ARTEMIS

ARixtra® (fondaparinux) for ThromboEmbolism prevention in a Medical Indications Study

NV Organon
Protocol 63129

Organon

sanofi~synthelabo

Objective

To demonstrate efficacy and to assess safety of once-daily subcutaneous (SC) injections of 2.5 mg fondaparinux sodium for the prevention of venous thromboembolic events (VTE), i.e. deep vein thrombosis (DVT) or symptomatic pulmonary embolism (PE), in acutely ill medical patients.

Inclusion criteria

- Acutely ill medical patients, aged ≥ 60 years and expected to require bedrest for ≥ 4 days, hospitalised for:
  - congestive heart failure (NYHA class III / IV)
  - acute respiratory illness in the presence of chronic lung disease
  - acute infectious or inflammatory disease
- Written informed consent

Exclusion criteria

Based on current risk of bleeding:

- Active clinically significant bleeding
- Documented congenital or acquired bleeding tendency/disorder(s)
- Documented angiodysplastic gastrointestinal disease or current ulceration
- Acute bacterial endocarditis
- Known cerebral metastasis

Exclusion criteria

Based on current risk of bleeding (continued):

- Recent (< 3 month prior to randomisation)
  - stroke (haemorrhagic or ischaemic),
  - brain-, spinal or ophthalmological surgery, or
  - spinal cord compression
- Indwelling intrathecal or epidural catheter
- Patients for who anticoagulant therapy is contraindicated

Exclusion criteria

Related to study procedures:

- Serum creatinine levels > 180 umol/L (2 mg/dL) in a well hydrated patient
- Documented hypersensitivity to contrast media
- Likelihood of no bilateral venous access
- Use of any contraindicated drug that can not be combined with the injection of contrast medium
- Planned surgery before mandatory venography

Exclusion criteria

Miscellaneous exclusion criteria:

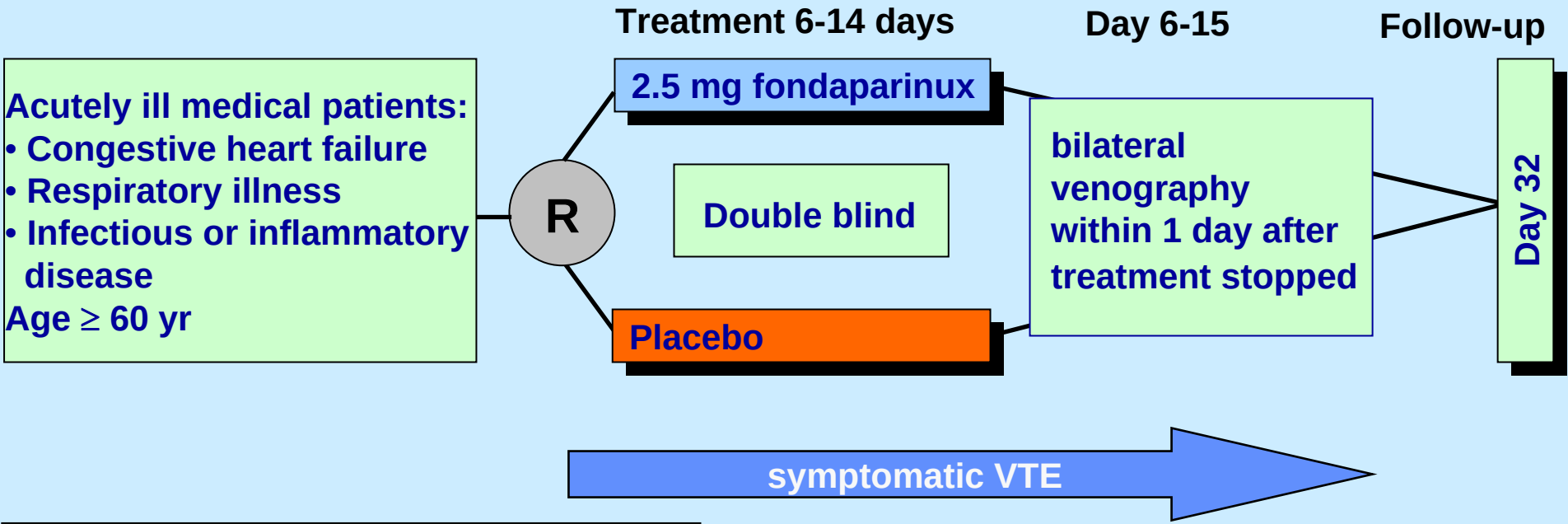
- Planned intubation for > 24 hours in a patient with acute respiratory illness
- Use of (LMW-)heparin(oid)s, hirudin, GPIIb-IIa blocking agents, oral anticoagulants, fibrinolytic agents or dextrans within 48 hours prior to randomisation
- Patients for whom anticoagulant therapy is indicated due to
  - a co-existing condition (e.g. prosthetic heart valve implant), or
  - the current reason for hospitalisation

