

Surgical bleeding after pre-operative unfractionated heparin and low molecular weight heparin for coronary bypass surgery

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ABSTRACT

Background and Objectives

Since the impairment of platelet function may cause excess peri-operative bleeding, pre-operative discontinuation of aspirin and heparin bridging are common for cardiac surgery. We evaluated the impact of pre-operative administration of enoxaparin and unfractionated heparin (UFH) on coagulation parameters and peri-operative bleeding in patients undergoing elective coronary artery bypass grafting (CABG) surgery after discontinuation of aspirin.

Design and Methods

Forty-three patients with three-vessel coronary artery disease undergoing elective CABG surgery discontinued aspirin and were randomized to receive either UFH 180 UI/Kg \times 2/day s.c. or enoxaparin 100 UI/Kg \times 2/day s.c. until 12 h before surgery (median pre-operative treatment 8 days, range 6-12 days). Surgery was performed as usual with UFH. Neither UFH nor any low molecular weight heparin was given in the immediate post-operative period. The effects of UFH and enoxaparin were monitored by the activated partial thromboplastin time (aPTT) and the Enox-test (sensitive to factor Xa inhibition) using a Rapidpoint® Coagulation Analyzer. aPTT and factor Xa activity were also measured by standard methods. Peri-operative bleeding and the nadirs of hemoglobin concentration, hematocrit and platelet count were monitored post-operatively.

Results

Patients in the two groups were similar for number of bypasses, on-pump time, total surgery time, and time from the last heparin administration. Coagulation parameters increased significantly and similarly at 30 min and 6 h with both treatments, but returned within the normal range at 12 h. Hemoglobin, hematocrit and platelet counts significantly decreased to the same extent after CABG and re-normalized at the same time. Transfusal requirements of blood and plasma units were similar in the two groups.

Interpretation and Conclusions

From the kinetics of coagulation parameters and the evaluation of bleeding, enoxaparin is a safe alternative to UFH as a bridging therapy to CABG after discontinuation of aspirin.

Key words: unfractionated heparin, enoxaparin, low molecular weight heparins, bypass surgery, bleeding.

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The use of heparins before coronary artery bypass surgery has two important rationales: (a) to prevent the occurrence of deep vein thrombosis, the risk of which is substantially increased in surgical patients in general and in coronary bypass graft (CABG) surgery patients in particular;¹ (b) to provide an antithrombotic substitute for aspirin, the prolonged action of which, when given throughout the pre-operative period, prevents the recovery of full hemostatic competence at the time of surgery. Indeed, while the post-operative use of aspirin is recommended early on after CABG surgery (even by naso-gastric tube administration)² to prevent early bypass thrombotic occlusion, and contributes to long-term bypass patency,^{3,4} the use of pre-operative aspirin, immediately before surgery, is controversial.⁵⁻⁹ In patients with chronic stable angina and low-risk plaque morphology, aspirin discontinuation 7-10 days before elective cardiac operations appears to be prudent to decrease the risk of peri-operative bleeding and thus the need for transfusion.² However, no indications for aspirin discontinuation exist for patients with acute coronary syndromes, in whom the benefit of aspirin is higher than in those with stable angina.¹⁰

In order to ensure some anti-thrombotic protection and, at the same time, allow rapid restoration of hemostatic competence at the time of surgery, bridging antithrombotic therapy with heparin may – at least partially – substitute aspirin until surgery is performed. Bridging therapy with subcutaneous unfractionated heparin (UFH) is therefore common practice in several general surgical settings and in CABG surgery in particular, in which coronary artery disease entails an increased risk of coronary thrombosis. Ideally, the administration of heparins should be continued as long as possible in the pre-operative period, in order to provide full anti-thrombotic coverage, but should also allow a complete recovery of hemostatic competence at the time of surgery.

Since low molecular weight heparins (LMWH) provide many pharmacokinetic advantages compared with UFH, including a more predictable anticoagulant response, higher bioavailability, lower binding to plasma proteins, platelet factor 4 and endothelial cells, lower plasma clearance and a longer plasma half-life,¹¹ as well as a lower incidence of heparin-induced thrombocytopenia,¹² and since they are a valid substitute for UFH in a number of settings, such as non-ST elevation acute coronary syndromes¹³ and prevention of venous thromboembolism,¹ LMWH may provide a useful bridge to revascularization in patients undergoing CABG surgery.

