

Fondaparinux Sodium: Recent Advances in the Management of Thrombosis

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Rupert M. Bauersachs, MD^{1,2} 

Abstract

Fondaparinux sodium is a chemically synthesized selective factor Xa inhibitor approved for the prevention and treatment of venous thromboembolic events, that is, deep vein thrombosis, pulmonary embolism, and superficial vein thrombosis, in acutely ill (including those affected by COVID-19 or cancer patients) and those undergoing surgeries. Since its approval in 2002, the efficacy and safety of fondaparinux is well demonstrated by many clinical studies, establishing the value of fondaparinux in clinical practice. Some of the advantages with fondaparinux are its chemical nature of synthesis, minimal risk of contamination, 100% absolute bioavailability subcutaneously, instant onset of action, a long half-life, direct renal excretion, fewer adverse reactions when compared with direct oral anticoagulants, and being an ideal alternative in conditions where oral anticoagulants are not approved for use or in patients intolerant to low molecular weight heparins (LMWH). In the last decade, the real-world use of fondaparinux has been explored in other conditions such as acute coronary syndromes, bariatric surgery, in patients developing vaccine-induced immune thrombotic thrombocytopenia (VITT) and in pregnant women with heparin-induced thrombocytopenia (HIT), or those intolerant to LMWH. The emerging data from these studies have culminated in recent updates in the guidelines that recommend the use of fondaparinux under various conditions. This paper aims to review the recent data and the subsequent updates in the recommendations of various guidelines on the use of fondaparinux sodium.

Keywords

fondaparinux sodium, anticoagulant, venous thromboembolic events, deep vein thrombosis, pulmonary embolism, superficial vein thrombosis, acute coronary syndromes, bariatric surgery, pregnancy

Introduction

Fondaparinux sodium (Arixtra[®]) is the first synthetic pentasaccharide and a selective inhibitor of factor Xa approved for the prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). It is widely prescribed for the prevention of venous thromboembolic events (VTE) in post-operative adults undergoing major orthopedic surgery of the hip and knee and abdominal surgery. Fondaparinux sodium is also approved for use in patients at a high risk for VTE who are immobilized due to acute illness. It is approved and used for the treatment of acute symptomatic spontaneous superficial vein thrombosis (SVT) of the lower limbs without concomitant DVT.^{1,2} Fondaparinux is also used for the treatment of acute coronary syndromes such as unstable angina or myocardial infarction with or without ST-segment elevation.

One of the main advantages of fondaparinux is that it is synthesized chemically, while heparins and heparinoids are prepared from animal extracts. This chemical nature of the synthesis ensures no general supply issues and minimal risk of contamination, and in theory, does not cause heparin-induced thrombocytopenia (HIT).³ Fondaparinux has 100%

absolute bioavailability subcutaneously (SC), instant onset of action, a long half-life (terminal half-life of 17–21 hours), direct renal excretion, and fewer adverse reactions when compared with direct oral anticoagulants.^{4–6} The efficacy and safety of fondaparinux in the prevention of VTE in lower extremities during major orthopedic surgeries and in high-risk abdominal surgery has been demonstrated in many clinical studies and it has been found to be superior or non-inferior to other antithrombotic agents.^{7–13} For the past 2 decades, fondaparinux has been one of the mainstays for VTE prevention in acutely ill adult patients.¹⁴ There are reports suggesting its off-label use under conditions such as HIT in pregnant women.¹⁵

¹ Department of Angiology, Cardioangiologic Center Bethanien, Frankfurt, Germany

² Center for Vascular Research, Munich, Germany

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Corresponding Author:

Rupert M. Bauersachs, Department of Angiology, Cardioangiologic Center Bethanien CCB, Im Prüfling 23, 60389 Frankfurt, Germany.
Email: bauersachs@em.uni-frankfurt.de



Fondaparinux is also considered for bridging therapy to switch to oral anticoagulants in perioperative anticoagulation management.¹⁶

Emerging data elaborate the advances in the use of fondaparinux, thereby warranting the need to revisit and update the recommendations of various guidelines on the management of thrombosis under different medical conditions and in very obese patients.¹⁷ This article aims to review and present recent data and findings (in the past 5 years) pertaining to the use of fondaparinux sodium as well as recent updates in the recommendations of various guidelines. This would pave the way for generating evidence-based recommendations and facilitate informed clinical decisions.

Fondaparinux—Clinical Development and Previous Studies

Fondaparinux was approved by the United States Food and Drug Administration in the year 2001 and by the European Medicines Agency in 2002 for the post-operative prophylaxis of VTE in patients undergoing hip fracture, hip replacement, and knee replacement surgeries.^{18,19}

In 2001, fondaparinux sodium was recognized as a new class of anticoagulant that selectively targets factor Xa.²⁰ Its pharmacokinetic profile (100% bioavailability, longer half-life, and rapid onset of action), ease of dosing (once daily administration), and acceptable tolerability (not affecting prothrombin/activated partial thromboplastin time and platelet function or aggregation, and no in vitro cross-reactivity to heparin antibodies) led to fondaparinux being considered an ideal antithrombotic agent²⁰ (Figure 1).

