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Eparine, fondaparinux e insufficienza renale

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LMWHs are eliminated through the kidneys

Risk of accumulation, depending on:

- Degree of renal impairment (> 60; 30-60; < 30 ml/min)
- Dose (prophylactic or therapeutic)
- Type of LMWH

2

A systematic review on the accumulation of prophylactic dosages of low-molecular-weight heparins (LMWHs) in patients with renal insufficiency

Ferdows Atiq[1] · Patricia M.L.A. van den Bemt[1] · Frank W.G. Leebeek[2] · Teun van Gelder[1,3] · Jorie Versmissen[3]

Eur J Clin Pharmacol (2015) 71:921–929

LMWH	Mean molecular weight (Da) [13, 47]	Accumulation therapeutic	Accumulation prophylactic
Bemiparin	3600	CrCl<30 ml/min [38]	CrCl<30 ml/min [38]
Certoparin	3800	CrCl<30 ml/min [48]	CrCl<30 ml/min [39]
Nadroparin	4300	Yes[a] [20]	No conclusion[b]
Enoxaparin	4500	CrCl<30 ml/min [21–24]	CrCl<30 ml/min 4 days [37] and 20–50 ml/min 8 days [35]
Dalteparin	6000	CrCl<30 ml/min after 6 days [32], but not after 3 [43]	No[c] [31–34]
Tinzaparin	6500	No[d] [25, 26]	No[d] [35]

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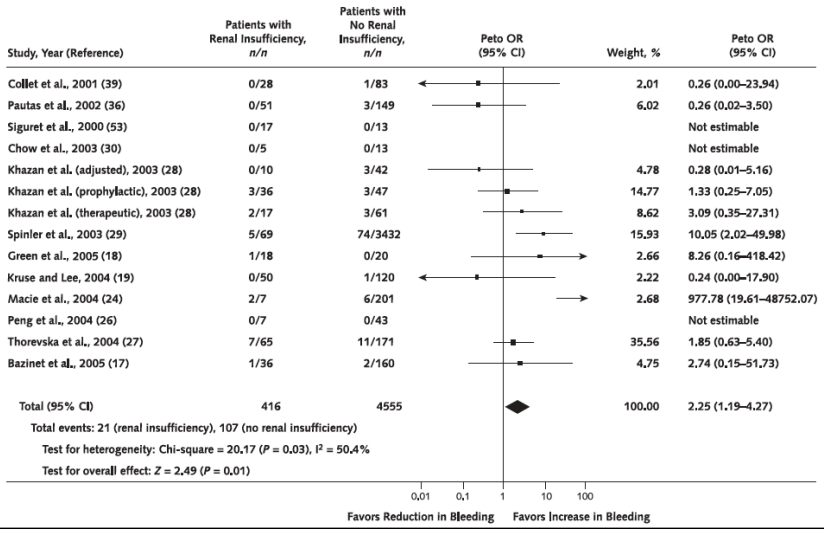
Annals of Internal Medicine | REVIEW

Meta-Analysis: Low-Molecular-Weight Heparin and Bleeding in Patients with Severe Renal Insufficiency

2006

Wendy Lim, MD, BSc; Francesco Dentali, MD; John W. Eikelboom, MBBS; and Mark A. Crowther, MD, MSc



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Annals of Internal Medicine | Review

Meta-Analysis: Low-Molecular-Weight Heparin and Bleeding in Patients with Severe Renal Insufficiency

2006

Wendy Lim, MD, BSc; Francesco Dentali, MD; John W. Eikelboom, MBBS; and Mark A. Crowther, MD, MSc

Conclusions:

- Non–dialysis-dependent patients with a creatinine clearance of 30 mL/min or less, treated with standard therapeutic doses of enoxaparin have elevated levels of anti-Xa and an increased risk for major bleeding.
- Empirical dose adjustment of enoxaparin may reduce the risk for bleeding and merits additional evaluation.
- No conclusions can be made regarding other LMWHs.

