Tolerability of percutaneous coronary interventions in patients receiving nadroparin calcium for unstable angina or non-Q-wave myocardial infarction: the Angiofrax study

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SUMMARY

Background: Nadroparin, a low-molecular-weight heparin (LMWH), is an alternative to unfractionated heparin for the acute management of patients with non-ST elevation acute coronary syndrome (ACS): unstable angina or non-Q-wave myocardial infarction. However, unfractionated heparin can be substituted for LMWH in patients requiring percutaneous coronary interventions (PCIs) for the duration of the procedure. The tolerability of this anti-thrombotic regimen (i.e. unfractionated heparin for the duration of PCIs, preceded and followed by subcutaneous injection of nadroparin) is not yet documented.

Design and methods: This open-label 6-day study was carried out in 302 patients to test the tolerability of this anti-thrombotic regimen in patients requiring PCIs. The primary end-point of the study was the incidence of major haemorrhage over the whole study duration (6 days). The secondary end-point was the need for transfusion and vascular repair after PCI.

Results: The incidence of major haemorrhage in patients undergoing coronary angiography (CA) without or with PCIs was 1.4% and 1.3%, respectively, and the incidence of minor haemorrhage was 10.7% and 23.5%, respectively. These results are consistent with published data.

Conclusions: These results suggest that CA and PCIs can be performed safely in patients being treated for unstable angina or non-Q-wave myocardial infarction receiving nadroparin pre- and post-coronary procedure and/or intervention, substituted by unfractionated heparin for the duration of the intervention.

Introduction

Recently, low-molecular-weight heparins (LMWHs) have been shown to be at least as effective as unfractionated heparin (UFH) in the prevention of venous thromboembolism. LMWHs are also safer and easier to use, without the constraint of needing to monitor anticoagulation. In this respect, LMWHs, in addition to acetyl-salicylic acid (aspirin), have been proposed as an alternative treatment in patients with unstable angina (UA) or non-Q-wave myocardial infarction (NQWMI)[1–6].

In previous studies testing LMWH as an alternative to UFH in patients with non-ST elevation acute coronary syndromes (ACS), no specific information was provided about the anti-thrombotic regimen recommended in patients included in these trials and who required percutaneous coronary interventions (PCIs). In the FRAXIS study[7], no information was provided about the interval between the coronary procedure and the previous and subsequent subcutaneous (SC) injections of nadroparin calcium (nadroparin) in patients undergoing PCI. There is therefore a need to establish the tolerability of CA and PCI strategy in a population similar to that of the FRAXIS study, and for which UFH was substituted for nadroparin for the duration of the procedure. This trial was specifically aimed at answering this question.

Methods and patients

Design

This was an international, open-label, non-randomised study, conducted in 27 European centres in seven countries (Belgium, France, Greece, Hungary, Italy, Poland and Spain).

The primary end-point was the incidence of bleeding as assessed in patients with UA and NQWMI who received, concomitantly to oral aspirin, nadroparin as an intravenous (IV) bolus of 86 anti-Xa IU/kg followed by a SC nadroparin injection 86 anti-Xa IU/kg twice daily during the peri-procedural period, with PCI carried out with UFH at a dose of 100 IU/kg. The secondary end-point was the efficacy of the anticoagulant regimen as determined by the occurrence of thrombotic coronary events during a 6-day period.

Patients

Male or female patients aged 18–80 years with a 40–110 kg body weight, were eligible if they presented with suspected UA or NQWMI. This was defined as severe effort or rest anginal pain, within the 48 h before

inclusion and ECG signs compatible with the clinical diagnosis (transient episodes of ST-segment changes, predominantly ST-segment depression). Patients who were candidates for coronary angiography within 2–4 days of starting nadroparin therapy were eligible.

Exclusion criteria were: patients on thrombolytic therapy, recent left bundle branch block, or ST segment elevation above 0.1 mV in two consecutive leads, pacemaker or previous coronary artery bypass graft (CABG) and the need for non-conventional angioplasty or intra-aortic balloon pump support. Other exclusion criteria were: a left ventricular ejection fraction ≤ 30%, contraindication to coronary angiography or to UFH or LMWH, an inherited or acquired haemostatic abnormality, renal impairment (serum creatinine > 20 mg/l), severe hepatic disease, treatment with oral anticoagulants or fibrinolytic agents < 48 h before study entry, a recent history (≤ 2 months) of gastrointestinal bleeding or peptic ulcer, any other lesions at risk of haemorrhage, acute infectious endocarditis, uncontrolled hypertension (diastolic blood pressure > 105 mmHg after 10 min rest), a history of allergy or thrombocytopoenia with UFH or with LMWH or heparinoids, a history of allergy to aspirin, any other contraindication to anticoagulant therapy, pregnancy, underlying psychiatric or addictive disorder, trauma or surgical procedure within the previous 2 weeks, a recent history of epidural or spinal anaesthesia.

