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Study No.: AR1104574 (63133 – ASPIRE)
Title: A randomized blinded pilot trial of fondaparinux sodium (Arixtra®) versus unfractionated heparin in addition to standard therapy in a broad range of patients undergoing percutaneous coronary intervention (ASPIRE)
Rationale: Fondaparinux sodium 2.5 mg (hereafter called FX) was used in this study as a single injection after three previous Phase II studies showed it to be potentially as or more effective than unfractionated heparin (UFH), which is usually used during percutaneous coronary intervention (PCI) to prevent early thrombotic complications.
Phase: IIb
Study Period: 10 June 2003 – 7 January 2004
Study Design: multicenter, randomized, blinded, controlled, parallel group pilot study. Randomization was stratified by upfront planned or not planned use of GP IIb/IIIa antagonists.
Centers: 10 in Canada, 7 in France, 5 in US
Indication: Prevention of thrombotic complications during PCI
Treatment: Single intravenous (IV) dose of one of the following (with or without upfront IV glycoprotein [GP] IIb/IIIa inhibitor): FX 2.5 mg, FX 5.0 mg, or unfractionated heparin (UFH); 100 U/Kg if no upfront GP IIb/IIIa inhibitor, or 60 U/kg with upfront IV GP IIb/IIIa inhibitor)
Objectives: To obtain experience in the use of FX as the primary anticoagulation strategy during PCI by evaluating the safety and efficacy of two dosages compared with UFH.
Primary Outcome/Efficacy Variable: <u>The primary efficacy outcome</u> was the first occurrence of any component of the composite of all-cause death, myocardial (re)infarction [(re)MI], urgent revascularization (UR) or need for bail-out GP IIb/IIIa inhibitor within 48 hours after randomization and confirmed by adjudication. <u>The primary safety outcome</u> was the first occurrence of major or minor bleeding events within 48 hours after randomization and confirmed by adjudication. Major bleeding was defined as clinically overt bleeding with one of the following criteria: fatal, symptomatic intracranial hemorrhage, retroperitoneal hemorrhage, intraocular hemorrhage, or a fall in haemoglobin (Hb) of ≥ 3.0 g/dL with each blood transfusion unit counting for 1.0 g/dL of Hb, or requiring transfusions of ≥ 2 units of blood. Minor bleeding was defined as any other clinically overt bleeding, not meeting the definition for major bleeding.
Secondary Outcome/Efficacy Variables: <u>Secondary efficacy outcomes</u> were: A.) <u>during the procedure</u> : ●occlusion of sidebranch >1.5 mm; ●abrupt closure; ●no-reflow; ●new or suspected new angiographic thrombus; B) <u>up to 48 hours after randomization</u> : ●TIMI (thrombolysis in myocardial infarction) flow <3 post procedure (providing TIMI flow was 2 or 3 at some point during the procedure); ●peri-procedural troponin elevation more than 3x upper limit of normal in those with normal pre-PCI troponin levels; ●death or (re)MI; C) <u>up to 30 days after randomization</u> : ●cardiovascular death; ●the primary efficacy composite outcome up to 30 days; ●death or (re)MI.
Statistical Methods: Adjudicated outcomes were analyzed descriptively as proportions and for statistical significance using a Cox proportional hazards model controlling for randomized strata. Treatment comparisons were considered statistically significant if the two-sided 95% confidence interval around the hazard ratio excluded one. The primary endpoint compared the combined FX doses with UFH. Pairwise comparisons between treatment groups were made for the composite efficacy endpoint. Descriptive statistics were presented for treatment subgroups stratified by use of GP-IIb/IIIa antagonist for outcomes related to the primary composite efficacy endpoint. Non-adjudicated secondary variables were analyzed by logistic regression or analysis of variance. Adverse experiences were analyzed descriptively as proportions of subjects who experienced AEs. <u>Sample size:</u> The sample size was based on the estimated event rate for the composite of major and minor bleeding in the UFH group, since the safety objective was to exclude the possibility of excessive risk due to the antithrombotic risk of FX. The estimated rate expected for the UFH group was 3%, which would provide 80% power to show a difference if the hazard ratio between the combined FX groups and the UFH group was 4.8. <u>Populations analyzed:</u> <i>'Randomized'</i> : consisted of all subjects who were randomized. This population was used for all safety and efficacy analyses <i>'Per Protocol'</i> : consisted of all subjects who were treated with study medication as randomized, who actually underwent the PCI procedure, and had no major protocol violations (<i>i.e.</i> no data available on primary outcomes; treated with GP IIb/IIIa antagonist within 72 hours of PCI if randomized to the planned no-treatment stratum; not treated with GP IIb/IIIa antagonist if randomized to the planned treatment stratum; in the planned GP IIb/IIIa group but

received the drug AFTER device activation; had activated clotting time >200 seconds immediately prior to PCI; used low-molecular-weight heparin in the previous 6 hours before PCI; was receiving an oral anticoagulant agent with an international normalized ratio > 1.8, had thrombolytic therapy for ST elevation MI (STEMI) in the previous 24 hours before PCI, had active internal bleeding or history of hemorrhagic diathesis; or had randomization irregularities). This population was used for primary efficacy analysis.

