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IN FOCUS

A randomized study comparing the efficacy and safety of nadroparin 2850 IU (0.3 mL) vs. enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer

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See also Tosetto A. Enoxaparin vs. nadroparin for venous thromboembolism prevention: too close to tell? This issue, pp 1691–2.

Summary. *Background:* The optimal thromboprophylactic dosage regimen of low-molecular-weight heparins in high-risk general surgery remains debatable. *Objectives:* We performed a randomized, double-blind study to compare the efficacy and safety of nadroparin 2850 IU (0.3 mL) and enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism (VTE) after colorectal surgery for cancer. *Patients and methods:* Patients undergoing resection of colorectal adenocarcinoma were randomized to receive once daily either 2850 IU nadroparin or 4000 IU enoxaparin s.c. for 9 ± 2 days. The primary efficacy outcome was the composite of deep vein thrombosis (DVT) detected by bilateral venography or documented symptomatic DVT or pulmonary embolism up to day 12. The main safety outcome was major bleeding. A blinded independent committee adjudicated all outcomes. *Results:* Out of 1288 patients analyzed, efficacy was evaluable in 950 (73.8%) patients. The VTE rate was 15.9% (74/464) in nadroparin-treated patients and 12.6% (61/486) in enoxaparin-treated patients, a relative risk of 1.27 (95% confidence interval; CI: 0.93–1.74) that did not met the criterion for non-inferiority of nadroparin. The rate of proximal DVT was comparable in the two groups (3.2% vs. 2.9%, respectively), but that of symptomatic VTE was lower in nadroparin-treated patients (0.2% vs. 1.4%). There was significantly ($P = 0.012$) less major bleeding in nadroparin- than in enoxaparin-treated patients (7.3% vs. 11.5%, respectively). *Conclusion:* Compared with those receiving enoxaparin 4000 IU, patients treated with nadroparin 2850 IU showed a higher incidence of asymptomatic distal DVT, but a lower incidence of symptomatic VTE. Nadroparin treatment was safer in terms of bleeding risk.

Keywords: cancer surgery, low-molecular-weight heparin, venous thromboembolism.

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Introduction

Cancer patients undergoing general surgery have at least twice the risk of postoperative deep vein thrombosis (DVT) and more than three times the risk of fatal pulmonary embolism (PE) compared with non-cancer patients undergoing similar procedures [1]. Without effective prophylaxis, the reported incidence of DVT, as assessed by the fibrinogen uptake test, is 29% (95% confidence interval; CI: 25–33) [1]. Consequently, experts recommend that such patients systematically receive prophylaxis with either unfractionated heparin (UH) or low-molecular-weight heparins (LMWHs) [2]. In view of their once-daily dosage regimen, and because their use does not require coagulation monitoring and is associated with a reduced risk of heparin-induced thrombocytopenia, LMWHs have now largely replaced UH as the prophylactic drug of choice in general surgery [3]. However, the optimal dosage regimen of LMWHs

remains debatable because it is different according to the type of LMWHs, and very few studies have directly compared different dosage regimens of LMWHs in general surgery [4–7]. Importantly, cancer surgery is also associated with an increased risk of bleeding [8,9]. We therefore performed a randomized, double-blind study to compare the efficacy and safety of once-daily 2850 antifactor (F) Xa IU of nadroparin and once-daily 4000 anti-FXa IU enoxaparin in the prevention of venous thromboembolism (VTE) after elective colorectal surgery for cancer. Of all abdominal operations, colorectal surgery carries one of the highest risks of VTE [3,10]. The dosage regimens of nadroparin and enoxaparin used in this trial were those approved by health authorities. They were shown to be as effective as 5000 IU of UH given three times daily in patients undergoing surgery for cancer, but there was a trend towards an increased risk of major bleeding in patients treated with 4000 IU of enoxaparin [11–13].

Patients and methods

This was a prospective, randomized, double-blind, double-dummy, parallel-group, multicenter trial comparing nadroparin and enoxaparin.