Obstacles to the spread of this practice are mainly the absence of solid evidence of equivalence (or superiority) of efficacy in this setting,^{9,14} and the proof of equal safety, namely the absence of excess bleeding. The safety of

LMWH vs UFH appears to be comparable in a number of surgical settings,^{15,16} but some studies have suggested an increased number of hemorrhagic complications after LMWH, particularly with the use of higher doses.^{17, 18} Evidence of excess bleeding might therefore limit the emphasis on the use of a LMWH in patients undergoing CABG surgery. This might be a problem, as such patients are generally at high risk of thrombotic events and for this reason need higher doses than those used for prevention of venous thromboembolism.

Against this background, we compared surgical bleeding after a 12 h discontinuation of either UFH or the LMWH enoxaparin in the setting of CABG surgery. The specific hypothesis of this study was that a 12 h interval is sufficient not to cause excess peri-operative bleeding, and is therefore an optimal compromise between antithrombotic efficacy and hemorrhagic safety.

Design and Methods

Patients

We included patients aged 35-75 years with three-vessel coronary artery disease (CAD) who were candidates for elective CABG. Exclusion criteria were the requirement for other additional (valve, carotid, etc.) simultaneous surgery (potentially altering the otherwise fairly standardized surgery times), the choice of off-pump surgery, any altered liver and kidney laboratory parameters, a history of any hemorrhagic disorder, platelet count <100,000 or >450,000/ μ L, as well as treatment with ticlopidine or clopidogrel in the last month.

Out of 50 consecutive patients admitted to the Cardiac Surgery Division at the University of Chieti Medical School for elective CABG surgery between November 2004 and May 2005, a total of seven patients were excluded from the study: two cases because of additional requirement of mitral valvuloplasty, one because of a platelet count of 80,000/ μ L, two because of recent treatment with a thienopyridine (ticlopidine), one because of chronic renal disease with a serum creatinine of 2.3 mg/dL, and one because of age (76 years). The remaining 43 patients were randomly allocated to receive either UFH (n=22) or enoxaparin (n=21).

We calculated a sample size of 21 subjects per group to provide a study power of 95% to detect a difference of 0.1 mg/dL in hemoglobin or a difference of 0.5% in hematocrit, with a one-sided type I error of 0.01. Such a sample size also provided a study power of 95% to detect a difference of 2×10^3 platelets/ μ L with a one-sided type I error of 0.05.

Patients were admitted to the Cardiac Surgery Division 9 ± 3 (mean \pm SD) days before the planned day of surgery. They all discontinued aspirin immediately and received UFH, 180 UI/Kg \times 2/day (volume range 0.3-0.6 mL \times 2/day) s.c. or enoxaparin 100 UI/Kg \times 2/day

(range 6000-8000 UI \times 2/day) s.c. until 12 h before surgery (median 8 days, range 6-12 days of treatment). All patients were operated by the same two surgeons (AC and GDG, among the authors of the study), using a standard surgical technique involving non-pulsatile cardiopulmonary bypass with systemic cooling. No anticoagulant was used after surgery. After 48 h, all patients resumed low-dose (100 mg) aspirin administration.

The study protocol was approved by the local ethics committee. Written informed consent was obtained from all subjects enrolled.

Coagulation tests

To monitor UFH, the (aPTT) activated partial thromboplastin time was evaluated by a traditional method,¹⁹ using the HemosIL SynthASil kit (Instrumentation Laboratory, Milan, Italy) and an Electra 1400 coagulometer (Instrumentation Laboratory), as well as by a Rapidpoint[®]Coagulation analyzer, consisting of a micro-processor-based analyzer and single-use assay-specific test cards: the analyzer photo-mechanically monitors fibrin clot formation in a flat capillary chamber on the surface of a test card.^{20,22} Values of the aPTT <35 s were considered normal, and values >40 s were considered in the therapeutic range.

To monitor enoxaparin, factor Xa was measured by both a chromogenic method²³ and the Enox-test. The Enox-test is a new-generation automated test specific for enoxaparin, performed by the Rapidpoint[®]Coagulation analyzer: factor Xa within a blood sample is rapidly generated by a specific factor X activator, thereby initiating the clotting cascade. Enoxaparin from the patient's blood complexes with antithrombin to inhibit factor Xa (and to a lesser extent factor IIa) and proportionally lengthens the clotting time.^{20,22} The instrument's display shows coagulation time in seconds, with 260 s corresponding to 1 antiXa U/mL. Here values <260 s were considered as sub-optimal anticoagulation.²⁴ The ENOX card is optimized for enoxaparin monitoring, but is known to be affected by other heparins.