Study Population: Subjects aged ≥21 years scheduled for PCI, including PCI for non-ST elevation acute coronary syndromes (ACS) primary PCI for STEMI, or elective PCI (with planned overnight stay in hospital). Subjects with active or potential bleeding complications or undergoing thrombolysis for STEMI in prior 24 hours were excluded.

	FX 2.5 mg	FX 5.0 mg	FX Total	UFH
Number of Subjects:				
Planned, N	100	100	200	100
Randomised, N	118	115	233	117
Per Protocol, N	110	109	219	110
Completed Treatment, n (% of randomised)	117 (99.2)	114 (99.1)	231 (99.6)	117 (100)
Total Number Subjects Withdrawn, N (% of randomized)	1 (0.8)	3 (2.6)	4 (1.7)	1 (0.9)
Withdrawn due to Adverse Event, n (% of randomized)	0	2 (1.7)	2 (0.9)	0
Withdrawn due to Lack of Efficacy, n (% of randomized)	0	0	0	0
Withdrawn for Other Reasons n (% of randomized)	1 (0.8)	1 (0.9)	2 (0.9)	1 (0.9)
Demographics				
N (Randomised)	118	115	233	117
Females: Males	29:89	24:91	53:180	25:92
Mean Age, years (SD)	63.6 (11.7)	63.6 (11.1)	63.6 (11.4)	62.3 (10.2)
European ethnicity, n (%)	109 (92.4)	97 (84.3)	206 (88.4)	101 (86.3)
Planned treatment with GP IIb/IIIa inhibitors, n (%)	48 (40.7)	47 (40.9)	95 (40.8)	52 (44.4)
No Planned treatment with GP IIb/IIIa inhibitors, n (%)	70 (59.3)	68 (59.1)	138 (59.2)	65 (55.6)
Primary Efficacy Results:				
Subjects with outcome of adjudicated death, re(MI), UR or bail-out up to 48 hours (Randomized population)	FX 2.5 mg	FX 5.0 mg	FX Total	UFH
All subjects, n/N (%)	5/118 (4.2)	9/115 (7.8)	14/233 (6.0)	7/117 (6.0)
		Hazard ratio	95% CI	P-value
FX Total vs. UFH		1.018	0.411, 2.524	0.969
FX 2.5 vs. UFH		0.710	0.225, 2.238	NA
FX 5 vs. UFH		1.341	0.499, 3.602	NA
FX 2.5 vs. FX 5		1.888	0.633, 5.634	NA
Secondary Efficacy Outcome Variables:				
Subjects with outcome of adjudicated death, re(MI), UR or bail-out up to 48 hours (Per Protocol population)	FX 2.5 mg	FX 5.0 mg	FX Total	UFH
All subjects, n/N (%)	5/110 (4.5)	9/109 (8.3)	14/219 (6.4)	6/110 (5.5)
		Hazard ratio	95% CI	P-value
FX Total vs. UFH		1.201	0.461, 3.127	0.708
FX 2.5 vs. UFH		0.844	0.258, 2.768	NA
FX 5 vs. UFH		1.568	0.558, 4.408	NA
FX 2.5 vs. FX 5		1.858	0.622, 5.544	NA
Subjects with outcome of adjudicated death, re(MI), UR or bail-out by strata (Randomized population)	FX 2.5 mg	FX 5.0 mg	FX Total	UFH
No planned GP IIb/IIIa , n/N (%)	2/48 (4.2)	5/47 (10.6)	7/95 (7.4)	4/52 (7.7)
Planned GP IIb/IIIa, n/N (%)	3/70 (4.3)	4/68 (5.9)	7/138 (5.1)	3/65 (4.6)
Subjects with outcome of adjudicated death up to 48 hours (Randomized population)				

