Dr.Reddy's

Red Bulletin on Fondaparinux

Where Practice Meets Evidence

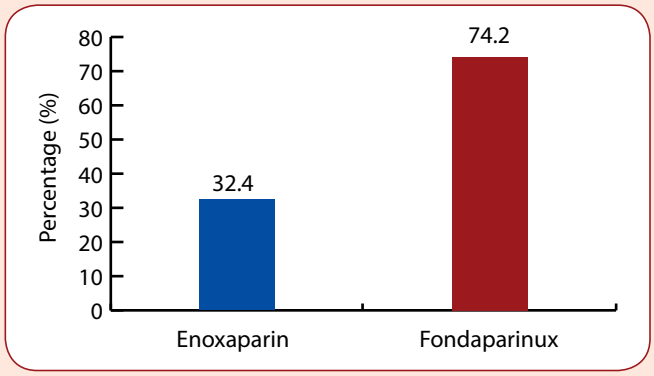
USE OF FONDAPARINUX IN DVT

- Deep vein thrombosis (DVT) prophylaxis following major hip and knee surgeries
- DVT prophylaxis following major abdominal surgery
- DVT and pulmonary embolism (PE) treatment

Sources: 1. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021345s010lbl.pdf [Accessed on 22/6/2017]. **2.** Fareed J, Adiguzel C, Thethi I. Differentiation of parenteral anticoagulants in the prevention and treatment of venous thromboembolism. *Thromb J*. 2011; 9: 5.

FONDAPARINUX MUCH MORE LIKELY TO PRODUCE TARGET PROPHYLACTIC ANTIFACTOR XA LEVELS THAN ENOXAPARIN

- A pilot randomized double blind study evaluated the pharmacodynamic parameters of fondaparinux and enoxaparin administered to patients undergoing bariatric surgery.
- Over a period of three years, 198 consecutive bariatric surgery patients were randomized to receive either enoxaparin (40 mg) twice daily or fondaparinux sodium (5mg) once daily.
- Adequate antifactor Xa levels were more common with fondaparinux than with enoxaparin (figure).
- A gradual increase in anti-Xa levels due to accumulation of fondaparinux results in achieving stable levels anti-Xa levels and could account for good clinical outcomes (no clotting problems).



Sources: 1. 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):672-83. **2.** Yukizawa Y, Inaba Y, Watanabe S, *et al*. Plasma accumulation of fondaparinux 2.5 mg in patients after total hip arthroplasty. *J Thromb Thrombolysis*. 2012;34(4):526-32. **3.** Speeckaert MM, Devreese KM, Vanholder RC, *et al*. Fondaparinux as an alternative to vitamin K antagonists in haemodialysis patients. *Nephrol Dial Transplant*. 2013;28(12):3090-5.

FONDAPARINUX HAS SIMPLE DOSING REGIMEN

DOSING ADVANTAGE OF FONDAPARINUX

Fondaparinux dosage is based on total body weight, unlike other anticoagulant agents, which are administered per kg of body weight

Fondaparinux dose for treatment of DVT and PE	
Body weight	**Fondaparinux dose**
<50 kg	**5 mg**
50-100 kg	**7.5 mg**
>100 Kg	**10 mg**

Sources: 1. Jenkins JS, Michael P. Deep Venous Thrombosis: An Interventionalist's Approach. *The Ochsner Journal.* 2014;14(4):633-640. **2.** Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021345s023lbl.pdf. Accessed on: 22-06-17.

PHARMACOKINETIC PROPERTIES OF FONDAPARINUX ADD TO ITS BENEFICIAL CLINICAL APPLICATION

- Bioavailability – 100% – therefore, rapidly absorbed, and reaches maximum concentration ~2 hour post dosing
- Terminal half-life –13 to 21 hour – permits once-daily dosing
- Reproducible linear pharmacokinetic profile –
  - » Minimal intra-subject and inter-subject variability
  - » No need of individual dose adjustments for vast majority of population
- Within therapeutic concentration range (<2 mg/L):
  - » Exhibits >94% binding to its target protein (antithrombin)
  - » No specific binding to plasma proteins commonly involved in drug binding – low potential for drug-drug interactions by protein displacement
- Chemically synthesized unlike antithrombotic agents prepared from animal extracts (heparins) –batch-to-batch consistency, and absence of potential risk of contamination.