As a control, the aPTT, performed by the two methods, was also measured in patients treated with enoxaparin. Both the Enox-test and factor Xa measurement were also performed in patients treated with UFH.

All coagulation parameters were assessed before the first administration of heparin (enoxaparin or UFH) and at 30 min, 6 h and 12 h after the last s.c. injection before surgery. Venous blood samples were collected into standard 3.8% (weight to weight) sodium citrate tubes, with a blood-to-sodium citrate ratio of 9:1 for both the Rapidpoint[®]Coagulation analyzer and the other laboratory measurements.

Assessment of peri-operative blood loss

Red blood cell count as well as hemoglobin concen-

tration, hematocrit and platelet count were measured immediately before and after surgery. Post-operative bleeding was classified as major or minor according to the TIMI bleeding classification.²⁵ Major bleeding was defined as intracranial hemorrhage or a ≥ 5 g/dL decrease in the hemoglobin concentration, or a $\geq 15\%$ absolute decrease in hematocrit. Minor bleeding was defined as (i) an observed blood loss with either ≥ 3 g/dL decrease in hemoglobin concentration or $\geq 10\%$ decrease in the hematocrit; (ii) a non-observed blood loss with ≥ 4 g/dL decrease in hemoglobin concentration or $\geq 12\%$ decrease in the hematocrit. Minimal bleeding was defined as any clinically overt sign of hemorrhage associated with <3 g/dL decrease in hemoglobin concentration or <9% decrease in the hematocrit.

Statistical analysis

Discrete variables were described as absolute values and percentages; continuous variables were described as mean \pm standard deviation (SD) after checking the normality of distributions. Hematologic parameters analyzed in the general study population were compared before and after CABG by the Student's *t*-test for paired data. Hematologic parameters and variations of such parameters, normalized for the basal values, were compared in the two randomization groups by the Student's *t*-test for unpaired data. Statistical significance was set at a *p* value <0.05.

Results of the aPTT and Enox-test performed with the Rapidpoint[®]Coagulation analyzer were related to the aPTT and factor Xa results measured by traditional laboratory methods, respectively, by linear regression analysis. Coagulation parameters measured at different times were analyzed by one way analysis of variance (ANOVA). In the presence of significant F values, results at different times were compared by the Bonferroni-Dunn's test and statistical significance was assumed for a *p* value <0.0083 (original *p*=0.05/number of comparisons). Analyses were performed with the Stat-View statistical software (Calabasas, CA, USA).

Results

Demographic and surgery-related characteristics, these latter including number of bypasses, on-pump time, total surgery time, and time elapsed between the last administration of heparins and the beginning of surgery, are reported in Table 1 and Table 2, respectively. All variables were similar between the two groups.

Coagulation tests

Values of the aPTT from all patients measured with the Rapidpoint[®]Coagulation analyzer correlated strongly with those measured with the traditional method ($R=0.85$, $p<0.0001$) (*data not shown*).

Results of the Enox-test from all patients measured

with the Rapidpoint®Coagulation analyzer correlated well with factor Xa units measured with the chromogenic method ($R=0.78$, $p<0.0001$) (data not shown).

Values of the aPTT and of the Enox-test measured with the Rapidpoint Coagulation®Analyzer were then used for further statistical analyses.

In patients treated with UFH, aPTT values, in a normal range at the basal measurement, increased significantly 30 min after drug administration and even more after 6 h, with a subsequent decline at 12 h, returning to the normal range, albeit at this point still significantly different from basal values (Figure 1). In patients treated with enoxaparin, the aPTT modifications were smaller, with a significant increase only detectable at 6 h; however, the mean aPTT value at 6 h was still within normal limits (Figure 1).

In contrast, in patients treated with enoxaparin, the Enox-test, in a normal range at baseline, increased significantly 30 min after drug administration and even more after 6 h; the Enox-test values then decreased significantly to normal values at 12 h (Figure 2). No significant differences were observed between the Enox-test values measured 12 h after drug administration and those of the basal Enox-test.

In patients treated with UFH, the Enox-test modifications were smaller, with a significant increase at 6 h and a decrease at 12 h; however, the mean Enox-test value at 6 h was <260 s (<1 antiXa U/mL), therefore still within normal limits (Figure 2).