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Treatment with Dalteparin is Associated with a Lower Risk of Bleeding Compared to Treatment with Unfractionated Heparin in Patients with Renal Insufficiency

J Gen Intern Med 2015

Doyun Park, MD[1], William Southern, MD, MS[2], Manuela Calvo, MD[2], Margarita Kushnir, MD[3], Clemencia Solorzano, RPH[4], Mark Sinnet, PharmD[4], and Henny H. Billett, MD, MSc[3]

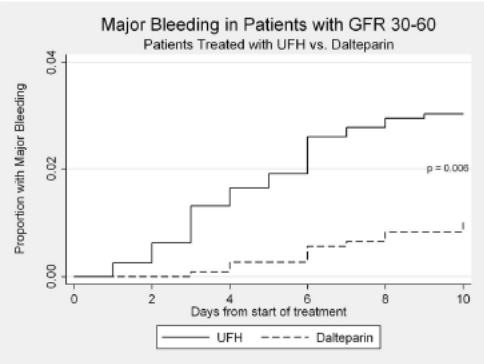

Figure 2. Major bleeding events for subgroup with GFR 30-60mL/min, censored at 10 days.

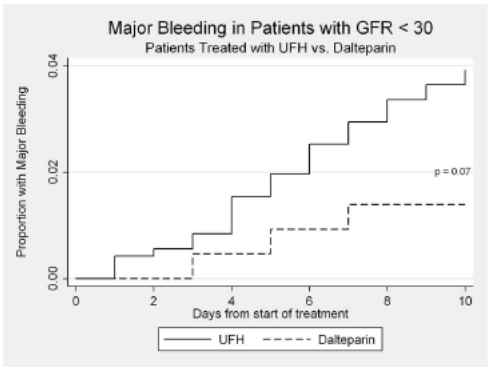

Figure 3. Major bleeding events for subgroup with GFR <30mL/min, censored at 10 days.

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Treatment with Dalteparin is Associated with a Lower Risk of Bleeding Compared to Treatment with Unfractionated Heparin in Patients with Renal Insufficiency

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CONCLUSION:

In patients with CKD, treatment with therapeutic dose dalteparin was associated with lower rates of bleeding than treatment with UFH.

For patients with severe CKD (GFR< 30), dalteparin was shown to be at least as safe as UFH.

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Low-molecular-weight or Unfractionated Heparin in Venous Thromboembolism: The Influence of Renal Function

2013

Javier Trujillo-Santos, MD, PhD,[a] Sebastian Schellong, MD, PhD,[b] Conxita Falga, MD, PhD,[c] Vanessa Zorrilla, MD, PhD,[d] Pedro Gallego, MD, PhD,[e] Manuel Barrón, MD,[f] Manuel Monreal, MD, PhD,[g] and the RIETE Investigators*

RIETE Registry
15-day outcome in 38,531 pts
Propensity score matching to compare UFH vs LMWH

Multivariate analysis showed that those initially treated with UFH were at increased risk for all-cause death (OR, 1.8; 95% CI, 1.3-2.4) and fatal pulmonary embolism (OR, 2.3; 95% CI, 1.5-3.6) compared with those treated with LMWH

Table 5 Multivariate Analysis for Overall Mortality and Fatal Pulmonary Embolism (After Matching)

Variables	Fatal PE OR (95% CI)	Overall Death OR (95% CI)
UFH as initial therapy (vs LMWH)	2.3 (1.5-3.6)‡	1.8 (1.3-2.4)‡
Creatinine clearance > 60 mL/min	—	1 (Reference)
30-60 mL/min	—	1.2 (0.8-1.9)
<30 mL/min	—	2.4 (1.6-3.6)‡
Gender (male)	1.6 (1.1-2.5)*	—
Age ≥70 y	2.0 (1.3-3.0)†	1.7 (1.2-2.5)†
Body weight <70 kg	1.9 (1.2-2.9)†	1.5 (1.1-2.0)*
Cancer	3.5 (2.3-5.3)‡	3.9 (2.9-5.3)‡
Immobility ≥4 d	3.3 (2.2-5.0)‡	3.2 (2.3-4.3)‡
Anemia	—	1.6 (1.1-2.1)†
Symptomatic PE	2.8 (1.4-5.5)†	2.0 (1.3-3.1)†

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Fondaparinux

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Journal of Thrombosis and Haemostasis, **10**: 2291–2297 DOI: 10.1111/j.1538-7836.2012.04908.x