Ethics

The study was conducted between April 1999 and January 2000. Written informed consent was obtained from each patient. The study was conducted in accordance with the Declaration of Helsinki. The trial protocol and subsequent amendments were reviewed and approved by independent ethics committees and/or institutional review boards, according to local legislation.

Study Treatment

All eligible patients received an open-label treatment with nadroparin at a dose of 86 anti-Xa IU/kg, first as an IV bolus and followed immediately and at subsequent 12-hourly intervals by a SC injection (Figure 1). Aspirin was started – or continued, if already prescribed – at a maximum oral dosage of 325 mg daily.

Whenever an invasive strategy was indicated, patients were taken to the catheterisation laboratory at least 8 h, but no more than 20 h, after the last nadroparin injection. PCI was carried out at the same time as the diagnostic procedure, using an IV bolus of UFH (100 IU/kg initial bolus up to a maximum of 10 000 IU) administered to maintain an activated clotting time (ACT) > 300 s. SC nadroparin was resumed 12 h after
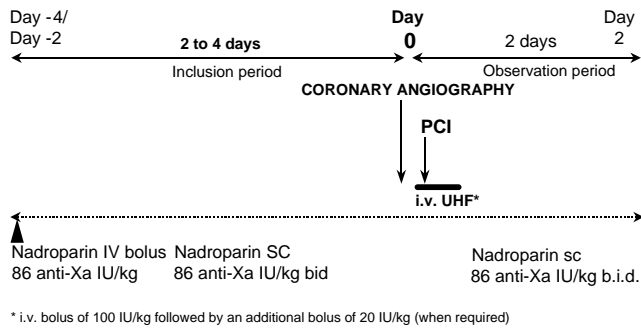
Day -4/
Day -2

2 to 4 days

Inclusion period

Day
0

CORONARY ANGIOGRAPHY

PCI

i.v. UHF*

2 days

Day
2

Observation period

Nadroparin IV bolus
86 anti-Xa IU/kg

Nadroparin SC
86 anti-Xa IU/kg bid

Nadroparin sc
86 anti-Xa IU/kg b.i.d.

* i.v. bolus of 100 IU/kg followed by an additional bolus of 20 IU/kg (when required)

Figure 1. ANGIOFRAX study design

the previous injection in patients who did not undergo PCI. For those undergoing PCI, SC nadroparin was resumed as soon as the activated partial thromboplastin time (aPTT) was lower than twice the control value. The total duration of nadroparin treatment did not exceed 6 days.

Concomitant Treatment

All other anti-thrombin treatments were not allowed for the duration of this trial, such as UFH (unless indicated for PCI), any other LMWH than the study drug, or heparinoids. Intramuscular injection of any other drug was also prohibited for the trial duration, as well as oral anticoagulants, ADP receptors antagonists such as clopidogrel bisulphate (clopidogrel) or ticlopidine, and GP IIb/IIIa inhibitors. Second-generation thrombolytic agents could be used whenever needed.

Clinical Evaluation

Clinical evaluation was performed on all patients on days 0, 1 and 2. Standard laboratory tests were performed at patient selection and repeated according to the routine practice of each cardiology centre. Patients undergoing coronary angiography with or without PCI received an additional evaluation 1 h before and 2 h after the start of arterial catheterisation on day 0.

End-points

The primary study end-point was the incidence of major haemorrhage over the whole study period of 6 days, as adjudicated by an independent Safety Review Committee. All haemorrhagic complications appearing during the observation period had to be reported. Major bleeding events were defined as: decrease in haemoglobin > 5 g/dl (31.05 mmol/l), retroperitoneal or intracranial haemorrhage, haemorrhage in another critical organ, haemorrhage requiring transfusion of ≥ 2 units of blood, or resulting in death. Any other clinically overt, unusual haemorrhage not meeting the criteria of major bleeding

was considered as minor.