Patients

All patients undergoing elective resection of colorectal adenocarcinoma under general anesthesia, regardless of the cancer stage, were eligible for the study, with the following exceptions: if surgery was performed as an emergency or under locoregional anesthesia; or if surgery did not result in adenocarcinoma resection or was associated with the resection of three or more liver metastases. Other main exclusion criteria were: hemorrhagic stroke or stroke of undetermined origin within the previous 2 months; neurosurgical intervention within the previous 2 months; acute bacterial endocarditis; pregnancy; documented hemostasis disorder; thrombocytopenia; contraindication for anticoagulant therapy; prior history of heparin allergy or heparin-induced thrombocytopenia; impaired renal (serum creatinine concentration above 200 μmol L^{-1}) or liver function; and impossibility of performing venography. Patients on long-term anticoagulant or antiplatelet therapy before surgery were also excluded.

Study design

Eligible patients were randomized before surgery using a predefined randomization list. Randomization was stratified by center and concealment of randomization was achieved through centralized distant randomization. Patients were assigned to receive once-daily s.c. injections of either 2850 anti-FXa IU of nadroparin (0.3 mL, Fraxiparine®; GlaxoSmithKline, Harlow, UK) and a placebo of enoxaparin, or 4000 anti-FXa IU of enoxaparin (40 mg, 0.4 mL, Lovenox®/Clexane®; Sanofi–Aventis, Paris, France) and a placebo of nadroparin. The first injection of the drugs took place 2–4 h before surgery. Thereafter, the drugs were given every morning once daily at the same dose. These dosage regimens were those recommended for use by the respective manufacturers when the trial was conducted.

The day of surgery was defined as day 1. Treatment was scheduled to last for 7–11 days and the primary efficacy outcome was assessed between days 1 and 12. A visit was scheduled between days 42 and 60, in which patients reported any symptoms or signs of VTE or bleeding and any other clinical events that had occurred since treatment completion. In the event of VTE, the administration of study drugs was discontinued and treatment was left to the investigator's discretion.

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by an independent ethics committee and written informed consent was obtained from all patients before randomization.

Medication

Study medications were packaged in boxes, one per patient, each containing 24 prefilled, single-dose syringes of either nadroparin (0.3 mL, 2850 anti-FXa IU) and matching placebos (isotonic saline), or enoxaparin (0.4 mL, 4000 anti-FXa IU) and matching placebos.

The use of aspirin, thienopyridines, non-steroidal anti-inflammatory drugs, UH, LMWHs other than the study drugs, heparinoids, or vitamin K antagonists was prohibited. All other types of treatment, including chemotherapy and radiotherapy, were permitted. The use of compression stockings was encouraged.

Outcome measures

The primary efficacy outcome was VTE defined as the composite of DVT detected by bilateral venography or documented symptomatic DVT or PE recorded up to day 12. Secondary efficacy outcomes were total, proximal and distal asymptomatic DVT, symptomatic VTE, and the composite of asymptomatic proximal DVT or symptomatic non-fatal VTE or VTE-related death up to day 12, and total and symptomatic VTE up to day 60. Symptomatic VTE events were recorded up to the first qualifying event (DVT, non-fatal or fatal PE). Patients were examined for DVT by systematic ascending bilateral contrast venography of the legs between days 8 and 12. If DVT was suspected before the mandatory venography, the event was confirmed by ultrasonography or venography. Symptomatic PE was confirmed by pulmonary angiography. In the event of death, fatal PE was considered to have occurred if it was documented at autopsy or if there was strong evidence that PE was the cause of death.

The primary safety outcome was major bleeding up to day 12, including fatal bleeding, overt bleeding leading to premature treatment discontinuation, surgical bleeding ≥ 1200 mL, bleeding associated with a need for transfusion of more than

3 U of packed red blood cells, bleeding associated with severe anemia, and bleeding declared as a serious adverse event. Secondary safety outcomes were all deaths, any other bleeds, transfusion requirements, thrombocytopenia and any other adverse events.

All efficacy outcomes, including review of all venograms, and safety outcomes, including bleeding and death, were adjudicated by a central independent Critical Event Committee, the members of which were unaware of the patients' treatment assignment.

Statistical analysis

The trial was designed to determine whether the efficacy of the registered regimen of nadroparin 2850 IU was different from that of enoxaparin 4000 IU in patients undergoing elective colorectal surgery for cancer, and if not, whether it was safer in terms of bleeding risk. As non-inferiority trials were not common in the 1990s, the trial was initially designed as a superiority trial. Patients were recruited between 1994 and 1999. Taking into account the evolution in statistical approaches during the 5-year study period, the Steering Committee decided in 2000, after recruitment had been completed but before database lock and unblinding of data, to switch from a superiority to a non-inferiority analysis, more consistent with the aim of the study [14]. The switch was performed according to the recommendations established by Health Authorities [15].

