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Embolia Polmonare: evidenze scientifiche del fondaparinux ed evidenza nella pratica clinica

Simone Magazzini
Dipartimento Emergenza- Area Critica
USL Toscana Centro

Classification of patients with acute PE

Early mortality risk (30 days)	Shock or hypotension	PESI III-IV; sPESI>1	RV dysfunction	Myocardial injury
High risk	+	(+)	(+)	(+)
Intermediate high risk	-	+	+	+
Intermediate low risk	-	+ -	+ -	+ -
Low risk	-	-	(-)	(-)

Konstantinides S et al. Eur Heart J 2014; 35:3033–69

How many patients with PE are at low-risk?

	% (95% CI)
PESI	44% (41–48)
Geneva	79.0% (73.0–85.0)
Simplified-PESI	34.0% (28.0–39.0)
Aujesky	22.0% (19.0–25.0)
Davies	43.6% (37.2–50.0)
Uresandi	47.8% (44.0–51.5)
Overall	**46% (41–51)**

Squizzato A et al. J Thromb Haemost 2012; 10:1276–1290.

VTE treatment: parenteral anticoagulants

Unfractionated heparin (UFH)[1,2]	LMWHs[1]	Fondaparinux[6]
▶ Inhibits further clot formation/propagation and permits the patient's fibrinolytic system (plasmin) to lyse clot ▶ Usually given as IV bolus followed by continuous IV infusion ▶ Anticoagulation level monitored by aPTT test ▶ Usually begun when PE is suspected, before confirmation[3] ▶ Heparin-induced thrombocytopenia (HIT) and osteoporosis are the most important non-haemorrhagic side effects	▶ Injectable, SC ▶ Compared to UFH, LMWHs have greater bioavailability, a more predictable dose response, and a longer half-life ▶ Enoxaparin (e.g. of LMWH) dosing is OD and weight-based[4] ▶ Generally, no need for monitoring (anti-Factor Xa assay if needed) ▶ HIT occurs 8 to 10 times less frequently than with UFH[5]	▶ Synthetic and selective inhibitor of activated Factor X (Xa) ▶ Injectable, SC ▶ Longer half-life vs LMWHs (17 hours vs 4 hours)[6,7] ▶ Recommended dosing is OD and based on patient's weight: <50 kg, 50–100 kg, or >100 kg ▶ Does not affect routine coagulation tests ▶ Predominantly dependent on renal clearance ▶ There are rare spontaneous reports of HIT in patients treated with fondaparinux

aPPT, activated partial thromboplastin time; SC, subcutaneous.

1. Garcia DA et al. *Chest* 2012;141(2):e24S–e43S;
2. Cohen AT. Personal communicationl; 3. Kearon C et al. *Chest* 2012;141(2 Suppl):e419S–e494S;
4. Enoxaparin SmPC. February 2014; 5. Warkentin TE et al. *Br J Haematol*. 2003;121:535–555;
6. Fondaparinux sodium SmPC. September 2014; 7. Colvin BT and Barrowcliffe TW. *J Clin Pathol*. 1993;46:97–103.

MATISSE studies

Open-label studies of fondaparinux for initial treatment of DVT and PE

DVT = deep vein thrombosis; PE = pulmonary embolism.

Study objectives: Outcomes

- Two studies were conducted, with the fondaparinux dose of 7.5 mg (5.0 and 10.0 mg)
- MATISSE DVT compared the efficacy and safety of fondaparinux *vs* (enoxaparin) for the initial treatment of patients with symptomatic DVT
- MATISSE PE compared the efficacy and safety of fondaparinux *vs* unfractionated heparin for the initial treatment of patients with symptomatic PE

  - **Recurrent VTE**
  - **Major bleeding**
  - **Non-inferiority assumption for efficacy**

DVT = deep vein thrombosis; PE = pulmonary embolism
VTE = venous thromboembolism

Büller HR, et al. *Ann Intern Med*. 2004;140:867-873;
The MATISSE Investigators. *N Engl J Med*. 2003;349:1695-1702.

Matisse study designs

2,213 patients with PE ± DVT

R

- 5 days IV UFH (aPTT 1.5–2.5) + OAC (INR 2–3)
- Open-label
- 5 days 7.5 mg fondaparinux* sc + OAC (INR 2–3)

2,205 patients with DVT

R

- Double-blind
- 5 days SC enoxaparin (1 mg/kg, bid) + OAC (INR 2–3)

90 ± 7 days

* 5 mg if bodyweight < 50 kg

10 mg if bodyweight > 100 kg

Primary efficacy outcome (3 months)

- Fatal PE/unexplained death
- Recurrent symptomatic non-fatal PE or DVT

Principal safety outcome (initial treatment)