Many studies have demonstrated the efficacy and safety of fondaparinux in preventing VTE across a range of medical and surgical settings, for example, major orthopedic surgeries involving lower limbs, abdominal surgeries, and for the treatment of DVT and PE.²¹

Fondaparinux was as effective and as safe as unfractionated heparin (UFH) in the initial treatment of hemodynamically stable patients with PE.²² In the initial treatment of patients with symptomatic DVT, fondaparinux was non-inferior to enoxaparin, and both were well-tolerated.²³⁻²⁵

A significant reduction in mortality and reinfarction was observed with fondaparinux (2.5 mg once daily SC) in patients with acute ST-elevation myocardial infarction (STEMI), particularly those not undergoing primary percutaneous coronary intervention without increasing bleeding and strokes.²⁶ In patients with non-STEMI, fondaparinux (2.5 mg once daily SC) was comparable to enoxaparin (1 mg/kg twice daily; 5.8% vs 5.7%; hazard ratio in the fondaparinux group, 1.01; 95% confidence interval [CI], 0.90–1.13) in reducing the risk of ischemic events (death, myocardial infarction, and refractory ischemia) in patients with acute coronary syndromes at Day 9. Fondaparinux substantially reduced major bleeding in this medical condition, which frequently leads to thrombotic complications and thereby translated to improving long-term mortality and morbidity.^{27,28}

The efficacy and safety of fondaparinux (2.5 mg once daily SC [vs placebo]) in patients with acute, isolated symptomatic SVT of the legs were evaluated in the CALISTO study, which was the first large randomized controlled study with clinical endpoints. Death from any cause or symptomatic PE, symptomatic DVT, or symptomatic extension to the saphenofemoral junction, or symptomatic recurrence of SVT at Day 47 was the primary efficacy outcome. A significant reduction in the incidence of each component of the primary efficacy outcome was observed in the fondaparinux group when compared with the placebo group, except for the outcome of death (0.1% in both groups). The rate of PE or DVT was 85% lower for fondaparinux versus placebo (0.2% vs 1.3%; 95% CI, 50–95; $P < .001$).²⁹

Two observational studies, namely POST (2010) and OPTIMEV (2011), included French patients with isolated SVT³⁰⁻³² and assessed the association between SVT, PE, and DVT. In spite of a high rate of initial anticoagulation, patients with SVT incur a significant risk of recurrent VTE and recurrent or extended SVT at 3 months. Hence, a venous ultrasound examination could be helpful in identifying anticoagulation in all patients with suspected SVT. The OPTIMEV study revealed that while PE with DVT has a substantial 3-month mortality, no association was observed with a higher 3-month mortality in PE without DVT. Hence, while diagnosing PE, it is important to consider the associated DVT to optimize appropriate management strategies.^{33,34}

Fondaparinux will require close monitoring of the anti Xa level when used concomitantly with drugs that affect hemostasis, and will be used with caution in patient weighing <50 kg or with a dose reduced in case of creatinine clearance between 30–50 mL/min.³⁵ As with most of the other anticoagulants cleared by the kidney, fondaparinux must not be used in patients with severe renal impairment (i.e., with a creatinine clearance <30 mL/min).^{35,36} Use in neurosurgery or spinal procedures should be avoided.

Along with the results from the randomized controlled trials (RCTs), the efficacy and safety of fondaparinux was also assessed in real-world studies. RCTs are designed carefully to provide control of bias, meticulous data collection and selection of patient population, and adherence to treatment protocol in order to reduce variation which could influence the study results. However, they are limited in terms of the patient population enrolled in the study, who match the inclusion/exclusion criteria and may not be fully representative of the patients observed in routine clinical practice. Hence, real-world studies are important to evaluate the efficacy and safety of the drug among diverse patient populations with varying health status and comorbidities and inform outcomes with long-term therapy. Thus, the results of both RCTs and real-world studies complement each other and help the clinician in making a treatment decision for the patient.^{37,38}

Recent Advances in the Use of Fondaparinux Sodium

This section describes the recent advances in the use of fondaparinux (both in approved indications and off-label use) in the