Assessment of peri-operative blood loss, bleeding and thrombotic events

Hemoglobin, hematocrit and platelet counts were similar in the two groups before and after CABG, decreasing significantly after CABG compared with values before CABG (Figure 3).

The percent changes ($\Delta\%$) of these parameters, each calculated as $\text{pre-operative value} - \text{post-operative value} / \text{pre-operative value} \times 100$, were similar in the two treatment groups (Table 3). In the UFH and in the enoxaparin groups, the mean absolute reductions of hemoglobin were 2.6 g/dL and 2.5 g/dL, the mean absolute reductions of hematocrit were 8% and 7%, and the mean absolute reductions of platelet counts were $50 \times 10^3/\mu\text{L}$ and $51 \times 10^3/\mu\text{L}$, respectively.

The numbers of transfused blood units and plasma units were similar in the two treatment groups: 17 blood units were transfused in the UFH group vs. 15 in the enoxaparin group; 3 plasma units in the UFH group vs. 1 in the enoxaparin group (for all, $p=N.S.$). The means (\pm SD) of blood and plasma units transfused per patient in the two groups are reported in Table 3.

No patient experienced a major bleed or needed repeat sternotomy. Two patients experienced minor bleeding: one patient in the group treated with UFH had

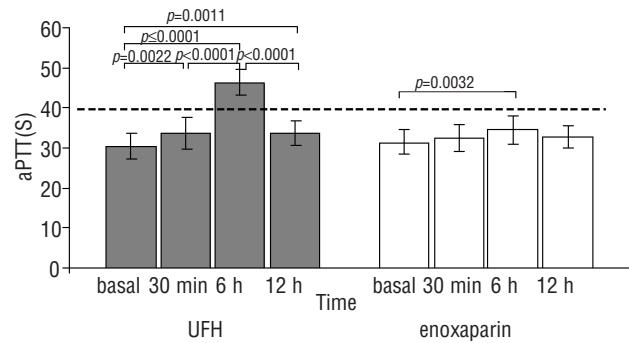


Figure 1. aPTT values in the two treatment groups. Gray columns on the left show mean aPTT values in patients treated with UFH, and white columns on the right show mean aPTT values in patients treated with enoxaparin, measured with the Rapidpoint® Coagulation analyzer before the first administration of the drug (baseline) and 30 min, 6 h and 12 h after a single s.c. injection during the day before surgery. Error bars indicate the standard deviation. Horizontal lines indicate statistically significant differences. The dashed line shows the upper normal limit of the aPTT.

Table 1. Demographic characteristics of the two groups of patients.

	UFH	Enoxaparin	p
Number	22	21	N.S.
Sex (male/female)	17/5	15/6	N.S.
Age (years)	63±8	64±10	N.S.
Height (cm)	171±9	168±10	N.S.
Weight (Kg)	73±11	74±12	N.S.
Body surface area (m ²)	185±16	183±17	N.S.

Age, height, weight and body surface area are expressed as mean \pm SD.

Table 2. Surgery-related characteristics of the two groups of patients.

	UFH	Enoxaparin	p
N. of bypasses/patient	3.27±0.46	3.19±0.40	N.S.
On-pump time (min)	121±46	120±44	N.S.
Total surgery time (min)	294±67	297±63	N.S.
Heparin-to-surgery time (min)	1054±273	1007±177	N.S.

Data are expressed as mean \pm SD.

a pericardial effusion with a decrease in hemoglobin of 3.5 g/dL, and one patient in the group treated with enoxaparin had a large wound hematoma with a decrease in hemoglobin of 3.2 g/dL.

Seven patients experienced minimal bleeding, such as ecchymoses (three patients in the UFH group and two in the enoxaparin group), wound hematoma near the incision (one patient in the enoxaparin group), and hematuria (one patient in the UFH group), all associated with a hemoglobin drop of <3 g/dL.

No patients experienced thrombotic events within 48

Table 3. Percent change of hematologic parameters and number of transfused blood and plasma units after CABG in the two groups of patients.

	UFH	Enoxaparin	p
Hemoglobin Δ%	19.6±7.8	18.8±9.1	N.S.
Hematocrit Δ%	19.8±7.9	17.8±8.5	N.S.
Platelet count Δ%	23.4±9.3	24.6±12.6	N.S.
Transfused blood units/patient	0.8±0.7	0.7±0.6	N.S.
Transfused plasma units/patient	0.1±0.3	0.05±0.2	N.S.