Exclusion criteria

Miscellaneous exclusion criteria (continued):

- Admission to hospital for > 48 hours prior to randomisation
- Participation in any other therapeutic drug (or device) study evaluating DVT prophylaxis within the last 90 days
- Previous participation in a study of fondaparinux sodium
- Current addictive disorder or other reasons that could interfere with study participation or compliance
- Expected inability to have a follow-up assessment and/or life-expectancy < 32 days

Study design



Study committees
- Steering Committee
- Independent and blinded adjudication committee
- Data Safety Monitoring Board

Primary efficacy outcome

Cluster of confirmed (by adjudication) VTE events up to Day 15*

- Mandatory venogram positive for DVT, and/or
- Symptomatic DVT, and/or
- Non-fatal PE, and/or Fatal PE

* up to the first venogram or Day 15, whichever comes first

Principal safety outcome

Incidence of confirmed Major Bleeding (by adjudication) between the first injection and two calendar days after last injection:

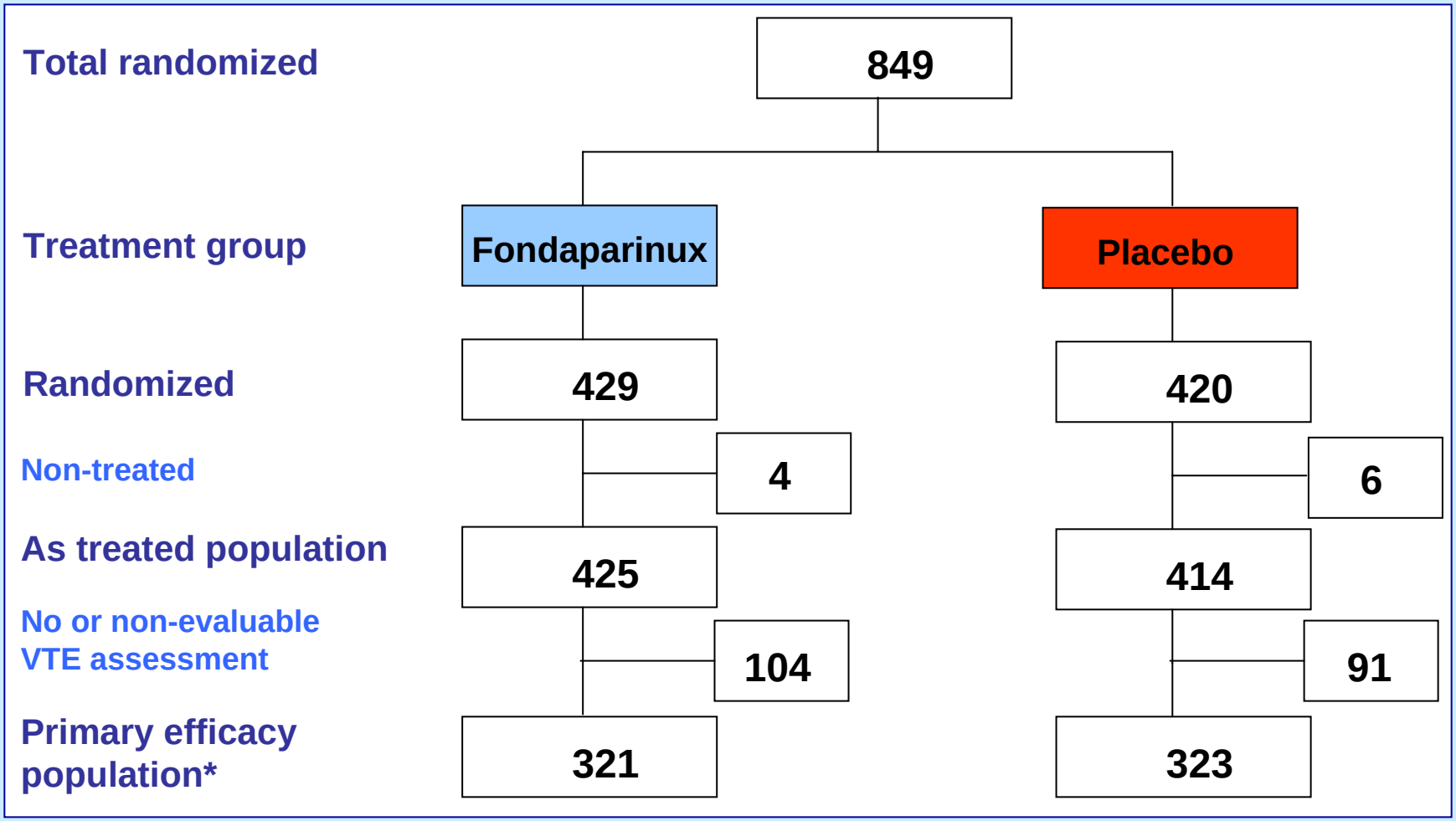
- Fatal bleeding
- Bleeding/haematoma requiring surgical intervention
- Bleeding into critical organ (intracranial, retroperitoneal, intra-ocular, spinal, pericardial, adrenal glands)
- Overt bleeding related to a Hb-fall $\geq$ 2 g/dL (within 48 hours), and/or transfusion of $\geq$ 2 units