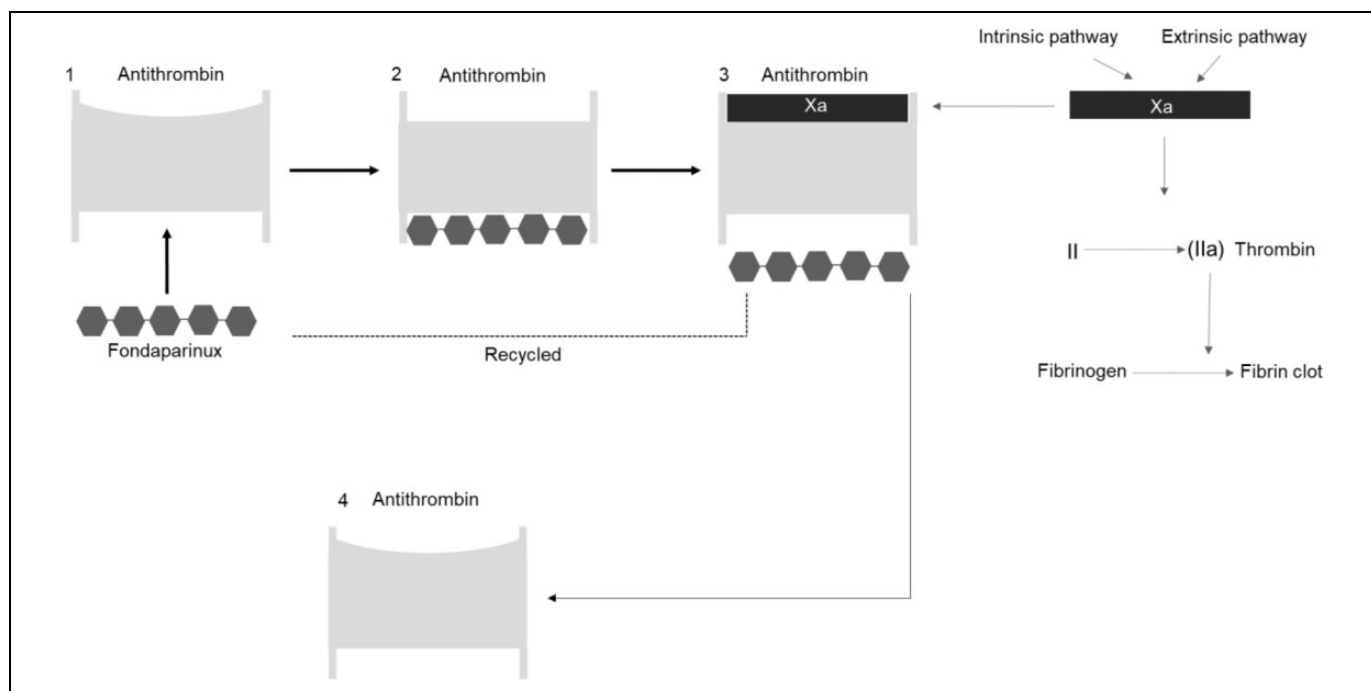


Figure 1. Mechanism of the action of fondaparinux. Factor Xa is located at the junction of both extrinsic and intrinsic pathway. 1. Binding of fondaparinux to antithrombin. 2. After binding to fondaparinux, a conformational change occurs in antithrombin. 3. When bound to fondaparinux, antithrombin selectively and rapidly inhibits Factor Xa, thereby blocking thrombin generation and fibrin formation. 4. Fondaparinux is released to interact with other antithrombins. Adapted from Turpie AG. Fondaparinux: a Factor Xa inhibitor for antithrombotic therapy. *Expert Opin Pharmacother.* 2004;5(6):1373-1384.

past 5 years, as reported in the literature. In the last decade, the real-world use of fondaparinux has been explored under conditions such as acute coronary syndromes, bariatric surgery, in patients developing HIT-like syndromes post vaccination and in pregnant women with HIT and the results obtained in the past 5 years are summarized in this section³⁹⁻⁴² (Table 1).

Acute Coronary Syndromes

The prospective data of non-ST-elevation acute coronary syndrome patients who received fondaparinux or enoxaparin from February 2015 to December 2017 were analyzed from the multicenter ARIAM Andalucia registry. The composites of clinically relevant bleedings and major adverse cardiovascular events were assessed for 30 days using survival models within a competing risks framework including site-specific random effects. A net clinical benefit was seen in the results from the multivariate analysis which was in favor of fondaparinux versus enoxaparin (sub hazard ratio [SHR] 0.59; 95% CI, 0.37–0.92), with a reduction in bleeding (SHR 0.57; 95% CI, 0.37–0.89). There was a significant 43% reduction in the adjusted risk of bleeding in the fondaparinux group with fewer clinically relevant major and non-major “actionable” bleeding events versus the enoxaparin group.⁴³ Furthermore, greater reductions in bleeding were observed in the exploratory analyses with fondaparinux among patients undergoing a transradial approach. The study demonstrated a significant interaction between treatment and vascular access on the multiplicative

scale ($P_{\text{interaction}} = .0056$), but not on an additive scale ($P = .457$).⁴³ Another inference is that considering the current aggressive antithrombotic treatment, higher doses of enoxaparin increase bleeding while fondaparinux 2.5 mg dose may provide a sweet spot of anticoagulant activity in such situations.

Bariatric Surgery

A retrospective cohort study (2010–2019) assessed the thrombotic and hemorrhagic risk in bariatric surgery with multimodal rehabilitation programs in vertical gastrectomy or gastric bypass surgeries (N = 675). Patients with similar baseline characteristics were treated with fondaparinux (fixed dose of 2.5 mg/day, n = 354) or enoxaparin (single daily dose adjusted to BMI: 40 mg/day for a BMI of 35–40 and 60 mg/day for a BMI 40–60, n = 321). The results showed no DVT or PE and 32 incidences of hemorrhage (4.7%), 15 in the fondaparinux group and 17 in the enoxaparin group ($P = .588$).⁴⁴ The reported rates of VTE, following bariatric surgery are generally in the range of 0.3%–2.2%. In the bariatric surgery population, PE is a frequent cause of postoperative mortality and is a common finding at autopsy.⁴⁷

Steele et al compared the prophylactic effect of fondaparinux (5 mg once daily) versus enoxaparin (40 mg twice daily) for routine VTE prophylaxis in patients undergoing bariatric surgery. This dosage of fondaparinux was higher than that proposed in the product information leaflet (2.5 mg); studies have shown that with a 2.5 mg dose, 53% of morbidly obese

Table I. Recent Advances in the Use of Fondaparinux Sodium.