Feature	Heparin	LMWH[a]	Fondaparinux
Source	Biological	Biological	Synthetic
Target	XIIa, IXa, XIa, Xa and IIa	Xa > IIa	Xa
Bioavailability[b]	30%	90%	100%
Half-life (h)	1	4	17

[a]Low molecular weight heparin, [b]Following subcutaneous injection

Sources: 1. 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. *Cardiovascular Drug Reviews.* 2002;20(1):37–52. **2.** Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Pharmacology of anticoagulants used in the treatment of venous thromboembolism. *J Thromb Thrombolysis* 2016;41:15–31.

GUIDANCE STATEMENTS ON USE OF FONDAPARINUX FOR TREATMENT OF ACUTE VENOUS THROMBOEMBOLISM

CLINICAL PRACTICE RECOMMENDATIONS

1. Dose fondaparinux based on weight as follows: <50 kg: 5 mg SC once daily; 50–100 kg: 7.5 mg SC once daily; >100 mg: 10 mg SC once daily
2. Most patients receiving fondaparinux do not require therapeutic drug monitoring.
3. Appropriate duration of therapy when transitioning to oral warfarin
   - » Parenteral anticoagulation with fondaparinux should be overlapped with warfarin for at least 5 days and until a single INR is 2.0 or greater.

Source: Smythe MA, Priziola J, Dobesh PP, *et al*. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41:165–186.

USE OF FONDAPARINUX IN ACS

GUIDANCE STATEMENTS ON USE OF FONDAPARINUX IN ACS

CLINICAL PRACTICE RECOMMENDATIONS

Unstable angina and Non ST Elevation MI (NSTEMI)	ST Elevation MI (STEMI)
Treatment of UA or NSTEMI in patients for whom urgent management (<120 mins) with PCI is not indicated **Dose:** Fondaparinux 2.5mg SC once daily for up to 8 days or until discharge.	Treatment of STEMI in patients who are to be managed with thrombolytics or who are to receive no other form of reperfusion therapy **Dose:** Fondaparinux 2.5mg by i/v injection for the first day followed by 2.5mg SC once daily for up to 8 days or until discharge

Source: Fondaparinux for the treatment of acute coronary syndromes (ACS). Available at: http://www.dbh.nhs.uk/Library/Pharmacy_Medicines_Management/Formulary/Formulary_S2/Fondaparinux.pdf [Accessed on: 1/7/2017].

EUROPEAN SOCIETY OF CARDIOLOGY (ESC) AND AMERICAN COLLEGE OF CARDIOLOGY/ AMERICAN HEART ASSOCIATION (ACC/ AHA) PRACTICE GUIDELINES ON MANAGEMENT OF PATIENTS WITH NSTE-ACS

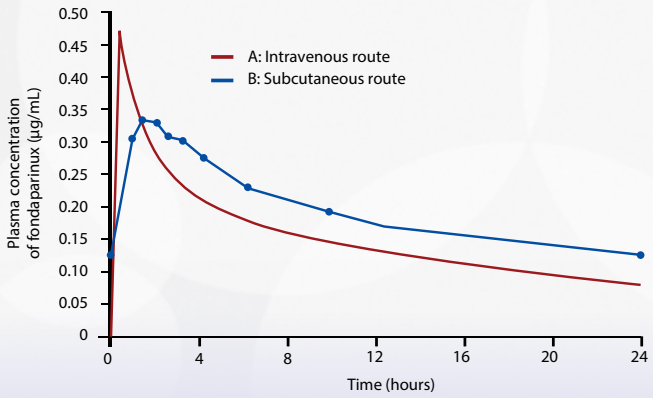
- Use of an anticoagulant drug has class IA recommendation.
- In patients with non-ST elevation acute coronary syndromes (NSTE-ACS), fondaparinux exhibited similar short-term efficacy compared with enoxaparin, but reduced major bleeding and 30 day mortality.
- Therefore, in the context of early invasive or conservative strategy, fondaparinux was given a prominent place (**class I recommendation**) by both societies, notably in patients at risk of bleeding.

ESC guidelines: Fondaparinux preferred over enoxaparin, regardless of initial strategy (excluding urgent revascularization for life-threatening conditions)

ACC/AHA guidelines: Fondaparinux considered the drug of choice in conservative strategy.