The number of patients to recruit was calculated on the basis of a superiority trial. Assuming that the incidence of VTE in the nadroparin group would be 18% [5], and that the relative risk (RR) reduction in the enoxaparin would be 35%, 500 patients were needed per group to show superiority, with a power of 90% and an α value of 0.05. The overall target number of patients was set at 1350 to allow for the likely failure to obtain primary efficacy data in approximately 30% of the patients. With regard to the non-inferiority analysis, the upper limit of non-inferiority was determined by two independent experts. Preserving at least 50% of the effect size for LMWHs relative to placebo (RR: 0.28, 95% CI: 0.14–0.54) [9] and taking into account the upper limit of the 95% CI (i.e. 0.54), it was calculated that nadroparin would be non-inferior to enoxaparin if the upper limit of the CI of the RR of nadroparin vs. enoxaparin on the primary efficacy endpoint (total VTE at day 12) was below 1.43. The Steering Committee considered that this potential loss of efficacy was clinically acceptable if a reduction of major bleeding was observed.

The primary efficacy analysis included data on all randomized patients who had an adequate VTE assessment (i.e. an evaluable venogram or adjudicated symptomatic VTE). Safety analyses included data on all randomized patients who had received at least one dose of study medication. The two-sided 95% CI for the RR between nadroparin and enoxaparin was calculated to demonstrate non-inferiority.

Data were processed and analyzed using SAS-WINDOWS^{TM} software (version 8.2). A two-tailed P-value < 0.05 was considered to indicate statistical significance. Exact 95% CIs for absolute difference and risk ratio between nadroparin and enoxaparin were calculated.

Results

Patients

Between September 1994 and February 1999, 1296 patients were recruited in 56 centers and randomized to receive either nadroparin or enoxaparin (Fig. 1). Eight patients did not

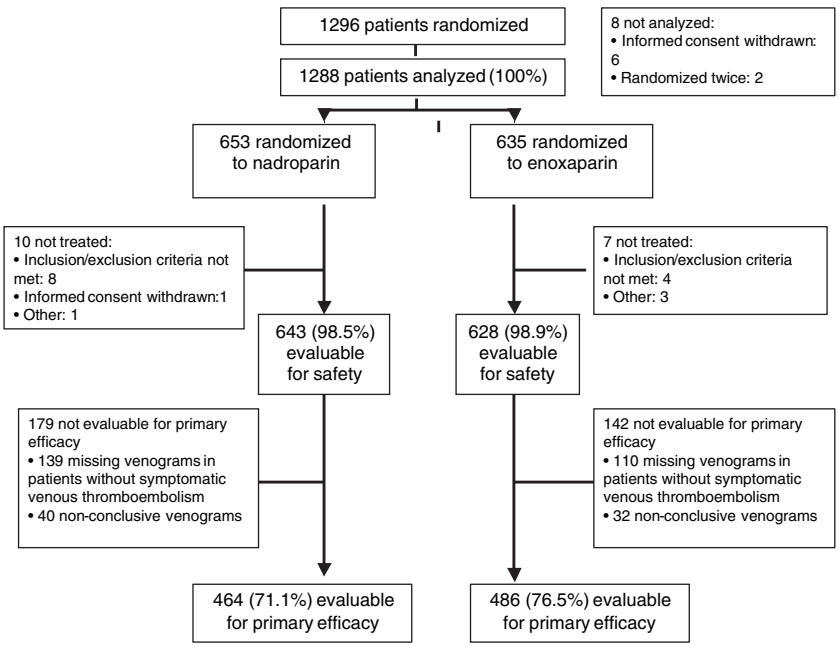

Fig. 1. Trial profile.

continue the study further because they either withdrew their consent or were randomized twice, leaving 1288 patients (100%) available for analysis. A total of 1271 patients (98.7%) received at least one dose of study drug and were available for safety analysis, and 950 patients (73.8%) with evaluable venography or with symptomatic thromboembolic event were available for primary efficacy analysis.