The secondary safety end-point was the need for transfusion of less than two units of blood and the need for vascular repair. Patients undergoing a CABG immediately after coronary angiography were not evaluable. Other adverse events (AEs) were recorded, as well as laboratory test results: red and white blood cell count, haemoglobin, haematocrit, platelet count, serum potassium, serum creatinine, creatinine phosphokinase (CK) and CK muscle band (CP-MB) levels.

The Safety Review Committee adjudicated all reported clinical events, including deaths, and classified all reported haemorrhages as either major or minor.

A further secondary end-point of the study was the efficacy, as assessed by the rate of thrombotic coronary events during the study period. Recurrence of symptoms, refractory angina, occurrence of Q-wave MI (QWMI) or NQWMI defined as enzyme release above three times the upper limit of normal (ULN) and need for target vessel revascularisation were recorded.

Statistics

The sample size was set at 150 patients undergoing PCI in order to ensure the report of adequate information on the safety of the study drug. This meant that at least 300 patients had to be included in the trial. Three groups were defined. Group 1 was composed of patients initially included in the trial, but who turned out not to be eligible for invasive strategy. Group 2 was composed of patients who underwent coronary angiography without indication for PCI. Group 3 was made up of patients who underwent both coronary angiography and PCI at the same time.

For the safety end-points, point estimates and 95% confidence intervals were calculated for major and minor haemorrhage in groups 2 and 3. For the efficacy secondary end-points estimates, 95% confidence intervals were calculated for each thrombotic event in all three groups, and in patients experiencing at least one of these events.

Results

Patient Population and Study Treatment

A total of 302 patients were included in the study; 13 received at least one dose of nadroparin but did not undergo coronary angiography (group 1), 140 underwent coronary angiography but not PCI (group 2), 149 underwent both coronary angiography and PCI (group 3). The three populations were similar in most

Table 1. *Summary of patient characteristics at baseline*

		Group 1 (no CA., no PCI: $n = 13$) n (%)	Group 2 (CA, no PCI: $n = 140$) n (%)	Group 3 (CA plus PCI: $n = 149$) n (%)	Total ($n = 302$) n (%)
Gender	Male	7 (54)	86 (61)	117 (79)	210 (70)
Race	Caucasian	13 (100)	140 (100)	149 (100)	302 (100)
Age (years)	Mean	63.5	63.0	61.1	62.1
	SD	7.8	10.5	11.2	10.8
BMI (kg/m^2)	Mean	25.1	26.4	26.8	26.5
	SD	4.2	3.8	3.4	3.6
Previous angina		7 (54)	68 (49)	73 (49)	148 (49)
Previous myocardial infarction		4 (31)	36 (25.7)	30 (20)	70 (23.2)
Previous revascularisation (PTCA, CABG, stenting)		2 (15)	24 (17)	22 (15)	48 (16)
At least one previous coronary ischaemic event		9 (69)	77 (55)	90 (60)	176 (58)
Previous peripheral vascular disease		0 (0)	17 (12)	16 (11)	33 (11)
Previous stroke or transient ischaemic attack		2 (15)	9 (6)	5 (3)	16 (5)
Diagnosis	UA	10 (77)	120 (86)	122 (82)	252 (83)
	NQWMI	3 (23)	20 (14)	27 (18)	50 (17)

CA, coronary angiography; PCI, percutaneous coronary intervention

demographic and clinical characteristics (Table 1). A history of at least one previous coronary thrombotic event, or other cardiovascular history, was present in 58% and 62% of all patients, respectively. Most patients had at least one cardiovascular risk factor and 34% presented with more than two such risk factors. Overall, 83% of patients presented with UA and 17% with NQWMI.

PCI consisted of angioplasty plus stent implantation in 109 patients (73%) and stand-alone balloon angioplasty in 40 patients (27%). The route of access was femoral in 96% of cases. Manual compression of the vascular access was used in 86%. The mean time interval between the last injection of nadroparin and arterial catheterisation for CA was 13 h 18 min (1 h 00 min–28 h 22 min) and 12 h 02 min (1 h 30 min–30 h 20 min) for patients with or without PCI, respectively. In patients undergoing PCI (group 3), the interval between the sheath removal after the procedure and the next nadroparin injection was in average 5 h 06 min (0 h 00 min–14 h 45 min).

Concomitant Treatment

All patients undergoing PCI (group 3) received UFH. Abciximab was used in 7% of patients undergoing PCI. Aspirin was used in 100%, 98% and 98%, respectively, of groups 1, 2 and 3. Clopidogrel or ticlopidine was used in 23%, 24% and 81%, respectively. No patient received alteplase. The majority of patients received a cardiovascular drug treatment: nitrates in 80%, β-blockers in 72%, lipid-lowering agents in 41% and ACE-inhibitors in 30% of cases.