Central Independent Adjudication Committee

Blind Adjudication of:

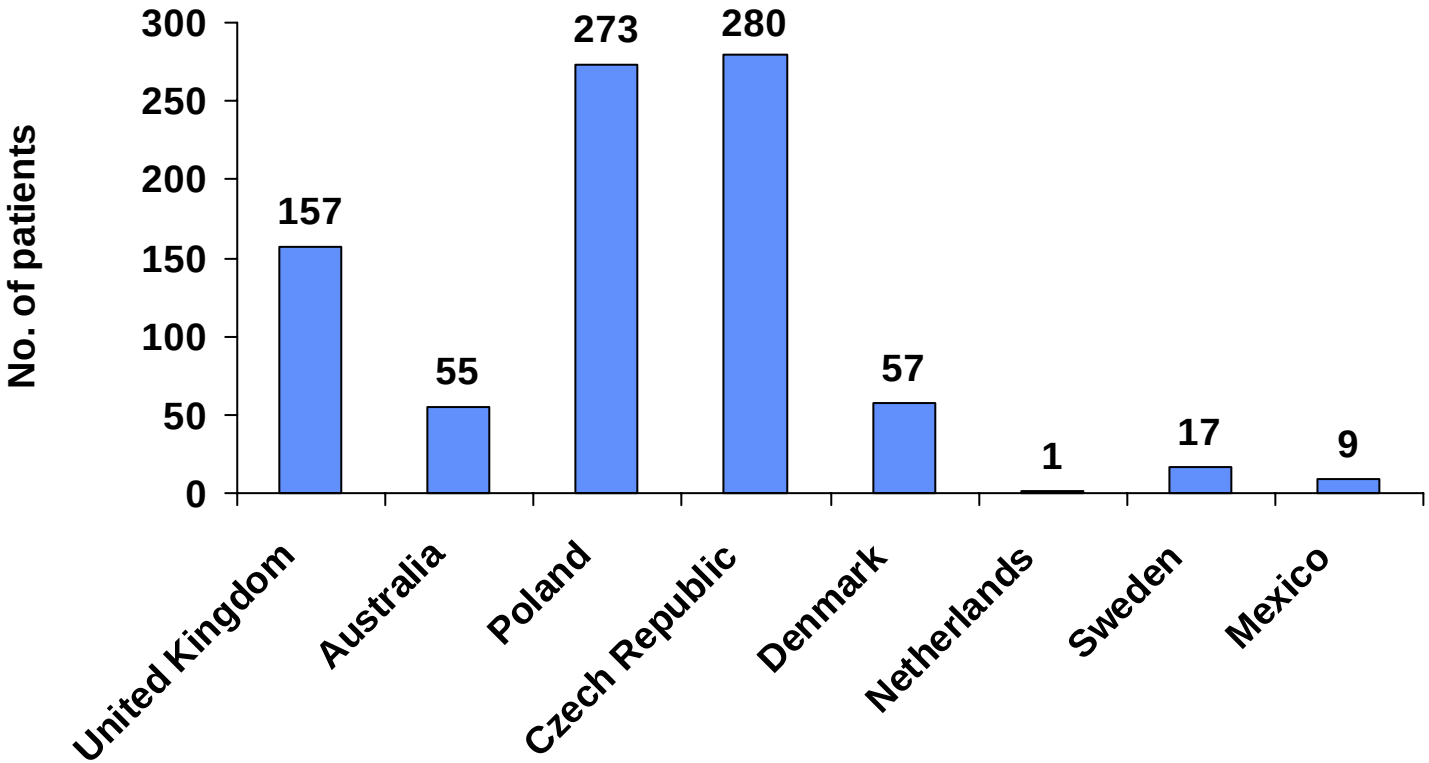
- Mandatory venograms (Day 6-15),
  to judge as No DVT or (proximal/distal) DVT.
- Symptomatic VTE events (up to Day 32),
  to judge as No DVT/PE, (proximal/distal) DVT or PE.
- Investigator reported unusual bleeding (up to Day 32),
  to judge as major, minor or no bleed, based on predefined definitions.
- Death (up to Day 32),
  to judge as haemorrhagic, venous thromboembolic or otherwise.