Baseline demographic, medical and surgical characteristics did not show any clinically relevant differences between the two study groups with regard to either the total patient population (Tables 1 and 2) or patients analyzed for efficacy (data not shown). Overall, the median age of the population was 69 years and 61.4% were men; 87.4% of patients had at least one risk factor for VTE. The majority of patients (41.2%) had a stage B adenocarcinoma, for the most part located in the colon (64.7%). The study groups did not differ in terms of type of surgery (data not shown). Fifteen patients (nine in the nadroparin group and six in the enoxaparin group) did not undergo surgery. Liver resection was performed in 2.0% (13 of 644) patients assigned to nadroparin and 1.9% (12 of 617) patients assigned to enoxaparin. Most of the patients (89.5%) received seven or more injections of the study drugs (Table 3). Use of graduated compression stockings was reported in 39.6%. After the treatment period, 1215 patients (94.3%) were followed up to day 60.

Incidence of VTE

VTE occurred up to day 12 in 14.2% of patients (Table 4). The rate of VTE was 15.9% in patients assigned to nadroparin and 12.6% in patients assigned to enoxaparin (RR: 1.27, 95% CI: 0.93; 1.74) (Fig. 2). The upper limit of the RR (1.74) was not below the predetermined criterion for non-inferiority between the two treatments (1.43), indicating that the non-inferiority of nadroparin relative to enoxaparin was not statistically demonstrated. The difference between the treatment groups was primarily because of a higher incidence of distal DVT in nadroparin-treated patients (12.5%) compared with enoxaparin-treated patients (8.6%) (RR: 1.45, 95% CI: 0.99; 2.11). The incidence of proximal DVT was similar (3.2% vs. 2.9%, respectively) (RR: 1.12, 95% CI: 0.55; 2.30). However, there were more cases of symptomatic VTE, including PE, in patients assigned to enoxaparin (1.4%) than in patients assigned to nadroparin (0.2%) (RR: 0.12, 95% CI: 0.01; 0.92). There was

Table 2 Cancer and surgical characteristics of the patients

	Nadroparin ($n = 653$)	Enoxaparin ($n = 635$)
Localization of cancer, *n* (%)*		
Colon cancer	425 (66.8)	387 (62.5)
Rectal cancer	190 (29.9)	219 (35.4)
Colorectal cancer	21 (3.3)	13 (2.1)
Histology of cancer, *n* (%)†		
Adenocarcinoma	604 (95.1)	587 (94.4)
Not an adenocarcinoma	31 (4.9)	35 (5.6)
Adenocarcinoma stage (Dukes classification), *n* (%)‡		
A	80 (13.2)	85 (14.5)
B	249 (41.2)	242 (41.2)
C	166 (27.5)	178 (30.3)
D	109 (18.0)	82 (14.0)
Duration of surgery (h: min), median (range)	2:30 (0:45–13:30)	2:30 (0:45–10:15)

*$n = 636$ in nadroparin patients and $n = 619$ in enoxaparin patients.
†$n = 635$ in nadroparin patients and $n = 622$ in enoxaparin patients.
‡$n = 604$ in nadroparin patients and $n = 587$ in enoxaparin patients.

Table 1 Demographic and clinical characteristics of the patients at baseline

	Nadroparin ($n = 653$)	Enoxaparin ($n = 635$)
Age (years), median (range)	69 (27–97)	68 (26–92)*
Sex (male/female)	401/252	390/245
Weight (kg), median (range)	69 (35–130)	70 (36–120)
Body mass index (kg m^{-2}), median (range)	24.7 (14.6–44.5)	24.7 (14.4–45.7)
Risk factor, *n* (%)		
Patients aged > 60 years	519 (79.5)	473 (74.5)*
Obesity†‡	83 (12.9)	89 (14.1)
History of venous thromboembolism	29 (4.4)	41 (6.5)
Varicose veins	132 (20.2)	161 (25.4)*
Decompensated congestive heart failure	5 (0.8)	2 (0.3)
Decompensated respiratory insufficiency	2 (0.3)	3 (0.5)
Estrogen therapy	5 (0.8)	13 (2.1)[1]
Bedridden before surgery	46 (7.0)	49 (7.7)
Infection within the previous 7 days	22 (3.4)	16 (2.5)
At least one risk factor	584 (89.4)	542 (85.4)*
No. risk factors		
0	69 (10.6)	93 (14.6)
1	300 (45.9)	245 (38.6)
2	226 (34.6)	212 (33.4)
≥ 3	58 (8.9)	85 (13.4)
Serum creatinine (μmol L^{-1}), median (range)	86 (44–443)	84 (44–195)

*$P < 0.005$. †Obesity if body mass index > 30 kg m^{-2} in men or > 28.6 kg m^{-2} in women. ‡Missing values: $n = 8$ in nadroparin patients and $n = 6$ in enoxaparin patients.