All, n/N (%)	0/118	1/115 (0.9)	1/233 (0.4)	0/117
No planned GP IIb/IIIa, n/N (%)	0/48	1/47 (2.1)	1/95 (1.1)	0/52
Planned GP IIb/IIIa, n/N (%)	0/70	0/68	0/138	0/65
Subjects with outcome of adjudicated (re)MI up to 48 hours (Randomized population)				
n/N (%)	4/118 (3.4)	9/115 (7.8)	13/233 (5.6)	7/117 (6.0)
No planned GP IIb/IIIa, n/N (%)	1/48 (2.1)	5/47 (10.6)	6/95 (6.3)	4/52 (7.7)
Planned GP IIb/IIIa, n/N (%)	3/70 (4.3)	4/68 (5.9)	7/138 (5.1)	3/65 (4.6)
Subjects with outcome of adjudicated UR up to 48 hours (Randomized population)				
n/N (%)	0/118	2/115 (1.7)	2/233 (0.9)	1/117 (0.9)
No planned GP IIb/IIIa, n/N (%)	0/48	2/47 (4.3)	2/95 (2.1)	1/52 (1.9)
Planned GP IIb/IIIa, n/N (%)	0/70	0/68	0/138	0/65
Subjects with outcome of adjudicated need for bail-out use of GP IIb/IIIa up to 48 hours (Randomized population)				
n/N (%)	1/118 (0.8)	3/115 (2.6)	4/233 (1.7)	2/117 (1.7)
No planned GP IIb/IIIa, n/N (%)	1/48 (2.1)	3/47 (6.4)	4/95 (4.2)	2/52 (3.9)
Planned GP IIb/IIIa, n/N (%)	0/70	0/68	0/138	0/65
Subjects with outcome of occlusion of sidebranch >1.5 mm during PCI procedure (Randomized population)		FX Total	UFH	
n/N (%)		3/233 (1.3)	1/117 (0.9)	
Odds ratio		0.653		
95% CI		0.067, 6.352		
Subjects with outcome of abrupt closure during PCI procedure (Randomized population)		FX Total	UFH	
n/N (%)		5/233 (2.1)	0/117	
Odds ratio		NA		
95% CI		NA		
Subjects with outcome of no reflow during PCI procedure (Randomized population)		FX Total	UFH	
n/N (%)		8/233 (3.4)	1/117 (0.9)	
Odds ratio		0.245		
95% CI		0.030, 1.986		
Subjects with outcome of new or suspected new angiographic thrombus during PCI procedure (Randomized population)		FX Total	UFH	
n/N (%)		14/233 (6.0)	1/117 (0.9)	
Hazard ratio		0.136		
95% CI		0.018, 1.050		
Subjects with outcome of troponin elevation > 3 x ULN within 48 hours (Randomized population)		FX Total	UFH	
n/N (%)		15/233 (6.4)	5/117 (4.3)	
Odds ratio		0.656		
95% CI		0.232, 1.852		
Subjects with outcome of TIMI flow <3 post procedure (if TIMI 2 or 3 flow during procedure) (Randomized population)		FX Total	UFH	
n/N (%)		3/233 (1.3)	3/117 (2.6)	
Odds ratio		NA		
95% CI		NA		
Subjects with outcome of adjudicated death or (re)MI within 48 hours (Randomized population)		FX Total	UFH	
n/N (%)		13/233 (5.6)	7/117 (6.0)	
Odds ratio		0.930		
95% CI		0.371, 2.332		