Analysis populations



* 75.9% of randomized patients

Randomization per Country



Demographics

		Fondaparinux (N=429)	Placebo (N=420)
Age (years)	mean (SD)	75.0 (8.3)	74.4 (8.3)
Body Weight (kg)	mean (SD)	70.1 (15.2)	70.1(16.8)
Female / Male	%	59% / 41%	56% / 44%
History of VTE	n (%)	18 (4.2%)	21 (5.0%)
(History of) Cancer	n (%)	62 (14.5%)	69 (16.4%)

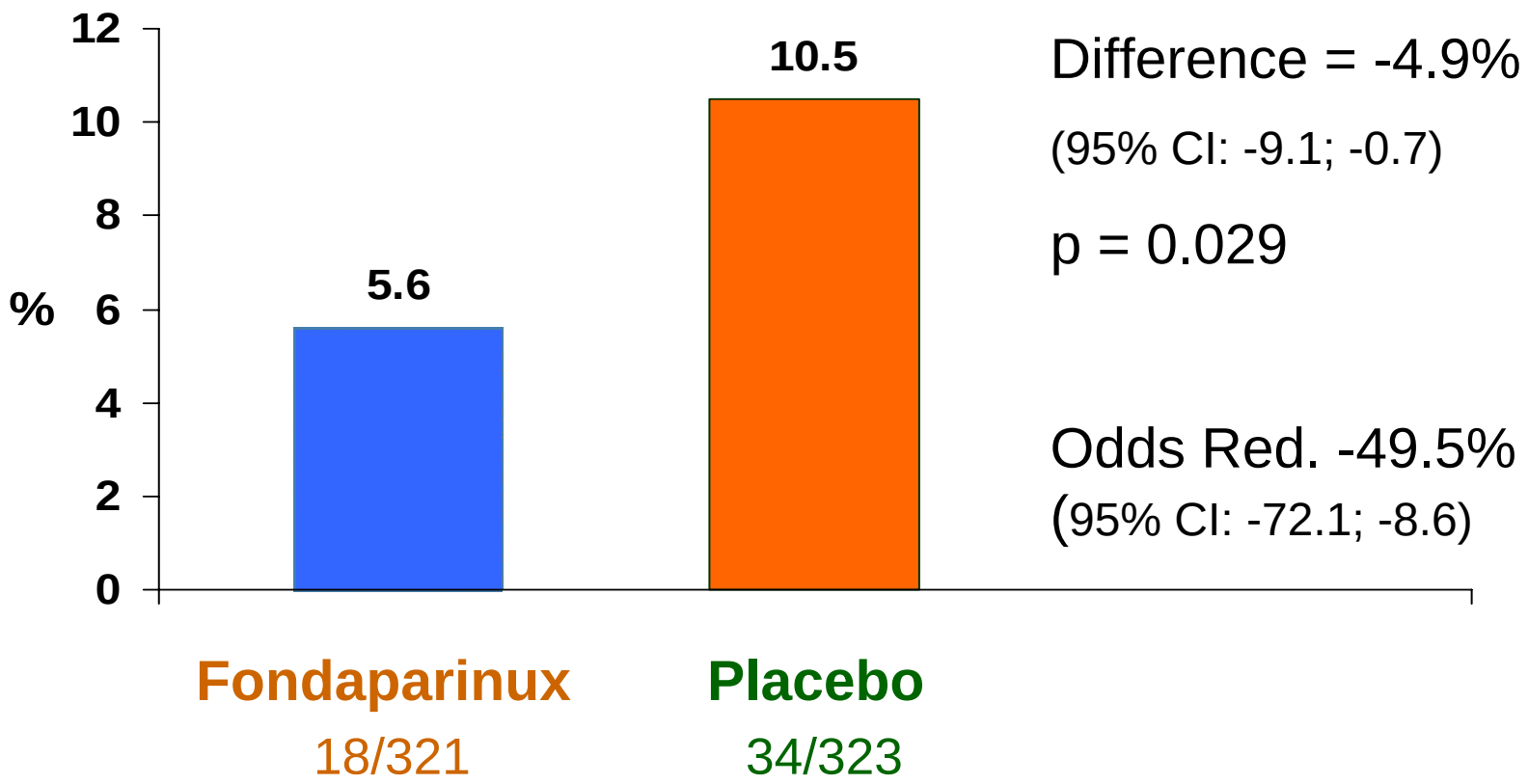
Reason for Hospitalization

	Fondaparinux (N=429)	Placebo (N=420)
Congestive Heart Failure		
• NYHA Class III	118 (27.5%)	111 (26.4%)
• NYHA Class IV	35 (8.2%)	44 (10.5%)
Acute Respiratory Disease	196 (45.7%)	181 (43.1%)
Acute Infect./Inflamm. Disease	229 (53.4%)	209 (49.8%)