Study (study period)	Study design	N	Fondaparinux	Comparator	Main results (fondaparinux vs comparator unless specified)
Acute coronary syndrome					
Almendro-Delia et al (2015–2017) ⁴³	Prospective multicenter registry	2094	n = 370	Enoxaparin (n = 1724)	Net adverse clinical event at 30 days as per multivariate analysis: SHR = 0.59; 95% CI, 0.37–0.92; P = .022 Clinically relevant bleeding: SHR = 0.57; 95% CI, 0.37–0.89; P < .0001
Bariatric surgery					
Calzada et al (2010–2019) ⁴⁴	Retrospective cohort study	675	n = 354	Enoxaparin (n = 321)	DVT or PE hemorrhage (n): 15 vs 17; P = .588
Steele et al (2010–2013) ⁴⁵	Randomized double blind study	198	n = 100	Enoxaparin (n = 98)	Antifactor Xa levels more common with fondaparinux (n [%]), 49 [74.2] vs 23 [32.4]
Superficial venous thrombosis					
Blin et al (2014–2015) ³²	Observational, cohort study	978	n = 725	LMWH/UFH: n = 127 Other anticoagulants: n = 28 Untreated: n = 88	Number of VTE events fondaparinux vs LMWH/UFH, n (%), [95% CI] group: Study period (3 months): 24 (3.3), [2.1 to 4.8] vs 7 (5.5), [2.3 to 11.0] During treatment period: 6 (0.8), [0.3 to 1.8] vs 3 (2.4), [0.5 to 6.7] Post treatment period: 18 (2.4), [1.5 to 3.8] vs 4 (3.1), [0.9 to 7.9]
Bauersachs et al. (2016–2019) ³³	Prospective observational study	1150	n = 756	LMWH: n = 261 UFH/VKA/ DOAC: n = 59 Untreated: n = 74	Incidence of symptomatic VTE; DVT, PE, and recurrent or extending SVT at 3 months, n (%): Fondaparinux: 33 (4.4) LMWH: 25 (9.6) UFH/VKA/DOAC: 5 (8.5) Untreated: 4 (5.4)
Use in pregnant women					
Dempfle et al (2004–2010) ⁴⁶	Retrospective, multicenter, cohort study	120	n = 118	LMWH/UFH prior to fondaparinux, n = 88	During fondaparinux treatment, 7 bleeding events were reported in 5 patients (4.2%). No VTE events or increased liver enzymes were reported. Fondaparinux was effective and well-tolerated.

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; N, total number of participants; n, number of participants in the specified subgroup; PE, pulmonary embolism; SHR, sub hazard ratio; SVT, superficial venous thrombosis; UFH, unfractionated heparin; VKA, Vitamin K antagonist; VTE, venous thromboembolism.

patients in the study population reached the target antifactor Xa levels, while with a 5 mg dose, the morbidly obese patients achieved target antifactor Xa concentrations more consistently. Fondaparinux was more commonly associated with adequate antifactor Xa levels (74.2%) than with enoxaparin (32.4%). However, both regimens were equally effective in reducing the risk of DVT.⁴⁵ A recent statement by the International Society on Thrombosis Scientific and Standardization Committee suggested to use a parenteral anticoagulant such as LMWH or fondaparinux in patients undergoing bariatric surgery and to prescribe direct oral anticoagulants in the post-acute phase following bariatric surgery.¹⁷ Since novel oral anticoagulants cannot be used in this acute setting, fondaparinux provides a safer and more consistent anticoagulant activity in such challenging high-risk patients.

Superficial Vein Thrombosis

The PERSEUS study, which was a post-marketing French cohort study, was conducted in adults with acute symptomatic spontaneous SVT of the lower limbs without concomitant DVT who received anti-thrombotic agents (fondaparinux, LMWH/UFH, aspirin, clopidogrel, rivaroxaban, or vitamin-K antagonist) and who received no treatment other than for SVT. This study was designed to include 1,000 adults (recruited prospectively and consecutively by physicians [up to 10 adults per health care practitioner over a 6-month period]) with a diagnosis of acute symptomatic spontaneous isolated SVT of the lower limbs who were followed up for 3 months. The main outcomes studied were symptomatic venous thromboembolism (VTE: DVT, PE, and SVT extension or recurrence) and major

bleeding through review of compression ultrasonography, hospital discharge summary, and other pertinent medical reports. The overall incidence of VTE events during the treatment and post-treatment period of the PERSEUS study was numerically lower with fondaparinux versus the LMWH/UFH group (3.3% [95% CI = 2.1–4.8] vs 5.5% [95% CI = 2.3–11.0], respectively). The results showed that the overall rate of symptomatic recurrent VTE was low with fondaparinux treatment. During the treatment period, the incidence of VTE was lower with fondaparinux versus LMWH/UFH (0.8% vs 2.4%). The incidence of VTE was 2.4% and 3.1% for patients during the post-treatment period, initially treated with fondaparinux and LMWH/UFH, respectively.³² These results demonstrated that fondaparinux (prescribed in 75% of the patients) was the first choice of vascular physicians in France for the treatment of SVT.⁴⁸ These real-world clinical practice outcomes confirm the benefits of fondaparinux, as was shown in the CALISTO study.²⁹

Another prospective, multicenter, observational study, the Investigating SIGNificant Health TrendS in the management of Superficial Vein Thrombosis (INSIGHTS-SVT), was conducted in Germany to collect representative data on patient characteristics, diagnosis, management, and outcomes of isolated SVT under real-world conditions.³³ A composite of symptomatic DVT, PE, and extension or recurrence of SVT at 3 months was the primary outcome assessed in the study. Clinically relevant bleeding was the primary safety outcome. After adjusting for the propensity score and duration of drug treatment, there was a 5.2% absolute reduction in the probability of the primary VTE outcome in patients treated with fondaparinux versus those treated with LMWH (4.4% vs 9.6%; 95% CI, 0.30–0.88; hazard ratio [HR] 0.51; $P = .017$). Lower rates of primary VTE outcome were observed in patients treated with fondaparinux, and this association was only significant in patients treated for >38 days (3.7% vs 10.5%; HR = 0.37, $P = .044$). These results confirmed the beneficial effect of fondaparinux versus LMWH in isolated SVT under clinical practice conditions, which is in line with previous controlled and observational studies.³³

