCP guidelines award a grade 2C recommendation for treatment with fondaparinux in case of HIT. However, fondaparinux is used for treatment of HIT and it is successful in the majority of patients [72,83–90].

In our practice, we use fondaparinux as therapy of first choice in case of HIT (7.5 mg OD s.c. until normalisation of platelet count and start VKA) due to the availability of and the high risk of adverse events with alternative anticoagulants. Although widely used, this approach is not recommended by the manufacturer or regulatory authorities [88].

Fondaparinux as a peri-interventional bridging agent

The data mentioned above suggest suitable characteristics of fondaparinux for use as a bridging agent in the peri-interventional and perioperative setting. However, the half-life of fondaparinux is longer than that of LMWH and safe timing of the last preoperative application is not established. Furthermore, only few case reports exist [22,73,98].

Based on the available data and our clinical experience we recommend to limit the use of fondaparinux to cases in which LMWH and UHF are contraindicated and no relevant renal impairment is present. Furthermore, we recommend using a wide application interval (24 hours preoperatively; 6 hours postoperatively) and measuring drug concentration before surgery.

Measuring drug concentration

Fondaparinux used in licensed indications does not require any measurement of drug concentration. If used in special situations, knowledge of plasma concentrations can be helpful for safety reasons. Different laboratory methods are proposed, with chromogenic assay of anti factor-Xa activity comparable to LMWH as the most common. Calibrated with fondaparinux, the assays produced reliable and reproducible results [99–102]. Other tests including clotting assays or thrombelastography proved either less reliable or less applicable [100,103].

In our clinical practice, we strongly recommend measuring drug concentration in patients with impaired renal function to detect possible accumulation. We strongly recommend measuring drug concentration in children to determine the dosage. Furthermore, we measure drug concentration before surgery or other interventions, in long term therapy, and in patients with a prophylactic dosage and very high body weight (>120 kg). Recommended time point for plasma sampling is two hours after application (peak plasma concentration) [9]. Target plasma concentrations are based on the levels measured in clinical studies. In patients treated with fondaparinux 2.5 mg (n = 333) plasma concentration ranged from 0.1 to 0.5 μg/ml [104]. In healthy young volunteers (n = 16) plasma concentration was 0.34 +/− 0.04 μg/ml after application of fondaparinux 2.5 mg [9]. In patients treated with therapeutic doses plasma concentration ranged from 0.6 to 1.5 μg/ml (numbers not reported) [100].

Management of bleeding complications

In case of critical bleeding, a fast reverse of the anticoagulant effect of a drug is desirable. It is shown that recombinant factor VIIa (rFVIIa) is capable of normalizing prolonged prothrombin and activated partial thromboplastin times as well as changes in thrombin generation as seen during treatment with fondaparinux (Table 6) [105,106]. It was shown that rFVIIa can correct the effects induced by fondaparinux, using rotational thrombelastometry [107] as well as a calibrated automated thrombogram (CAT) [108]. Furthermore, rFVIIa was able to improve the anticoagulant effect of fondaparinux in vitro as measured by thrombin generation test [109] and thrombelastography [103]. These investigations are confirmed by case reports on the successful use of rFVIIa in bleeding complications under treatment with fondaparinux [110,111]. In the reports mentioned above, the dosage of rFVIIa was 90 μg per kg body weight.

In an animal model, the application of prothrombin complex concentrate (PCC) was effective in reducing blood loss and reversing thrombelastometry changes during therapy with fondaparinux in a animal model [112]. Another recent investigation showed the antidote effect of a recombinant antithrombin both in-vitro and in an animal model [113]. However, there are no reports available regarding treatments of patients. Results of investigations with FEIBA (factor eight inhibitor bypassing activity) , fresh frozen plasma (FFP) or protamine sulphate were less promising [108,109], so rFVIIa remains the only substance recommended [114].

In our practice, we recommend the use of rFVIIa (90 μg per kg body weight) in case of critical bleeding. However, these cases are very rare.

Conclusion

Clinical trials regarding fondaparinux treatment in special situations are limited. Based on the data mentioned above, fondaparinux appears to be a reasonable option in special clinical situations, in

Table 6
Studies on management of bleeding complications.

Study/year	Clinical situation	Design	No of patients/ Age (years)	Intervention/ Treatment	Outcomes
					Efficacy/Safety
Bijsterveld NR 2002 [105]	Healthy male subjects	RCT	16 (18–45)	rFVIIa†	rFVIIa normalized prolonged aPTT, PT and decreased prothrombin activation fragments, and thrombin-generation time
Bordes J 2008 [111]	Traumatic subdural Haematoma during anticoagulation with fondaparinux 7.5 mg	Case report	1 (76)	rFVIIa†	Bleeding stopped
Huvers F 2005 [110]	Haemorrhagic shock in an orthopaedic patient	Case report	1 (79)	rFVIIa† + tranexamic acid	Bleeding stopped
Young G 2007 [103]	Young healthy volunteers	Ex vivo	Not specified	rFVIIa	rFVIIa reverses effects of fondaparinux on thrombelastography but not on anti-Xa
Lisman T 2003 [107]	Pooled plasma samples,young healthy volunteers	In vitro / ex vivo	-	rFVIIa	rFVIIa reverses effects of fondaparinux on clot formation and maximum clot lysis of thrombelastometrie
Godier A 2011 [112]	-	Animal model	-	PCC	PCC normalized increased blood loss and impaired thromboelastometry parameters after fondaparinux application
Bianchini EP 2011 [113]	Normal human plasma/ mice	In vitro/ animal model	-	Recombinant antithrombin variant	Recombinant antithrombin variant reverses effects of fondaparinux on anti-Xa
Gatt A 2008 [108]	Healthy subjects (plasma pool)	In vitro	-	rFVIIa, protamine sulphate, FEIBA, FFP	rVIIa reverses effects of fondaparinux on CAT*, but not on anti-Xa no effects of protamine sulphate, FEIBA, FFP
Desmurs-Clavel H 2009 [109]	PRP of healthy volunteers	In vitro	6	rFVIIa, FEIBA, PCC	Partial reversal of fondaparinux effect on thrombin generation after application of rVIIa and FEIBA.
Gerotziafas GT 2004 [106]	Normal human plasma	In vitro	-	rFVIIa	rFVIIa reverses partially inhibitory effect on thrombin generation

* CAT = calibrated automated thrombogram. † 90 μg kg^{-1}.

which anticoagulation therapy is necessary and heparin derivates or VKA are not appropriate. Data do not indicate any concerns regarding efficacy or safety in long-term therapy, in cases of mechanical heart valve, moderately impaired renal function, obesity, pregnancy and heparin-induced thrombocytopenia as well as in children. Monitoring with an anti-Xa based assay appears reliable and is recommended for safety reasons, at least in patients with impaired renal function and in children. In case of a rare bleeding event rFVIIa is an option. Although new oral anticoagulants have been, and will be, approved for various indications; it will still take many years until data for special situations is available. At least until then, fondaparinux appears to be a reasonable option in these special situations. However, the use of fondaparinux in all of the situations mentioned above has to be approved by more formal investigations.

Financial support

None.

Conflict of interest statement

Dr. Wuillemin reports having received lecture honoraria and consulting fees from Bayer, GlaxoSmithKline, Pfizer and Sanofi-Aventis. Dr. Michael Haslauer, was invited by the other authors to provide support in collecting scientific papers and also to scientifically review the article. The authors received no financial contribution from GSK for this article and the conclusions do not represent the views of GSK. There is no other potential conflict of interest relevant to this article.

Acknowledgments

No financial assistance was received.

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