- Major bleed
- Clinically relevant non-major bleed

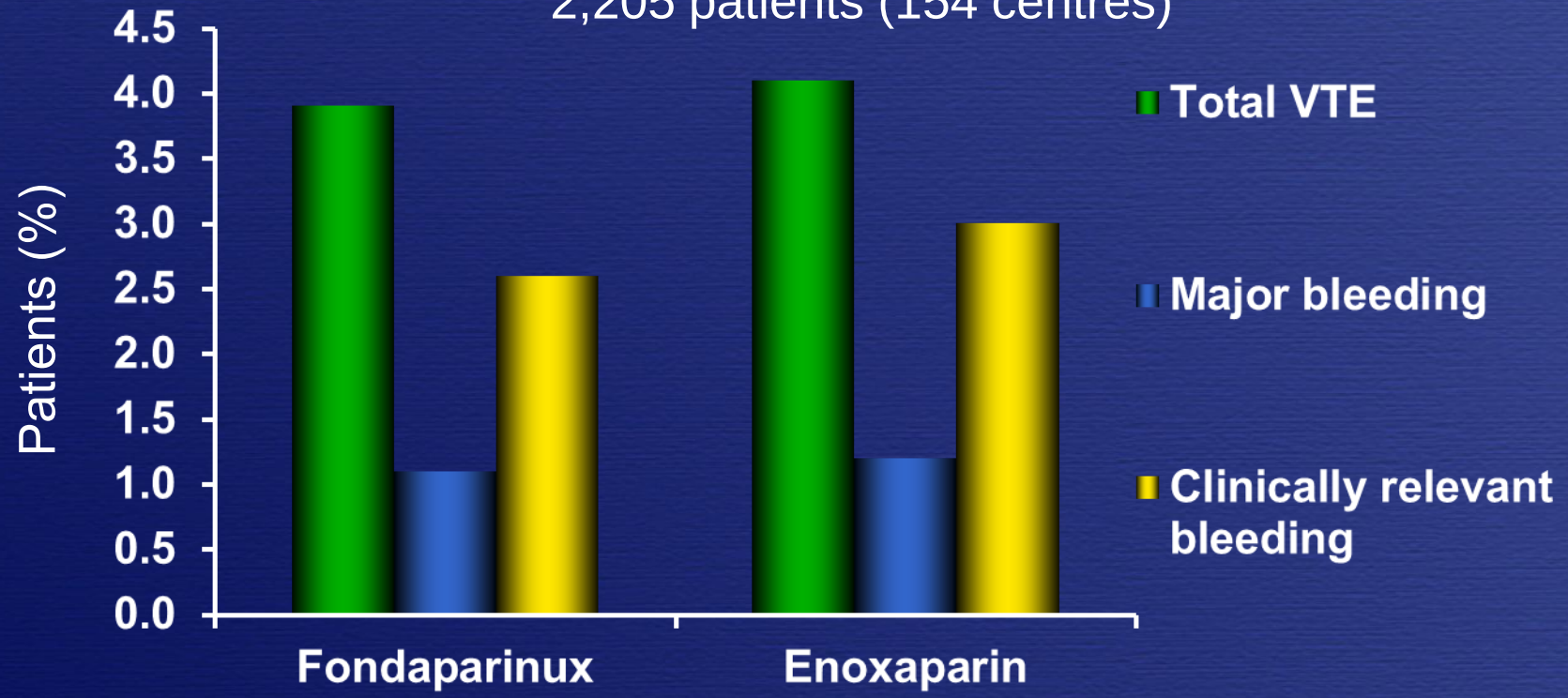
aPTT = activated partial thromboplastin time;DVT = deep vein thrombosis;
INR = international normalized ratio;OAC = oral anticoagulant;
PE = pulmonary embolism;VTE = venous thromboembolism.

Büller HR, et al. *Ann Intern Med*. 2004;140:867-873;
The MATISSE Investigators. *N Engl J Med*. 2003;349:1695-1702.

MATISSE: DVT results

Fondaparinux* vs enoxaparin (1 mg/kg bid) for treatment of symptomatic DVT

2,205 patients (154 centres)



*5.0, 7.5 or 10.0 mg in patients weighing < 50, 50–100, or > 100 mg, respectively.

bid = twice daily; DVT = deep vein thrombosis;
VTE = venous thromboembolism.

Büller HR, et al. *Ann Intern Med*. 2004;140:867-873.

MATISSE: DVT results

	Incidence	
Endpoints	**Fondaparinux, %**	**Enoxaparin, %**
Fatal PE	0.5	0.5
Non-fatal PE/DVT	3.5	3.6
Total VTE	3.9	4.1
Major bleeding	1.1	1.2
Clinically relevant bleeding	2.6	3.0
2,205 patients (154 centres)		