Data are expressed as mean ± SD.

h, after which time all patients recommenced aspirin treatment. We observed no case of heparin-induced thrombocytopenia in either group of patients.

Discussion

In this trial we performed a comparison of surgical bleeding after a 12-hour discontinuation of either UFH or the LMWH enoxaparin in the setting of coronary bypass surgery, showing a substantial equivalence of the two treatments.

Both UFH and enoxaparin therapies were monitored with a Rapidpoint®Coagulation analyzer, measuring the aPTT and using a new-generation monitoring test specific for enoxaparin, the Enox-test. Values of the aPTT obtained with this point-of-care analyzer correlated strictly with those obtained with the traditional method, and the Enox-test times correlated with factor Xa units obtained by the standard chromogenic method. Changes in both the aPTT and the Enox-test were in agreement with the expected pharmacokinetic properties of the two drugs, with the peak anticoagulant effect occurring at about 6 h after the s.c. injection and a normalization at 12 h. Changes in the aPTT, although present in both groups, were more evident, reaching a therapeutic range (>40 s) at 6 h, in the group treated with UFH, because of the greater sensitivity of this test to a drug – UFH – that affects thrombin activity more than enoxaparin. Likewise, variations in the Enox-test were more evident, reaching a therapeutic range (>260 s) at 6 h, in the group treated with enoxaparin because this test, although affected also by UFH and other LMWH, is optimized for enoxaparin monitoring. In agreement with previous experience,²¹ in our study the Enox-test range before treatment was 76-199 s, reached 265-434 s at 6 h after enoxaparin administration, and decreased to 91-220 s at 12 h. In the Evaluating of Enoxaparin Clotting Times (ELECT) study,²¹ a non-randomized and open-label observational study, the Enox-test was used to discern a target range of anticoagulation for enoxaparin during percutaneous coronary intervention: the Enox-test range of 250-450 s was sug-

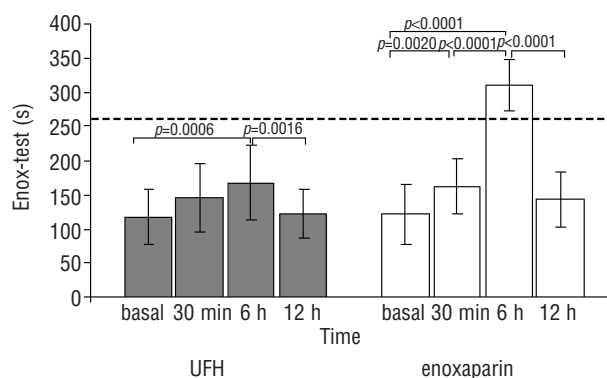


Figure 2. Enox-test times in the two treatment groups. Gray columns on the left show mean Enox-test times in patients treated with UFH and white columns on the right in patients treated with enoxaparin, measured before the first administration of the drug and 30 min, 6 h and 12 h after a single s.c. injection during the day before surgery. Error bars indicate the standard deviation. Horizontal lines indicate statistically significant differences. The dashed line shows the upper normal limit of the Enox-test.