Table 3 Treatments received during the study treatment period in patients assessed for primary efficacy

	Nadroparin ($n = 653$)	Enoxaparin ($n = 635$)
No. injections with active study drug, *n* (%)*		
1 to 4	64 (10.0)	49 (7.8)
5 to 6	15 (2.3)	6 (1.0)
7 to 11	336 (52.3)	310 (49.4)
> 11	228 (35.5)	263 (41.9)
Duration of treatment in patients who completed the study, *n* (%)†		
7 days	5 (0.9)	2 (0.4)
8–11 days	313 (56.7)	284 (51.4)
12 days	234 (42.4)	267 (48.3)
Patients receiving graduated compression stockings postoperatively, *n* (%)‡	230 (39.4)	229 (39.8)

*$n = 643$ in nadroparin patients and $n = 628$ in enoxaparin patients.
†$n = 552$ in nadroparin patients and $n = 553$ in enoxaparin patients.
‡$n = 584$ in nadroparin patients and $n = 575$ in enoxaparin patients.

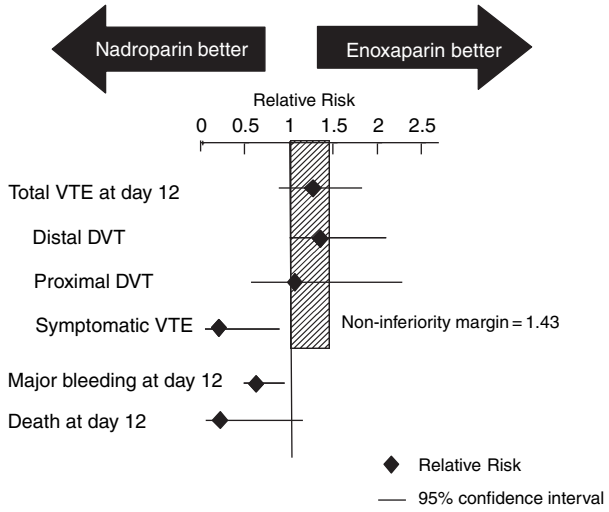

Fig. 2. Relative risks (RR) and 95% CIs of efficacy and safety criteria comparing nadroparin 2850 IU and enoxaparin 4000 IU. Non-inferiority is demonstrated if the upper limit of the CI of the RR of nadroparin vs. enoxaparin on the primary efficacy endpoint (total venous thromboembolism at day 12) is below 1.43. Regarding major bleeding and death, nadroparin 2850 IU is safer ($P < 0.05$) than enoxaparin 4000 IU if the upper limit of the CI of the RR of nadroparin vs. enoxaparin is less than 1.

one fatal PE in enoxaparin-treated patients and none in nadroparin-treated patients. Thus, the rate of the composite of asymptomatic proximal DVT or symptomatic non-fatal VTE or VTE-related death (secondary endpoint) was 3.2% in patients assigned to nadroparin and 3.9% in patients assigned to enoxaparin (RR: 0.82, 95% CI: 0.43; 1.56).

Between days 12 and 60, the overall incidence of symptomatic VTE was 0.6% (7 of 1271): 0.5% (3 of 643) in nadroparin-treated patients and 0.6% (4 of 628) in enoxaparin-treated patients.

Safety outcomes

The overall rate of major bleeding occurring during the treatment period was 9.4% (Table 5). Most surgical bleeds involved a blood loss of ≥ 1200 mL. The incidence of major bleeding was significantly ($P = 0.012$) lower in patients treated with nadroparin (7.3%) than in patients treated with enoxaparin (11.5%). The result was consistent regardless of the type of major bleeding. There were two fatal bleeds (melena and intra-peritoneal hemorrhage) in enoxaparin-treated patients and none in nadroparin-treated patients. Likewise, the number and volume of postoperative transfusions were lower in nadroparin than in enoxaparin patients (Table 6). The incidence of any other adverse events, including severe thrombocytopenia, did not differ between groups.