Sources: 1. Trailokya A, Dhall A, Kumbla DK. Fondaparinux in Acute Coronary Syndromes. *JAPI*2015;63:83-87. **2.** Bassand JP. The place of fondaparinux in the ESC and ACC/AHA guidelines for anticoagulation in patients with non-ST elevation acute coronary syndromes. *European Heart Journal Supplements* 2008;10 (Supplement C):C22–C29. **3.** Schiele F. Fondaparinux and acute coronary syndromes: update on the OASIS 5–6 studies. *Vasc Health Risk Manag.* 2010;6:179–187.

FONDAPARINUX HAS A QUICK ONSET OF ACTION



Administered subcutaneously, fondaparinux exhibits rapid onset of action, half of the maximum plasma level being reached within 30 min after injection.

Figure: Pharmacokinetic profile of fondaparinux (2.5 mg) administered via intravenous (A) or subcutaneous (B) route. (B) Plasma concentration vs. time profile of fondaparinux in healthy volunteers following a single subcutaneous dose of 2.5 mg. (B) T_{max}=1.7±0.4h; T_{max}/2=25±5 min

Source: Turpie AGG. Selective factor Xa inhibition with fondaparinux: from concept to clinical benefit. *European Heart Journal Supplements* 2008;10 (Supplement C):C1–C7.

FONDAPARINUX IS ASSOCIATED WITH A CONSIDERABLE REDUCTION IN BLEEDING COMPLICATIONS

- In OASIS-5 study, Rate of major bleeding at nine days was markedly lower with fondaparinux (2.5 mg daily) than with enoxaparin (1 mg/kg body weight twice daily): **4.1% versus 2.2%**

Sources: 1. Schiele F. Fondaparinux and acute coronary syndromes: update on the OASIS 5–6 studies. *Vasc Health Risk Manag*. 2010;6:179–187. **2.** The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes. *N Engl J Med* 2006;354:1464-1476.

FONDAPARINUX: EASE OF USE IN ACS

- With its simplicity of use (single dose, one daily injection, no monitoring), fondaparinux could become one of the widely used anticoagulants in ACS.
- A single daily subcutaneous administration of 2.5 mg fondaparinux provides a stable and predictable anticoagulation without the need for laboratory control of coagulation parameters.

Sources: 1. Wienbergen H, Zeymer U. Management of acute coronary syndromes with fondaparinux. *Vasc Health Risk Manag.* 2007;3(3):321–329. **2.** Schiele F. Fondaparinux and acute coronary syndromes: update on the OASIS 5–6 studies. Vasc Health Risk Manag. 2010;6:179–187.

This **RED BULLETIN** Newsletter has been conceptualized following inputs gained from the IMPACT (Initiative for Management and Prophylaxis with Anticoagulation in Thrombosis) Preceptorship Program Meetings held at Delhi, Mumbai, and Bangalore, and attended by eminent Opinion Leaders in medical domains encompassing care of patients with acute coronary syndrome (ACS) and deep vein thrombosis (DVT).

Bangalore: *DVT Scientific Session*: Dr. Robby George; Dr. Ambarish; Dr. Vinoth; Dr. Hemanth; Dr. Chennakeshava; Dr Anand Sattar. *ACS Scientific Session*: Dr. Girish Navasundi; Dr. G G Shetty; Dr. Ranjan Shetty; Dr. Anupama Bambani; Dr. Kannan; Dr. Ashok; Dr. Vikram Kholari; Dr. Sanjay Bhat; Dr. B K Raghunandan.

Delhi: *DVT Scientific Session*: Dr. V S Bedi; Dr. Rajiv Parakh; Dr. Kumud Rai; Dr. Deven Juneja; Dr. Ajay Gupta; Dr. Shishir Seth. *ACS Scientific Session*: Dr. NC Krishnamani; Dr. Subhash Chandra; Dr. K K Saxena; Dr. Sameer Srivastava; Dr. Kuldeep Arora; Dr. Amit Gupta; Dr. Sanjat Chiwane

Mumbai: *DVT Scientific Session*: Dr. Bharesh Dhedhia; Dr. Yogesh Velaskar; Dr. Sameer Tulpule; Dr. Khusrav Bhajan; Dr. Sanjeet Sasidharan; Dr. Raghuram Sekhar; Dr. Pankaj Patel; Dr. Girish Warwadekar; Dr. Paresh Pai; Dr. C Tulsagiri. ACS Scientific Session: Dr. Uday Jadhav; Dr. C K Ponde; Dr. Manoj Mashru; Dr. Rajeev Sharma; Dr. Rahul Gupta; Dr. Brian Pinto; Dr. Vidya Suratkal; Dr. Vivek Mahajan.

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