The Surprise study was a prospective, randomized, open-label, blinded adjudication trial conducted in patients with superficial phlebitis treated for 45 days with rivaroxaban versus fondaparinux which aimed to demonstrate non-inferiority of rivaroxaban with fondaparinux in preventing the combined efficacy endpoint of thrombus progression, SVT recurrence, DVT, PE, and death. This study was conducted after the placebo-controlled CALISTO trial and allowed patients with a high risk for thromboembolic complications to be included. Though the study met the noninferiority criterion, the clinically relevant non-major bleeding and more severe treatment-emergent adverse events were numerically higher in the rivaroxaban group than in the fondaparinux group. Hence, the study results revealed that patients with SVT at high-risk require at least 45 days anticoagulation and a prophylactic dose of 2.5 mg of

fondaparinux (over rivaroxaban) was sufficient for the high-risk patients with a low rate of recurrence during treatment.⁴⁹

Pregnancy

During pregnancy, women at risk of VTE who receive LMWH can develop HIT. LMWH is the preferred option for the prevention and treatment of VTE during pregnancy, as it does not cross the placenta and is non-teratogenic in nature. The approved treatment options argatroban and danaparoid are expensive and also associated with some limitations. Argatroban is correlated with an increased risk of bleeding and requires monitoring during intravenous infusion. Danaparoid is administered intravenously (IV) or through multiple SC injections and is not available in some countries. In such scenarios, where approved treatments cannot be used, fondaparinux is considered as the next choice.⁵⁰ Although there are reports of its off-label use in HIT, no clinical study has been conducted yet; hence, there is no clear posology.

To expand the evidence available in literature for this condition, a systematic literature study reported that fondaparinux is an effective and safe anticoagulant for the treatment of acute HIT despite the absence of randomized trials. However, it should be used cautiously in patients with renal insufficiency.⁵¹

Dempfle et al conducted a retrospective, multicenter, cohort study in Germany including women who received fondaparinux pre-, peri-, and/or post-partum for ≥ 7 days for prophylaxis/VTE. All participants received LMWH as the first-line therapy and unfractionated heparin. The treatment was changed to fondaparinux, owing to heparin allergy (41.7%) or HIT (10.0%). During the treatment, there were no observations of VTE events or increased liver enzymes. The study results showed that fondaparinux was well-tolerated by those pregnant women.⁴⁶ Fondaparinux is an available treatment option in the pregnant women when LMWHs are contraindicated or not well tolerated.

Recent Recommendations From Guidelines

Fondaparinux is still recommended as one of the treatment options for the prevention and treatment of VTE by various guidelines in acutely ill (including those affected by COVID-19), cancer patients and those undergoing surgeries. The emerging data have culminated in recent updates in the guidelines that recommend the use of fondaparinux under various conditions (Table 2).

Recently, there were reports of thrombotic events associated with the administration of COVID-19 vaccines, a condition called vaccine-induced immune thrombotic thrombocytopenia (VITT). Non-heparin anticoagulants including direct oral anticoagulants, direct thrombin inhibitors, and fondaparinux are recommended for the treatment of VITT.⁵⁹

Table 2. Recommendations From Various Recent Guidelines for the Use of Fondaparinux.

Guideline	Recommendations for use of fondaparinux
American Society of Hematology (ASH) guideline panel (2018)	For breastfeeding women who have an indication for anticoagulation, the ASH guideline panel recommends using UFH, LMWH, warfarin, acenocoumarol, fondaparinux, or danaparoid as safe options. ⁵²
American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients	UFH, LMWH, or fondaparinux to be used rather than no parenteral anticoagulant in acutely ill medical patients and in patients with stroke requiring VTE prophylaxis. Among these anticoagulants, the panel suggests using LMWH or fondaparinux rather than UFH. ⁵³
American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients	LMWH or fondaparinux to be used for thromboprophylaxis rather than UFH for patients with cancer undergoing a surgical procedure. ⁵⁴
European Society of Cardiology (2020)	In cases of medical treatment or logistical constraints for transferring the patient to percutaneous coronary intervention (PCI) within the required time frame, fondaparinux is recommended, and, in such cases, a single bolus of UFH is recommended at the time of PCI. ⁵⁵
European Society for Vascular Surgery Clinical Practice Guidelines on the Management of Venous Thrombosis (2021)	Fondaparinux 2.5 mg once daily to be used as the first option for patients with lower limb SVT ≥ 3 cm away from the junction with deep veins and extending ≥ 5 cm in length. ⁵⁶
International Society on Thrombosis Scientific and Standardization Subcommittee (2021)	Fondaparinux is an option for obese patients for the treatment of VTE. ¹⁷
NCCN for cancer-associated VTE disease clinical practice guidelines (2021)	In surgical oncology patients, an SC dose of fondaparinux 2.5 mg daily to be used no earlier than 6–8 h post-operation as a VTE prophylaxis option. ⁵⁷ In hospitalized medical oncology patients, fondaparinux is to be avoided in patients weighing < 50 kg and to be used cautiously if creatinine clearance levels is in the range of 30–49 mL/min. ⁵⁷
World Health Organization's report (2021)	Fondaparinux 2.5 mg SC injection to be used every 24 h among other options as thromboprophylaxis in patients with COVID-19 infection. ⁵⁸

Abbreviations: ASH, American Society of Hematology; COVID, corona virus disease; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; SC, subcutaneous; SVT, superficial venous thrombosis; UFH, unfractionated heparin; VTE, venous thromboembolism.