2012

ORIGINAL ARTICLE

Safety and efficacy of low-dose fondaparinux (1.5 mg) for the prevention of venous thromboembolism in acutely ill medical patients with renal impairment: the FONDAIR study

W. AGENO,* N. RIVA,* P. NORIS,† M. DI NISIO,‡ M. LA REGINA,§ D. ARIOLI,¶ L. RIA,** V. MONZANI,†† S. CUPPINI,‡‡ E. LUPIA,§§ M. G. PIERFRANCESCHI¶¶ and F. DENTALI* FOR THE FONDAIR STUDY GROUP

Moderate/severe renal impairment is frequent in very elderly acutely ill medical patients who have risk factors for VTE.
The lower prophylactic dose of fondaparinux (1.5 mg/day) appears to be a safe and relatively effective in these patients

Table 2 Study outcomes

Outcomes	*n* events/*N*	% (95% CI)
Major bleeding	1/206	0.49 (0.03–3.10)
Non-major clinically relevant bleeding	8/206	3.88 (1.81–7.78)
Major bleeding + non-major clinically relevant bleeding	9/206	4.37 (2.15–8.40)
Symptomatic venous thromboembolism	3/206	1.46 (0.38–4.55)
Death	23/206	11.17 (7.36–16.48)

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Eur J Clin Pharmacol (2012) 68:1403–1410
DOI 10.1007/s00228-012-1263-0

PHARMACOKINETICS AND DISPOSITION

Pharmacokinetics of fondaparinux 1.5 mg once daily in a real-world cohort of patients with renal impairment undergoing major orthopaedic surgery

Xavier Delavenne · Paul Zufferey · Philippe Nguyen · Nadia Rosencher · Charles-Marc Samama · Céline Bazzoli · Patrick Mismetti · Silvy Laporte · for The PROPICE Study Group

Venous thromboembolism prevention with fondaparinux 1.5 mg in renally impaired patients undergoing major orthopaedic surgery

A real-world, prospective, multicentre, cohort study

Patrick Mismetti[1]; Charles-Marc Samama[2]; Nadia Rosencher[3]; Claude Vielpeau[4]; Philippe Nguyen[5]; Beatrice Deygas[6]; Emilie Presles[6]; Silvy Laporte[7]; for The PROPICE Study Group*

T&H 2012

Conclusion
fondaparinux 1.5 mg is a valuable thromboprophylactic option in MOS patients with renal impairment who are at risk of bleeding.

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Use of LMWH in elderly/renal impairment

(from Samama, Drug Aging 2011, modified)

Agent	Elderly	30-60 ml	<30 ml
Enoxaparin	Suggested monitoring if < 45 Kg (therapy)	No dose adjustment; careful observation	Prophyl.: 30 mg (?) Therap.: 1mg/Kg OID
Dalteparin	Suggested monitoring if < 45 Kg (therapy)	No dose adjustment; careful observation	Dose adjustment should be considered
Fondaparinux	Use with caution Prophyl.: > 6 h after surgery	20-50 ml/min = 1.5 mg OID (clearance < 40%)	20-50 ml/min = 1.5 mg OID (clearance < 55%)

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LE TERAPIE ANTICOAGULANTI IN TASCA

Cristina Legnani

LMWH

Test da richiedere	Espressione risultati	Range terapeutico o valori di riferimento	Timing del prelievo
Attività anti Xa	Anti Xa IU/ml	Doppia somministrazione: ≈ 0.5-1.0 IU anti Xa IU/ml Unica somministrazione: ≈ 1.0-2.0 IU anti Xa IU/ml	Indifferente in situazioni di emergenza Negli altri casi: a valle (subito prima della successiva somministrazione) e/o a picco (dopo 4 ore circa dall'ultima somministrazione)

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LE TERAPIE ANTICOAGULANTI IN TASCA

Cristina Legnani

Fondaparinux

Test da richiedere	Espressione risultati	Range terapeutico o valori di riferimento	Timing del prelievo
Attività anti Xa	mg/L	2.5 mg/die: ≈ 0.15-0.50 mg/L 5, 7.5 o 10 mg/die: ≈ 0.50-1.30 mg/L	Indifferente in situazioni di emergenza Negli altri casi: a valle (subito prima della successiva somministrazione) e/o a picco (dopo 3 ore circa dall'ultima somministrazione)

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