Primary Efficacy Outcome

Confirmed VTE up to Day 15

Primary efficacy population



Difference = -4.9%

(95% CI: -9.1; -0.7)

p = 0.029

Odds Red. -49.5%

(95% CI: -72.1; -8.6)

Confirmed Symptomatic VTE

Day 15

All randomized patients

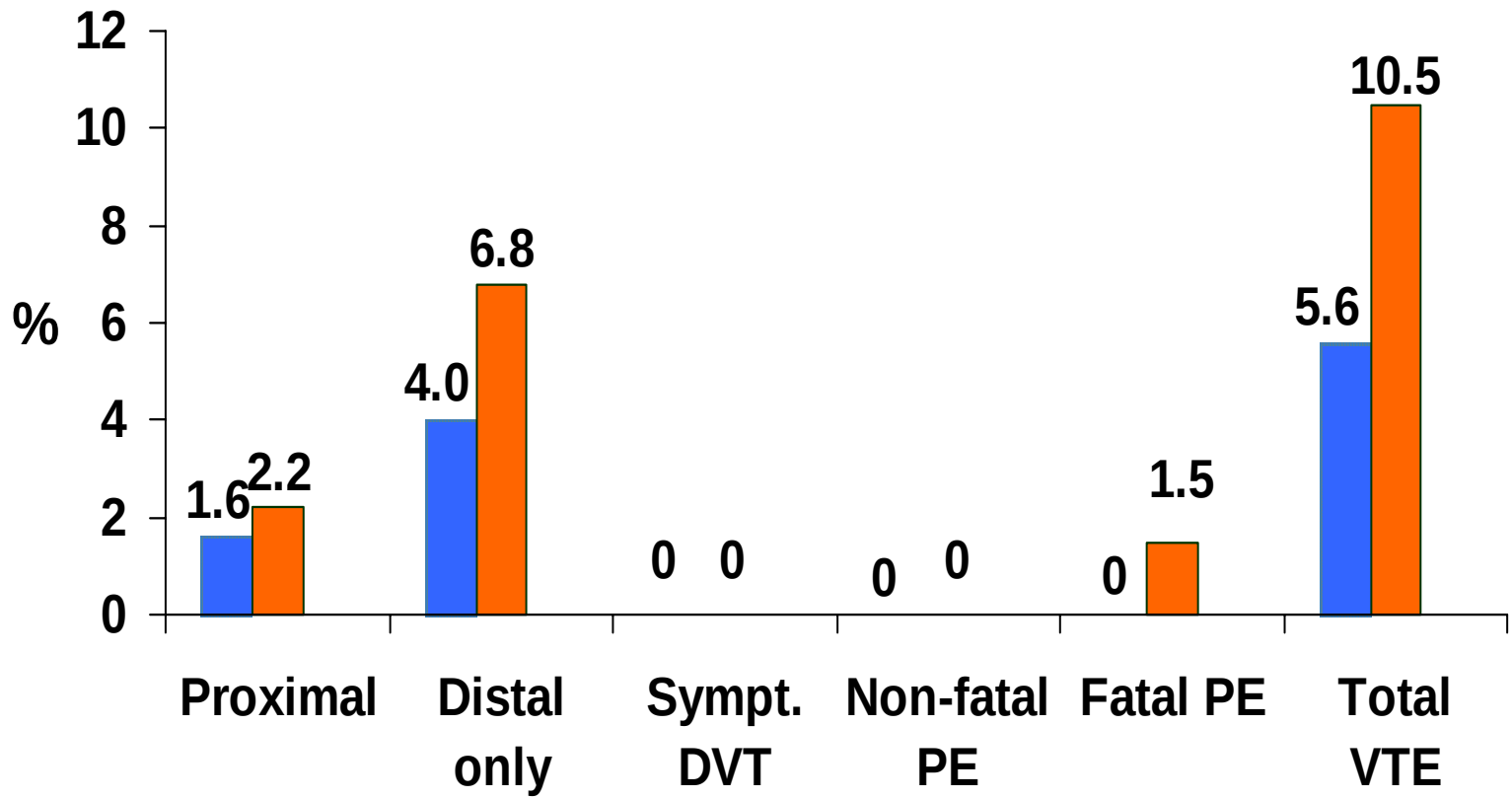
	Fondaparinux (N=429)	Placebo (N=420)
Patients symptomatic for:		
VTE (%)	0	5 (1.2%)
DVT (%)	0	0
Non-fatal PE (%)	0	0
Fatal PE (%)	0	5* (1.2%)