Future Directions

Fondaparinux has been approved for the prevention and treatment of VTE in 2001 and is being recommended for use by various guidelines. The evidence and scientific knowledge available in the literature demonstrates the efficacy and safety of fondaparinux sodium. Future research can be aimed at generating additional real-world data on the use of fondaparinux in bariatric surgery. Further studies may provide more insights regarding the use of fondaparinux in HIT, particularly in pregnant women, and it might rationalize the current off-label use to being approved for this indication. Apart from the evidence demonstrated by the clinical trials, the prescribing decisions are also influenced by other factors such as clinical experience, positive outcomes, patient demographics, guideline recommendations, health needs, preferences, cost, treatment access, and insurance coverage (more common in North America than in Europe).⁶⁰ Fondaparinux is cost-effective compared with LMWH by preventing the incidence of VTE, especially when being considered for long-term prophylaxis,^{61–63} which supports its wider patient access and hence good compliance.⁶⁴ Real-world evidence studies in the future should aim to include long-term efficacy, safety, cost-effectiveness, and compliance to generate evidence that would be helpful in clinical- and policy-decision making.

Conclusions

Fondaparinux is a unique synthetic injectable pentasaccharide, whose efficacy as an ideal anti-thrombotic agent has been demonstrated by many studies. With its well-established efficacy and safety, recent updates in guidelines recommend its use in medical and surgical settings to prevent and treat VTE. Recent real-world data of fondaparinux support the results observed in the clinical trials. Fondaparinux plays a critical role in the prevention of VTE in acutely ill patients including COVID-19 patients. Reports suggest that fondaparinux can be a therapeutic option in pregnant women with HIT or those not tolerating LMWH. However, further research is warranted to provide more insights on the benefits that fondaparinux could offer in these settings.

Authors' Note

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Author Contributions

The author contributed to data interpretation, development, and review of this manuscript. The author confirms that he has read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The sponsor also provided a formal review of this manuscript. The author meets the ICMJE criteria and had access to the study data, made the final decision about where to publish these data and approved submission to this journal.


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ORCID iD

Rupert M. Bauersachs  <https://orcid.org/0000-0001-6192-1741>

References

- Summary of product characteristics. 2002. Accessed December 14, 2022. https://www.ema.europa.eu/en/documents/product-information/arixtra-epar-product-information_en.pdf
- Bauersachs RM. Fondaparinux: an update on new study results. *Eur J Clin Invest*. 2005;35(suppl 1):27-32.
- Bauer KA, Hawkins DW, Peters PC, et al. Fondaparinux, a synthetic pentasaccharide: the first in a new class of antithrombotic agents—the selective factor Xa inhibitors. *Cardiovasc Drug Rev*. 2002;20(1):37-52. doi:10.1111/j.1527-3466.2002.tb00081.x
- Ding Y, Vara Prasad CV, Wang B. Advances in chemical synthesis of fondaparinux. *J Chem*. 2019;1-17. doi:10.1155/2019/9545297
- Zhang Y, Zhang M, Tan L, Pan N, Zhang L. The clinical use of fondaparinux: a synthetic heparin pentasaccharide. *Prog Mol Biol Transl Sci*. 2019;163:41-53. doi:10.1016/bs.pmbts.2019.02.004
- Donat F, Duret JP, Santoni A, et al. The pharmacokinetics of fondaparinux sodium in healthy volunteers. *Clin Pharmacokinet*. 2002;41(suppl 2):1-9. doi:10.2165/00003088-200241002-00001
- Turpie AGG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the prevention of deep vein thrombosis after total hip replacement. *N Engl J Med*. 2001;344(9):619-625.
- Bauer KA, Eriksson BI, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med*. 2001;345(18):1305-1310.
- Eriksson BI, Bauer KA, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip fracture surgery. *N Engl J Med*. 2001;345(18):1298-1304.
- Lassen MR, Bauer KA, Eriksson BI, Turpie AGG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip replacement surgery: a randomised double-blind comparison. *Lancet*. 2002;359(9319):1715-1720.
- Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet*. 2002;359(9319):1721-1726.
- Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux versus enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery. A meta-analysis of four randomized studies. *Arch Intern Med*. 2002;162(16):1833-1840.
- Eriksson BI, Lassen MR. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery. A multicenter, randomized, placebo controlled, double-blind study. *Arch Intern Med*. 2003;163(11):1337-1342.
- Haas S. The role of low molecular weight heparins for venous thromboembolism prevention in medical patients—what is new in 2019? *Hamostaseologie*. 2019;39(1):62-66. doi:10.1055/s-0038-1677522
- Schindewolf M, Steindl J, Beyer-Westendorf J, et al. Frequent off-label use of fondaparinux in patients with suspected acute heparin-induced thrombocytopenia (HIT)—findings from the GerHIT Multi-Centre Registry Study. *Thromb Res*. 2014;134(1):29-35.
- Zhang F, Zhao D, Peng X, et al. Clinical outcomes of bridging therapy with fondaparinux versus low-molecular-weight heparin in patients undergoing atrial fibrillation ablation. *Nan Fang Yi Ke Da Xue Bao*. 2014;34(4):448-452.
- Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *J Thromb Haemost*. 2021;19(8):1874-1882. doi:10.1111/jth.15358
- Food and Drug Administration. 2001. Accessed December 14, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-345_Arixtra_Approv.pdf
- European Medicines Agency. 2010. Accessed December 14, 2022. https://www.ema.europa.eu/en/documents/overview/arixtra-epar-summary-public_en.pdf
- Bauer KA. Fondaparinux sodium: a selective inhibitor of factor Xa. *Am J Health Syst Pharm*. 2001;58(suppl 2):S14-S17. doi:10.1093/ajhp/58.suppl_2.S14
- Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med*. 2002;162(16):1833-1840. doi:10.1001/archinte.162.16.1833
- Büller HR, Davidson BL, Decousus H, et al; Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N*