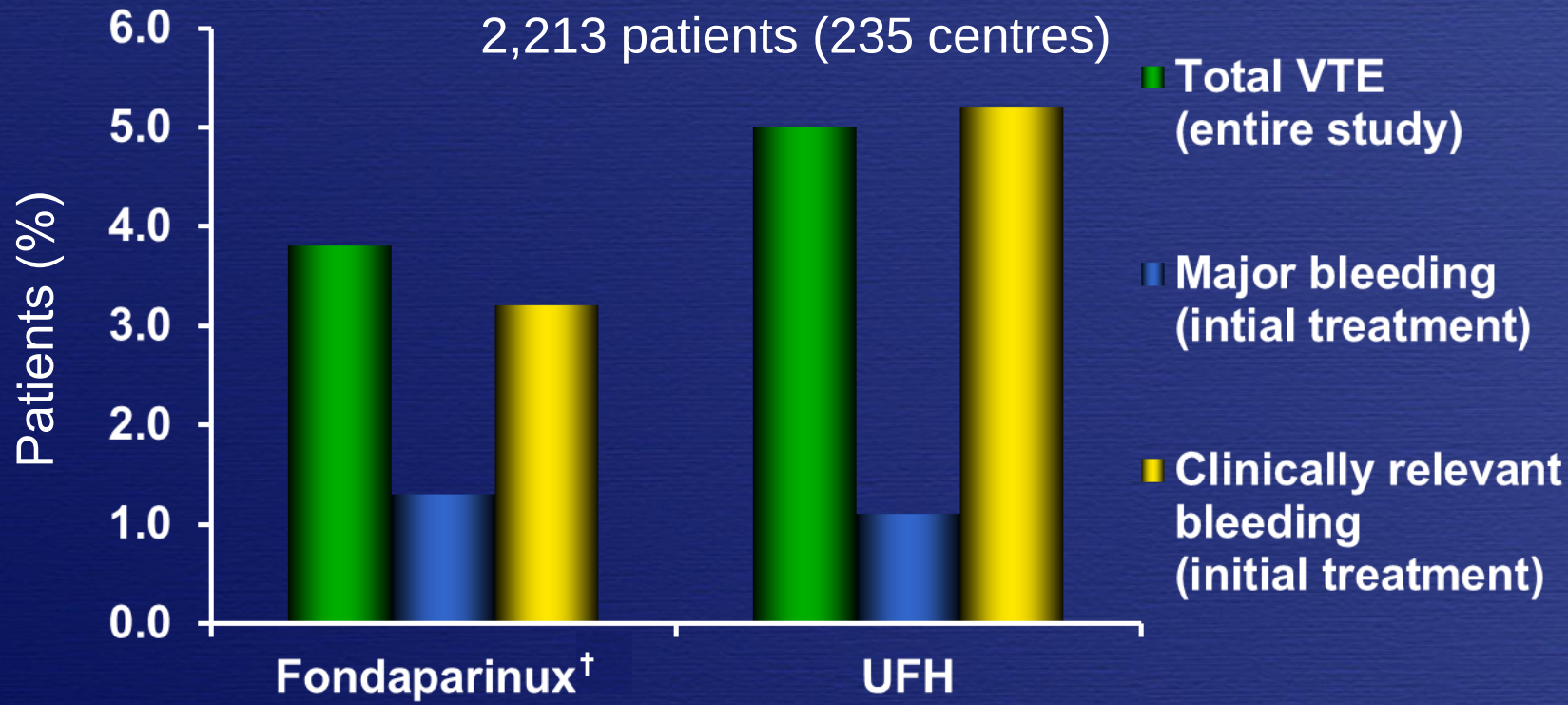
DVT = deep vein thrombosis; PE = pulmonary embolism;
VTE = venous thromboembolism.

Büller HR, et al. *Ann Intern Med*. 2004;140:867-873.

MATISSE: PE results

Fondaparinux* vs UFH (5000 IU bolus followed by 1250 IU/h IV) for treatment of symptomatic PE

2,213 patients (235 centres)



*5.0, 7.5 or 10.0 mg in patients weighing < 50, 50–100, or > 100 mg, respectively.

†15% treated in outpatient setting.

PE = pulmonary embolism; IU – international units;
IV = intravenous; UFH = unfractionated heparin;
VTE = venous thromboembolism.

The MATISSE Investigators. *N Engl J Med*. 2003;349:1695-1702.

MATISSE: PE results

	Incidence	
End-points	**Fondaparinux, %**	**Unfractionated heparin, %**
Fatal PE	1.5	1.4
Non-fatal PE/DVT	2.4	3.7
Total VTE	3.8	5
Major bleeding	1.3	1.1
Clinically relevant bleeding	3.2	5.2
2,213 patients (235 centres)		

DVT = deep vein thrombosis; PE = pulmonary embolism;
VTE = venous thromboembolism.

The MATISSE Investigators. *N Engl J Med*. 2003;349:1695-1702.

MATISSE: Conclusions

- DVT: fondaparinux (once daily) is as effective and safe as enoxaparin (twice daily)
- PE: fondaparinux (once daily) is as effective and safe as unfractionated heparin (continuous IV perfusion)

DVT = deep vein thrombosis; PE = pulmonary embolism.

Büller HR, et al. *Ann Intern Med*. 2004;140:867-873;
The MATISSE Investigators. *N Engl J Med*. 2003;349:1695-1702.

Advantages of fondaparinux over LMWH

- Synthetic synthesis
- No HIT
- Once daily
- Large separate trials for DVT and PE
- Fixed dosing regimens (also for extremes of body weight)

DVT = deep vein thrombosis; HIT = heparin induced thrombocytopenia;
LMWH = low-molecular-weight heparin; PE = pulmonary embolism.

Grazie dell’attenzione