*difference (95% CI): -1.2%[-2.2;-0.2]; p=0.029

Confirmed VTE

Day 15

Primary efficacy population



Blue: Fondaparinux

Red: Placebo

Confirmed Symptomatic VTE

Day 32

All randomized patients

	Fondaparinux (N=429)	Placebo (N=420)
Patients symptomatic for:		
Symptomatic VTE	4 (0.9%)	11 (2.6%)
DVT	0	0
Non-fatal PE	1 (0.2%)	4 (1.0%)
Fatal PE	3 (0.7%)	7 (1.7%)

Safety Outcome

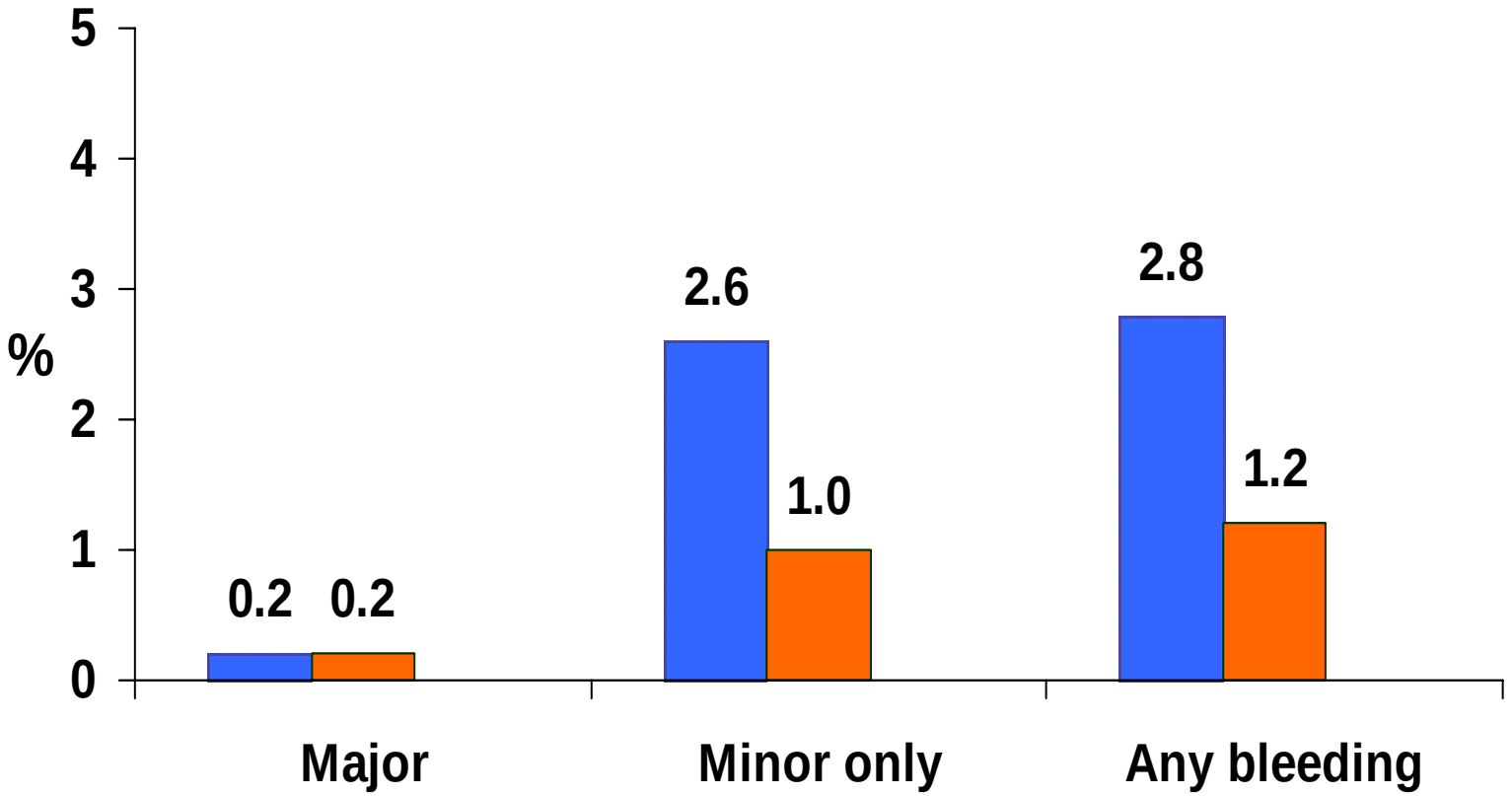
	Fondaparinux (N=425)	Placebo (N=414)
Confirmed bleeding on treatment		
Major bleeding		
• Fatal	0	0
• Surgical intervention	0	0
• Critical organ	0	0
• Bleeding Index ≥ 2	1 (0.2%)	1 (0.2%)
Minor bleeding	11 (2.6%)*	4 (1.0%)