- Engl J Med.* 2003;349(18):1695-1702. doi:10.1056/NEJMoa035451. Erratum in: *N Engl J Med.* 2004;350(4):423.
23. Büller HR, Davidson BL, Decousus H, et al; Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med.* 2004;140(11):867-873. doi:10.7326/0003-4819-140-11-200406010-00007
 24. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M; PEGASUS Investigators. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *Br J Surg.* 2005;92(10):1212-1220. doi:10.1002/bjs.5154
 25. Cohen AT, Davidson BL, Gallus AS, et al; ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ.* 2006;332(7537):325-329. doi:10.1136/bmj.38733.466748.7C
 26. Yusuf S, Mehta SR, Chrolavicius S, et al; OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA.* 2006;295(13):1519-1530. doi:10.1001/jama.295.13.joc60038
 27. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med.* 2006;354(14):1464-1476. doi:10.1056/NEJMoa055443
 28. Budaj A, Eikelboom JW, Mehta SR, et al; OASIS 5 Investigators. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. *Eur Heart J.* 2009;30(6):655-661.
 29. Decousus H, Prandoni P, Mismetti P, et al; CALISTO Study Group. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med.* 2010;363(13):1222-1232. doi:10.1056/NEJMoa0912072
 30. Decousus H, Quéré I, Presles E, et al; POST (Prospective Observational Superficial Thrombophlebitis) Study Group. Superficial venous thrombosis and venous thromboembolism: a large, prospective epidemiologic study. *Ann Intern Med.* 2010;152(4):218-224. doi:10.7326/0003-4819-152-4-201002160-00006
 31. Galanaud JP, Bosson JL, Quere I. Risk factors and early outcomes of patients with symptomatic distal vs. proximal deep-vein thrombosis. *Curr Opin Pulm Med.* 2011;17(5):387.e91.
 32. Blin P, Sevestre MA, Pouchain D, Gillet JL. Management and 3-month outcomes of isolated superficial vein thrombosis of the lower limb: a real-world cohort study. *Thromb Res.* 2017;157:117-119. doi:10.1016/j.thromres.2017.07.009
 33. Bauersachs R, Gerlach HE, Heinken A, et al. Management and outcomes of patients with isolated superficial vein thrombosis under real life conditions (INSIGHTS-SVT). *Eur J Vasc Endovasc Surg.* 2021;62(2):241-249. doi:10.1016/j.ejvs.2021.04.015
 34. Sevestre MA, Quashié C, Genty C, et al; Optimev Study Investigators. Clinical presentation and mortality in pulmonary embolism: the Optimev study. *J Mal Vasc.* 2010;35(4):242-249. doi:10.1016/j.jmv.2010.05.004
 35. Sindhu S, Silberstein P. *Vascular Medicine: A Companion to Braunwald's Heart Disease.* 2nd ed. 2013. Accessed December 14, 2022. <https://www.sciencedirect.com/topics/medicine-and-dentistry/fondaparinux>
 36. Porto GBF, Jeffrey Wessell DO, Alvarado A, Arnold PM, Buchholz AL. Anticoagulation and spine surgery. *Global Spine J.* 2020;10(1 suppl):53S-64S. doi:10.1177/2192568219852051 PMID: 31934522; PMCID: PMC6947673
 37. Kim HS, Lee S, Kim JH. Real-world evidence versus randomized controlled trial: clinical research based on electronic medical records. *J Korean Med Sci.* 2018;33(34):e213.
 38. Villines TC, Cziraky MJ, Amin AN. Awareness, knowledge, and utility of RCT data vs RWE: results from a survey of US cardiologists: real-world evidence in clinical decision making. *Clin Med Insights Cardiol.* 2020;14. doi:10.1177/1179546820953410
 39. Islam A, Bashir MS, Joyce K, et al. An update on COVID-19 vaccine induced thrombotic thrombocytopenia syndrome and some management recommendations. *Molecules.* 2021;26(16):5004. doi:10.3390/molecules26165004
 40. Nazy I, Sachs UJ, Arnold DM, et al. Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: communication from the ISTH SSC Subcommittee on Platelet Immunology. *J Thromb Haemost.* 2021;19:1585-1588. doi:10.1111/jth.15341
 41. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med.* 2021;384(22):2092-2101.
 42. Lavin M, Elder PT, O'Keeffe D, et al. Vaccine-induced immune thrombotic thrombocytopenia (VITT)—a novel clinicopathological entity with heterogeneous clinical presentations. *Br J Haematol.* 2021;195(1):76-84. doi:10.1111/bjh.17613
 43. Almendro-Delia M, Izquierdo-Bajo Á, Madrona-Jiménez L, et al. Fondaparinux versus enoxaparin in the contemporary management of non-ST-elevation acute coronary syndromes. Insights from a multicenter registry. *Int J Cardiol.* 2021;332:29-34. doi:10.1016/j.ijcard.2021.02.081
 44. Calzada M, Matías A, de la Madriz A, et al. Thrombotic and hemorrhagic risk in bariatric surgery with multimodal rehabilitation programs comparing 2 reduced guidelines for pharmacological prophylaxis. *Cir Esp (Engl Ed).* 2022;100(1):33-38. doi:10.1016/j.cireng.2021.03.020
 45. Steele KE, Canner J, Prokopowicz G, et al. The EFFORT trial: preoperative enoxaparin versus postoperative fondaparinux for thromboprophylaxis in bariatric surgical patients: a randomized double-blind pilot trial. *Surg Obes Relat Dis.* 2015;11(3):672-683. doi:10.1016/j.soard.2014.10.003
 46. Dempfle CE, Koscielny J, Lindhoff-Last E, et al. Fondaparinux Pre-, Peri-, and/or Postpartum for the prophylaxis/treatment of venous thromboembolism (FondaPPP). *Clin Appl Thromb Hemost.* 2021:10760296211014575. doi:10.1177/10760296211014575
 47. Bartlett MA, Mauck KF, Daniels PR. Prevention of venous thromboembolism in patients undergoing bariatric surgery. *Vasc Health Risk Manag.* 2015;11:461-477. doi:10.2147/VHRM.S73799
 48. Decousus H, Prandoni P, Mismetti P, et al. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med.* 2010;363(13):1222-1232.