Primary Safety End-points

No patient in group 1 experienced either a major or a minor haemorrhage. Two patients in each of groups 2 and 3 experienced a major haemorrhage (1.4% and 1.3%, respectively) (Table 2). Fifteen (10.7%) and 35 (23.5%) patients, respectively, experienced a minor haemorrhage ($p < 0.05$). Most haemorrhages occurred after the coronary procedure.

Table 2. *Major haemorrhage (primary end-point) and minor haemorrhage*

Population	Major haemorrhage n (%) [95% CI]	Nature of event	Minor haemorrhage n (%) [95% CI]	Nature of event
Group 2 (CA, no PCI: $n = 140$)	2 (1.4) [0.2;5.1]	1 melaena leading to transfusion 1 death due to haemorrhagic shock	15 (10.7) [6.1;17.1]	11 (7.9) at the procedural puncture site
Group 3 (CA plus PCI: $n = 149$)	2 (1.3) [0.2;5.1]	2 haematomas at puncture site leading to transfusion	35 (23.5) [16.9;31.1]	33 (22.1) at the procedural puncture site

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Table 3. *Other bleeding*

	Need for transfusion n (%)	Need for vascular repair n (%)
Group 2 (CA, no PCI: n = 140)	1 (0.7)	0 (0)
Group 3 (CA plus PCI: n = 149)	3 (2.0)	1 (1)

CA, coronary angiography; PCI, percutaneous coronary intervention

Secondary Safety End-points

Other Bleeding Variables

The need for transfusion (< 2 units of blood) and need for vascular repair are shown in Table 3. Only one patient needed vascular repair for haematoma developed at the puncture site.

Other Adverse Events

A total of 124 patients (41%) experienced at least one AE; the proportions of patients with adverse events were similar in groups 2 and 3 (41% and 42%, respectively) and somewhat higher than in group 1 (31%). A total of 69 patients (23%) – 24/140 (17%) and 45/149 (30%) in groups 2 and 3, respectively – had at least one AE considered as study drug-related by the investigator. The AEs linked specifically to bleeding disorders have been reported on Table 4.

Deaths

Three patients (1%), all in group 2, died during the study period. Two of these patients died from new myocardial infarction, one occurring after CABG performed 2 weeks after discontinuation of nadroparin. The third patient died from haemorrhagic shock, which was not related to the study drug according to the judgement of the investigator.

Withdrawals

Sixteen patients withdrew from the study drug due to the occurrence of AEs; six of these AEs were serious:

one recurrent UA, one ischaemic stroke, one moderate melaena and one coronary thrombosis were reported in group 2, whereas one haematoma and one bleeding, both occurring at puncture site, were notified for group 3.

Laboratory Evaluations

Fifteen patients had abnormal haematological test results which, in ten cases, were associated with haemorrhage.

Secondary Efficacy End-points

The number and percentage of patients with at least one thrombotic coronary event were similar in groups 2 and 3. A similar proportion of patients in groups 2 and 3 experienced recurrence of symptoms, refractory UA, MI (NQWMI of QWMI) and/or needed rescue PTCA/CABG (Table 5). However, the proportion of each group experiencing at least one such event was similar: 11/122 (9.0%) and 2/27 (7.4%), respectively.

Discussion

UFH is currently used in patients hospitalised for UA and NQWMI[8]. Several comparative trials[1–7] suggested that the use of LMWH was a useful alternative to UFH, being as efficient and easier to use in this setting of patients.

In the FRAXIS study[7], nadroparin, a LMWH, was shown to be as efficient and safe as UFH, when given to patients with UA and NQWMI for a 6-day period. However, in the FRAXIS study, there was no information available on the interval between the coronary procedure and the previous and subsequent SC injection of nadroparin in patients undergoing PCI. Moreover, the patients receiving other antithrombotic agents, apart from UFH and aspirin, were excluded.