*** NS**

Confirmed Bleeding

on treatment

As treated patients population



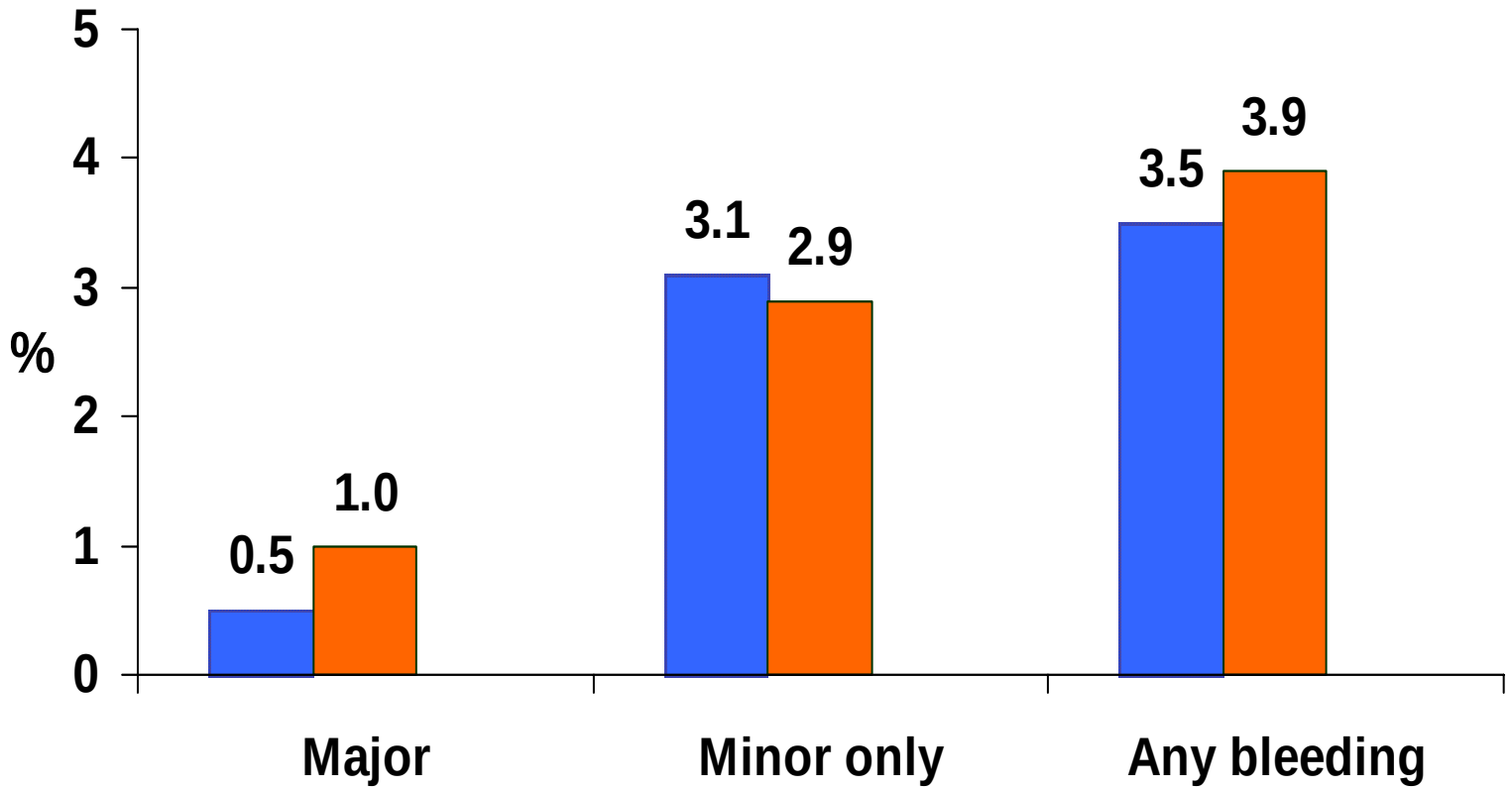
Blue: Fondaparinux

Red: Placebo

Confirmed Bleeding

Day 32

As treated patients population



Blue: Fondaparinux

Red: Placebo

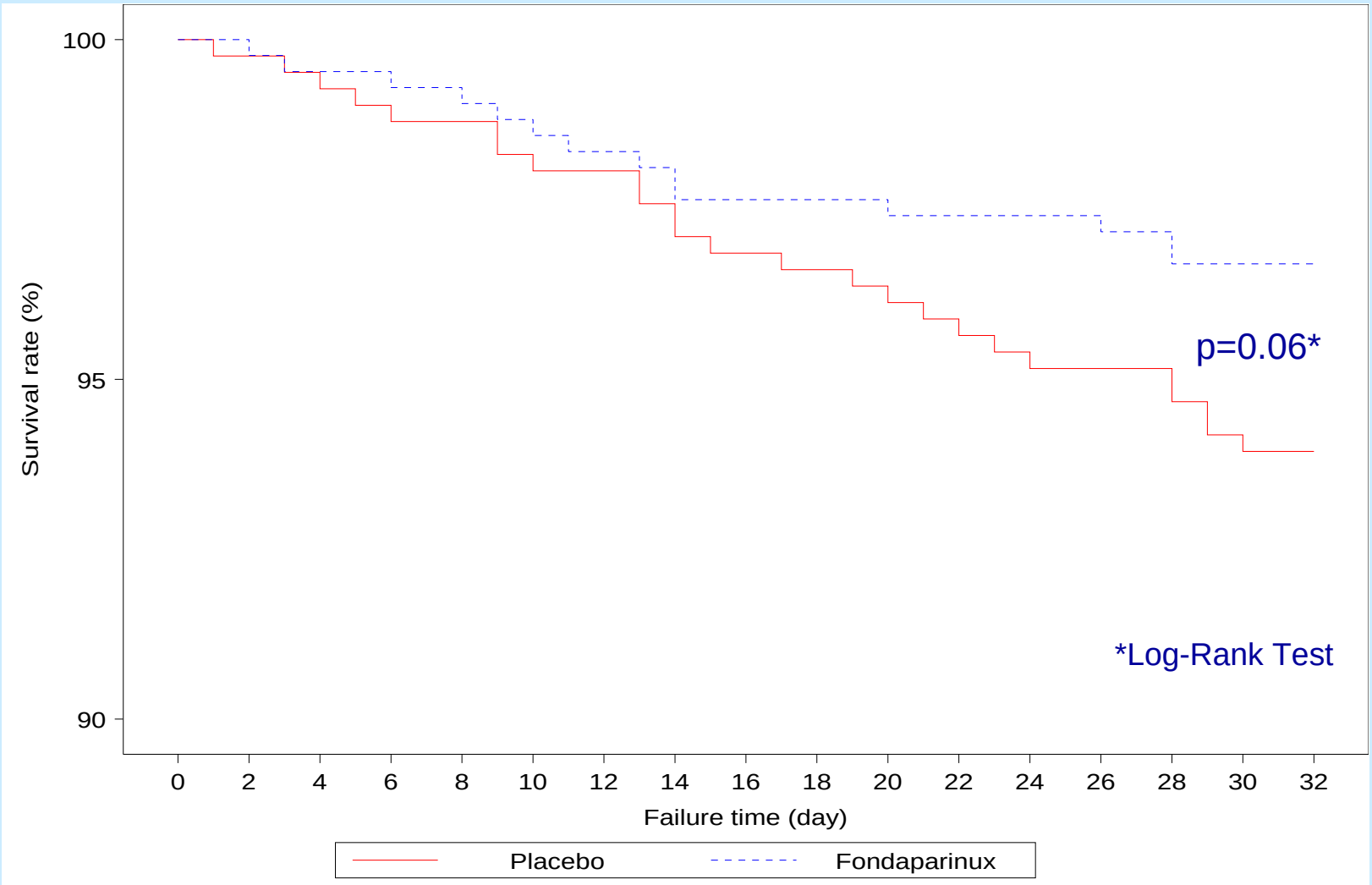
Death adjudication outcome

Day 1 - 32

	Fondaparinux (N=425)	Placebo (N=414)
Fatal PE*	3 (0.7%)	7 (1.7%)
Fatal bleeding**	2 (0.5%)	1 (0.2%)
Death not associated with PE or bleeding	9 (2.1%)	17 (4.1%)
Total***	14 (3.3%)	25 (6.0%)

* 0 vs 5 patients, respectively, in primary efficacy period
** 0 in both groups on treatment *** p=0.06 (Log-rank Test)

Survival Estimates



Conclusion

- Fondaparinux 2.5 mg once-daily significantly reduced the risk of VTE in acutely ill medical patients from 10.5% to 5.6% (Odds Reduction 49.5%; p=0.029).
- Fondaparinux reduced fatal PE (p=0.029).
  During follow-up, VTE occurred to a similar extent in both groups.
- Fondaparinux administration is associated with a low rate of major bleeding, similar to placebo.
- Acutely ill medical patients are at significant risk of VTE, including fatal PE.