49. Werth S, Bauersachs R, Gerlach H, Rabe E, Schellong S, Beyer-Westendorf J. Superficial vein thrombosis treated for 45 days with rivaroxaban versus fondaparinux: rationale and design of the SURPRISE trial. *J Thromb Thrombolysis*. 2016;42(2):197-204.
50. Schindewolf M. Fondaparinux in heparin-induced thrombocytopenia: a decade's worth of clinical experience. *Res Pract Thromb Haemost*. 2018;3(1):9-11. doi:10.1002/rth2.12169
51. Linkins LA, Hu G, Warkentin TE. Systematic review of fondaparinux for heparin-induced thrombocytopenia: when there are no randomized controlled trials. *Res Pract Thromb Haemost*. 2018; 2(4):678-683. doi:10.1002/rth2.12145
52. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2(22):3317-3359. doi:10.1182/bloodadvances.2018024802
53. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and non-hospitalized medical patients. *Blood Adv*. 2018;2(22):3198-3225. doi:10.1182/bloodadvances.2018022954
54. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv*. 2021;5(4):927-974. doi:10.1182/bloodadvances.2020003442
55. Collet JP, Thiele H, Barbato E, et al; ESC Scientific Document Group. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289-1367. doi:10.1093/eurheartj/ehaa575
56. Kakkos SK, Gohel M, Baekgaard N, et al. Editor's choice—European Society for Vascular Surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis. *Eur J Vasc Endovasc Surg*. 2021;61(1):9-82. doi:10.1016/j.ejvs.2020.09.023
57. Streiff MB, Holmstrom B, Angelini D, et al. Cancer-associated venous thromboembolic disease, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2021; 19(10):1181-1201. doi:10.6004/jnccn.2021.0047
58. World Health Organization report. COVID-19 clinical management living guidance. Published January 25, 2021. Accessed December 14, 2022. <https://apps.who.int/iris/handle/10665/338882>
59. Alam W. COVID-19 vaccine-induced immune thrombotic thrombocytopenia: a review of the potential mechanisms and proposed management. *Sci Prog*. 2021;104(2):368504211025927.
60. Johnston A, Hsieh SC, Carrier M, et al. A systematic review of clinical practice guidelines on the use of low molecular weight heparin and fondaparinux for the treatment and prevention of venous thromboembolism: implications for research and policy decision-making. *PLoS One*. 2018;13(11):e0207410. doi:10.1371/journal.pone.0207410
61. Bjorvatn A, Kristiansen F. Fondaparinux sodium compared with enoxaparin sodium: a cost-effectiveness analysis. *Am J Cardiovasc Drugs*. 2005;5(2):121-130. doi:10.2165/00129784-200505020-00006
62. Latour-Pérez J, de-Miguel-Balsa E. Cost effectiveness of anticoagulation in acute coronary syndromes. *Pharmacoeconomics*. 2012;30(4):303-321. doi:10.2165/11589290-000000000-00000
63. Lundkvist J, Bergqvist D, Jönsson B. Cost-effectiveness of extended prophylaxis with fondaparinux compared with low molecular weight heparin against venous thromboembolism in patients undergoing hip fracture surgery. *Eur J Health Econ*. 2007;8(4):313-323. doi:10.1007/s10198-006-0017-2
64. Di Benedetto P, Vetrugno L, DE Franceschi D, et al. Patient compliance with new oral anticoagulants after major orthopaedic surgery: rivaroxaban and dabigatran compared with subcutaneous injection of fondaparinux. *Joints*. 2017;4(4):214-221. doi:10.11138/jts/2016.4.4.214