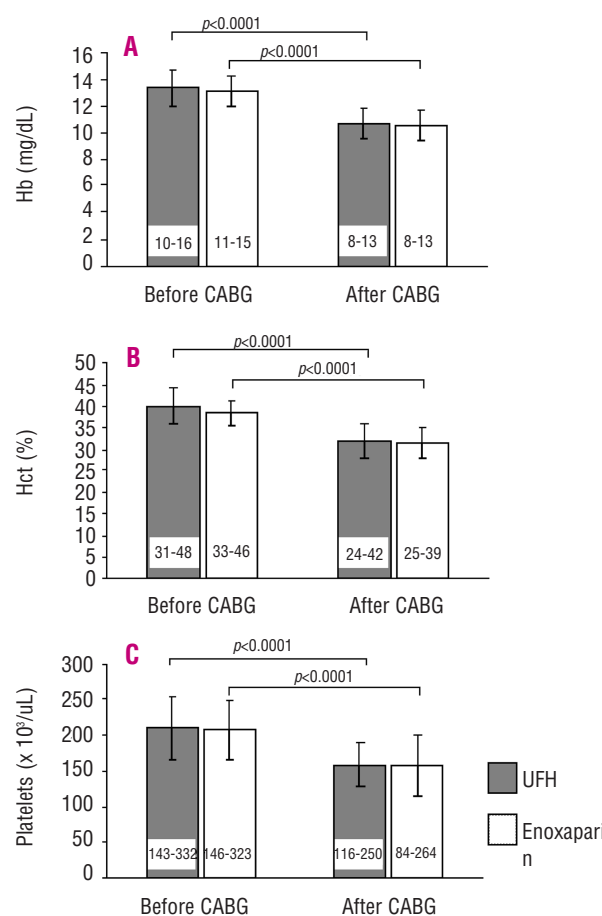


Figure 3. Hematologic parameters before and after CABG in the two treatment groups. Panel A shows mean hemoglobin concentration, panel B mean hematocrit, and panel C mean platelet count, determined before and about 1 hour after CABG surgery. Gray columns refer to the UFH group and white columns to the enoxaparin group. Error bars indicate the standard deviation. The numbers inside the columns indicate the ranges of the data. Horizontal lines indicate statistically significant differences.

gested for percutaneous coronary interventions (corresponding to anti-Xa level of 0.8 to 1.8 IU/mL) and 200-250 s for safe arterial sheath removal. Moreover, in that study the Enox-test time was correlated with clinical outcome, with a nadir of ischemic events between 300 and 350 s and an increase of both ischemia and bleeding events with an Enox-test time exceeding 450 s (>1.8 IU/mL antiXa).²¹ In our study, 12 h after the last injection of UFH or enoxaparin, both the aPTT and the Enox-test indicated a substantial recovery of hemostatic competence in all cases, albeit with slower kinetics for enoxaparin than for UFH.

As in our previous experience,²⁶ we chose hemoglobin concentration, hematocrit and platelet count as indices of peri-operative bleeding. These parameters decreased in all patients, but their relative variation did not differ between the two treatment groups, resulting in an equal number of blood and plasma units transfused in the two groups. In our patients, who discontinued aspirin 7 days before surgery and underwent surgery 16-17 h after the last administration of UFH or enoxaparin, the decline of these hematologic parameters was related to surgical variables, such as the extent of chest opening, the number of bypasses, the duration of surgery and extracorporeal circulation, as well as to the rapidity and skill of the surgeon. Since these variables were equally distributed in the two groups, the observation of no differences in bleeding complications detected between patients treated with UFH and those treated with enoxaparin speaks in favor of a similar recovery of hemostatic function at the time of surgery, as confirmed by the normalization of coagulation tests.

Another recent study assessed blood loss in patients undergoing coronary bypass grafting, dividing the patients into four treatment groups¹⁴: (i) elective patients who stopped aspirin 5 days before the operation; (ii) unstable angina patients maintained on aspirin and UFH infusion; (iii) unstable angina patients maintained on aspirin and dalteparin, stopped at least 12 h before surgery; (iv) unstable angina patients maintained on dalteparin until <12 h before cardiac surgery. In that study, dalteparin was compared with UFH in patients with unstable angina continuing on aspirin until surgery. Significantly more bleeding, assessed as blood losses through mediastinal drainages, was noted in both groups maintained on aspirin and UFH or dalteparin compared with that in the group of patients who stopped aspirin, but there were no differences between the group assigned to UFH and the group receiving dalteparin stopped 12 h before surgery. On the contrary, significantly greater blood loss was observed in patients who stopped dalteparin <12 h before surgery, related to a residual interference with coagulation. However, dalteparin is not the LMWH of choice in patients with unstable angina, because its use is not supported by the same amount of literature as enoxaparin in this set-

ting.^{27,28} Enoxaparin was compared with UFH in a retrospective study in patients presenting with an acute coronary syndrome and sent directly to open-heart surgery while still on anticoagulation.²⁹ In that study, the pre-operative use of enoxaparin, compared with UFH, was associated with a significantly increased incidence of re-exploration for post-operative bleeding. However no difference between the groups was noted in the average number of units of packed red blood cells or platelets transfused, and, likewise, no difference was noted in the total numbers of patients requiring any blood product transfusion. Moreover, in that study the last dose of enoxaparin was administered up until 3-40 hours (range) before surgery, and therefore many patients received enoxaparin <12 hours before the operation, a time probably insufficient for full restoration of hemostatic competence.

The object of our present study was to compare surgical bleeding after a ≥ 12 -hour discontinuation of either UFH or of the most widely used LMWH – enoxaparin – in the setting of elective CABG surgery.