This therefore justified the present, open-label, study in which nadroparin administration was interrupted on average at least 8 h before the administration of UFH for

Table 4. *Adverse events linked to platelet, bleeding and clotting disorders with incidence ≥ 1% reported study drug-related*

Platelet, bleeding and clotting disorders	Group 1 (no CA, no PCI: n = 13) n (%)	Group 2 (CA, no PCI: n = 140) n (%)	Group 3 (CA plus PCI: n = 149) n (%)	Total (n = 302) n (%)
All	0 (0)	18 (13)	39 (26)	57 (19)
Haematoma	0 (0)	9 (6)	16 (11)	25 (8)
Haematuria	0 (0)	2 (1)	1 (< 1)	3 (< 1)
Haemorrhage (not otherwise specified)	0 (0)	2 (1)	17 (11)	19 (6)
Haemorrhage of surgical wound	0 (0)	0 (0)	2 (1)	2 (< 1)
Purpura	0 (0)	3 (2)	5 (3)	8 (3)

CA, coronary angiography; PCI, percutaneous coronary intervention

Table 5. Summary of thrombotic coronary events and rescue PTCA and CABG procedures

Patients who experienced:	Group 1 (no CA no PCI: n = 13) n (%) [CI]	Group 2 (CA, no PCI: n = 140) n (%) [CI]	Group 3 (CA plus PCI: n = 149) n (%) [CI]	Total (n = 302) n (%) [CI]
≥1 event	3 (23.1) [5.0;53.8]	12 (8.6) [4.5;14.5]	13 (8.7) [4.7;14.5]	28 (9.3) [6.0;12.5]
Recurrent angina	0 (0)	8 (5.7) [2.5;10.9]	10 (6.7) [3.3;12.0]	18 (6.0) [3.3;8.6]
Refractory angina	2 (15.4) [1.9;45.4]	2 (1.4) [0.2;5.1]	1 (0.7) [0.0;3.7]	5 (1.7) [0.2;3.1]
Q-wave or non-Q-wave MI	1 (7.7) [0.2;36.0]	2 (1.4) [0.2;5.1]	2 (1.3) [0.2;4.8]	5 (1.7) [0.2;3.1]
Need for rescue PTCA	3 (23.1) [5.0;53.8]	0 (0.0)	2 (1.3) [0.2;4.8]	5 (1.7) [0.2;3.1]
Need for emergency CABG	0 (0)	3 (2.1) [0.4;6.1]	0 (0)	3 (1.0) [–0.1;2.1]

CA, coronary angiography; PCI, percutaneous coronary intervention

PCI, and resumed after PCI when the aPTT was less than or equal to twice the control values, on average 5 h after the procedure. The overall incidence of major haemorrhage was 1.3% (95% CI: 0.0; 2.6) – consistent with the 1.0% reported at 6 days for the pooled data of the two nadroparin groups in the FRAXIS study[7].

It should also be noted that, in the current study, 289/302 patients (95.7%) and 149/302 patients (49.3%), respectively, underwent CA and CA followed by PCI with the concomitant use of UFH. In the FRAXIS study, in contrast, only 4.9% of patients receiving nadroparin had undergone either PCI or CABG by day 6 (the proportion undergoing PCI was not reported separately).

In the current study, furthermore, half of the four major haemorrhages occurred at the arterial puncture site and there were no intracranial haemorrhages. Minor haemorrhage was reported in 23.5% of patients undergoing PCI. This is consistent with a minor haemorrhage incidence of 10.7% in patients undergoing coronary angiography alone. Most minor haemorrhages occurred at the nadroparin injection site or at the access site – haemostasis usually being achieved at the latter after a 20–30 min compression. The incidence of coronary thrombotic events was 9.3% overall, and 8.7% and 8.6%, respectively, for patients undergoing coronary angiography with and without PCI.

Globally, the rate of the coronary thrombotic events as observed in this series was consistent with the published data[9]. Only three deaths (1% overall) were reported during the study period and all occurred among the patients undergoing coronary angiography without PCI. All three were reported as serious adverse events unrelated to the study drug. The diagnosis of MI was established as the cause of two of these deaths. The third death was likely due to an haemorrhagic shock, whereas nadroparin was stopped some time before the event.

Conclusion

The results of the present study suggest that coronary angiography with or without PCI can be safely performed in aspirin-treated patients receiving nadroparin 86 IU/kg as an initial IV bolus, substituted by unfractionated heparin for the duration of the procedure and/or intervention, and then nadroparin as a SC injection every 12 h during the acute phase of UA or NQWMI, provided there is an interval of at least 8 h between the last injection of nadroparin and the start of the coronary procedure. Most of the bleeding events were minor and occurred mainly at the puncture site. The incidence of major haemorrhage was low (1.3%) and consistent with that reported in other studies. According to these results, the tolerability of nadroparin is favourable and in line with the previous published data, even in patients undergoing PCI for non-ST elevation ACS.

Acknowledgment

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