Subjects with outcome of adjudicated death, (re)MI, UR, or need for bail-out use of GP IIb/IIIa up to 30 days (Randomized population)	FX 2.5 mg	FX 5.0 mg	FX Total	UFH
All, n/N (%)	5/118 (4.2)	11/115 (9.6)	16/233 (6.9)	7/117 (6.0)
No planned GP IIb/IIIa, n/N (%)	2/48 (4.2)	5/47 (10.6)	7/95 (7.4)	4/52 (7.7)
Planned GP IIb/IIIa, n/N (%)	3/70 (4.3)	6/68 (8.8)	9/138 (6.5)	3/65 (4.6)
Subjects with outcome of adjudicated death up to 30 days (Randomized population)				
All, n/N (%)	0/118	2/115 (1.7)	2/233 (0.9)	0/117
No planned GP IIb/IIIa, n/N (%)	0/48	1/47 (2.1)	1/95 (1.1)	0/52
Planned GP IIb/IIIa, n/N (%)	0/70	1/68 (1.5)	1/138 (0.7)	0/65
Subjects with outcome of adjudicated (re)MI up to 30 days (Randomized population)				
n/N (%)	4/118 (3.4)	10/115 (8.7)	14/233 (6.0)	7/117 (6.0)
No planned GP IIb/IIIa, n/N (%)	1/48 (2.1)	5/47 (10.6)	6/95 (6.3)	4/52 (7.7)
Planned GP IIb/IIIa, n/N (%)	3/70 (4.3)	5/68 (7.4)	8/138 (5.8)	3/65 (4.6)
Subjects with outcome of adjudicated UR up to 30 days (Randomized population)				
n/N (%)	0/118	3/115 (2.6)	3/233 (0.9)	1/117 (0.9)
No planned GP IIb/IIIa, n/N (%)	0/48	2/47 (4.3)	2/95 (2.1)	1/52 (1.9)
Planned GP IIb/IIIa, n/N (%)	0/70	1/68 (1.5)	1/138 (0.7)	0/65
Subjects with outcome of adjudicated need for bail-out use of GP IIb/IIIa up to 30 days (Randomized population)				
n/N (%)	1/118 (0.8)	3/115 (2.6)	4/233 (1.7)	2/117 (1.7)
No planned GP IIb/IIIa, n/N (%)	1/48 (2.1)	3/47 (6.4)	4/95 (4.2)	2/52 (3.8)
Planned GP IIb/IIIa, n/N (%)	0/70	0/68	0/138	0/65
Subjects with outcome of cardiovascular death up to 30 days (Randomized population)				
n/N (%)	0/118	2/115 (1.7)	2/233 (0.9)	0/117
No planned GP IIb/IIIa, n/N (%)	0/48	1/47 (2.1)	1/95 (1.1)	0/52
Planned GP IIb/IIIa, n/N (%)	0/70	1/68 (1.5)	1/138 (0.7)	0/65
Safety Results: Adverse Event Results: On-therapy AEs and SAEs were recorded during the treatment period, which is from first injection of study medication continuing to 48 hours after randomization.				
	FX 2.5 N=118	FX 5 N=115	UFH N=117	
Most Frequent Adverse Events – On-Therapy (Days 1-2), in decreasing order of frequency (Randomized Population)	n (%)	N (%)	N (%)	
Subjects with any AE(s), n(%)	36 (31)	39 (34)	32 (27)	
Puncture site hemorrhage	3 (3)	9 (8)	8 (7)	
Angina pectoris	3 (3)	4 (3)	5 (4)	
Headache	2 (2)	4 (3)	6 (5)	
Syncope vasovagal	2 (2)	4 (3)	4 (3)	
Coronary artery embolism	4 (3)	2 (2)	0	
Hypotension	4 (3)	1 (<1)	2 (2)	
Thrombocytopenia	3 (3)	0	1 (<1)	
Hematoma	1 (<1)	2 (2)	0	
Back pain	2 (2)	1 (<1)	2 (2)	
Blood pressure decreased	0	2 (2)	1 (<1)	
Contusion	0	2 (2)	0	
Vomiting	0	2 (2)	0	
Dizziness	2 (2)	0	0	
Non-cardiac chest pain	2 (2)	0	1 (<1)	
Post-procedural discharge	2 (2)	0	0	
Chest pain	1 (<1)	1 (<1)	3 (3)	

Nausea	1 (<1)	1 (<1)	2 (2)
Chest discomfort	0	0	3 (3)
Vascular pseudoaneurism	0	0	2 (2)
Serious Adverse Events			
	FX 2.5 N=118	FX 5 N=115	UFH N=117
All SAEs On-Therapy (Days 1-2) -includes both fatal and non-fatal events (Randomized Population)	n (%) [related]	n (%) [related]	n (%) [related]
Subjects with any SAE, n (%) [considered by investigator to be related to study medication]	4 (3) [1]	4 (3) [2]	3 (3) [1]
Thrombocytopenia	2 (2) [0]	0	0
Hematoma	0	2 (2) [0]	0
Cerebral hemorrhage	1 (<1) [1]	0	0
Third Nerve Paralysis	1 (<1) [0]	0	0
Coronary artery thrombosis	0	1 (<1) [1]	0
Puncture site hemorrhage	0	1 (<1) [1]	1 (<1) [0]
Shunt stenosis	0	0	1 (<1) [1]
Vascular pseudoaneurysm	0	0	1 (<1) [0]
	FX 2.5 N=118	FX 5 N=115	UFH N=117
Subjects with fatal SAEs On-Therapy (Days 1-2) (Randomized Population)	n (%) [related]	n (%) [related]	n (%) [related]
Coronary artery thrombosis, n (%) [considered by investigator to be related to study medication]	0	1 (<1) [1]	0
Conclusion: See publication below.			
Publications: Mehta SR, et al. Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: Arixtra Study in Percutaneous coronary Intervention: A Randomized Evaluation (ASPIRE) Pilot Trial. 2005. <i>Circulation</i> 111:1390-1397.			

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