We can provide no data on a comparative group of patients treated with aspirin throughout the peri-operative period, because of the preference of our surgeons to avoid excess bleeding. We also have no data on a comparative group of untreated patients (no aspirin, no heparin), because this would imply the lack of any antithrombotic coverage throughout the pre-operative period. Some information is available, from a case-control study, suggesting that pre-operative aspirin use, within 7 days from CABG, is associated with decreased mortality, compared with aspirin discontinuation, without a significant increase in bleeding, or in the requirements of blood products, or in related morbidities.⁵ However, the authors did not report on the timing of aspirin use within the 7-day pre-operative period, or on whether patients were treated or not before that time.⁵

In the limited sample size of patients enrolled in our study, no patient experienced symptoms or signs attributable to thrombotic events - such as unstable angina - after aspirin discontinuation in the peri-operative period, lasting up to 48 hours after surgery, at which time they all resumed aspirin. Although we could not compare our two groups of patients (who both discontinued aspirin) with a third group who remained on aspirin pre-operatively, and although there are no clinical randomized trials evaluating cardiovascular risk after aspirin withdrawal, it has been suggested that withholding aspirin peri-operatively for 7 days would add a very little risk to patients treated for secondary prevention of vascular events.³⁰ Moreover, although there is some evidence suggesting that rebound phenomena may occur when long-term aspirin is discontinued, with the promotion of a pro-thrombotic state,³¹⁻³³ recent data have shown that - on average - 10 days typically elapse between aspirin withdrawal and thrombotic events, which is in line with

the normal mean platelet survival.³⁴

Because of our sample size limitations, precluding large-group comparisons of bleeding, we also evaluated surrogate parameters for bleeding in our study, including the fall of hematologic parameters. Most studies comparing peri-surgical bleeding in patients discontinuing aspirin before cardiac surgery and that in patients treated with aspirin until surgery evaluated chest-tube drainage and the amount of blood transfused as parameters of blood loss, as synthesized in a recent review.³⁵ Some of these studies suggested that pre-operative aspirin therapy, although able to improve graft patency, also increases the risk of post-operative bleeding and the need for re-operation.³⁵ On the other hand, other studies have shown that pre-operative aspirin does not increase transfusion requirements.³⁵ Therefore this issue is still controversial. Unfortunately, there are no data in any clinical study comparing hemoglobin, hematocrit and platelet count in these patients. However, a recent review³⁶ did recommend that laboratory testing before cardiac surgery should include a full blood count to assess both hemoglobin and platelet numbers, since significant reductions in these parameters may occur, with most cases probably occurring in the absence of symptoms and therefore only detectable by hematologic testing. The results of our surrogate measurements fully support the conclusion deriving from the actual assessment of peri-operative bleeding.

We found an overall similar efficacy of enoxaparin and UFH on coagulation parameters. On the one hand, coagulation tests indicated a complete recovery of hemostatic function at 12 h after the last s.c. injection of both UFH and enoxaparin, also with no differences in

the kinetics of hematologic parameters between the two treatment groups. On the other hand, bleeding complications were similar in the two groups, and mostly not relevant.

One important aspect of enoxaparin vs. UFH s.c. use is the predictability of the anticoagulant effect due to the much larger bioavailability and the lesser interference with plasma proteins and cellular surfaces. Another potential advantage of LMWH in general is the reduced risk of heparin-induced thrombocytopenia. Although in our study we did not observe any case of such a severe complication, the risk of heparin-induced thrombocytopenia, occurring after 5-10 days of heparin therapy, is known to be significantly lower with LMWH than with UFH¹² therefore conferring LMWH an important safety advantage. This is another strong argument for advocating the use of enoxaparin in our setting.

We performed this study in stable ischemic patients, in whom enoxaparin may provide an *antithrombotic bridge* to revascularization during discontinuation of aspirin. These results should now also be confirmed in patients with unstable angina, in whom, however, aspirin discontinuation is not recommended.

Authors' Contributions

GR: designed and coordinated the study, and wrote the manuscript; RDP: performed blood sampling; AD'A: performed blood sampling; AS: performed blood sampling; MZ: statistical analysis; EDC: factor Xa assays; RL: coordination of factor Xa assays; GDM: one of the two cardiac surgeons operating patients; AC: one of the two cardiac surgeons operating patients; RDC: rdcater@unich.it: designed the study and wrote the manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest.

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