Table 4 Venous thromboembolic events

	Nadroparin *n*/*N**(%)	Enoxaparin *n*/*N** (%)	*P*-value	Relative risk (RR) (95% CI)
Treatment period (up to day 12)				
VTE (primary outcome)	74/464 (15.9)	61/486 (12.6)	NS	1.27 (0.93–1.74)
Asymptomatic DVT	73	56		
Distal DVT only	58	42		
Any proximal DVT	15	14		
Symptomatic VTE	1/643 (0.2)	9/628 (1.4)†		
DVT	1	5		
PE	0	5		
Asymptomatic proximal DVT or symptomatic non-fatal VTE or VTE-related death‡	16/504 (3.2)	20/518 (3.9)	NS	0.82 [0.43–1.56]
Study period (up to day 60)				
Symptomatic VTE	4/643 (0.6)	13/628 (2.1)		
DVT	2	8		
PE	2	6		

**n* is the number of patients with events and *N* is the total number of patients assessed for this event. †One patient exhibited both symptomatic DVT and PE. ‡Composite endpoint currently recommended in non-inferiority trials [16].
DVT, deep vein thrombosis; NS, not significant; PE, pulmonary embolism; VTE, venous thromboembolism; 95% CI, 95% confidence interval.

Table 5 Major safety outcomes

	Nadroparin n/N*(%)	Enoxaparin n/N*(%)	*P*-value	RR (95% CI)
Treatment period				
Major bleeding[†]	47/643 (7.3)	72/628 (11.5)	0.012	0.64 (0.45–0.91)
Fatal bleeding	0	2		
Overt bleeding leading to treatment discontinuation	14	18		
Surgical bleeding of ≥ 1200 mL	20	30		
Bleeding associated with a need for transfusion of > 3 units of packed red blood cells	10	24		
Bleeding declared as severe adverse event	11	15		
Severe anemia	1	1		
Severe thrombocytopenia[‡]	9/643 (1.4)	8/628 (1.3)	–	
Death from any cause	2/653 (0.3)	8/635 (1.3)	0.07	0.24 (0.05–1.15)
Death associated with venous thromboembolism or bleeding	0	3		
Study period (up to day 60)				
Death from any cause	23/653 (3.5)	23/635 (3.6)		

n is the number of patients with events and *N* is the total number of patients assessed for this event. [†]A patient may present more than one type of major bleeding. [‡]Thrombocytopenia was defined as severe if blood platelet count was < 50 Giga L^{-1} or if blood platelet count decreased by more than 40% relative to baseline value. 95% CI, 95% confidence interval.

Table 6 Bleeding events other than major bleeds and transfusion requirements

	Nadroparin ($n = 643$)	Enoxaparin ($n = 628$)
Minor bleeding (excluding anemia), *n* (%)	23 (3.6)	22 (3.5)
Anemia (excluding severe anemia), *n* (%)	23 (3.6)	36 (5.7)
Profuse per-operative bleeding, *n* (%)	43 (6.7)	67 (10.7)
Blood loss (mL), median (range)	300 (0–4000)	300 (0–13000)
Postoperative transfusions, *n* (%)	70 (10.9)	100 (16.0)
Postoperative transfusions (mL), median (range)	600 (280–2000)	750 (200–5250)
Total transfusions (mL), median (range)	700 (280–3600)	790 (0–9750)

During study treatment, two (0.3%) patients in the nadroparin group and eight (1.3%) in the enoxaparin group died (RR: 0.24, 95% CI: 0.05; 1.15), with a *P*-value near significance level (Table 5). There were no deaths related to VTE or major bleeding in nadroparin patients, compared with three (0.5%) in enoxaparin patients. The respective numbers of deaths by day 60 were 23 (3.5%) and 23 (3.6%). None of the deaths between days 12 and 60 was related to PE.

Discussion

In this study of patients undergoing colorectal surgery for cancer, the non-inferiority of nadroparin 2850 IU relative to enoxaparin 4000 IU with regard to the primary efficacy outcome (i.e. total VTE) was not statistically demonstrated. The observed difference in favor of enoxaparin on the primary efficacy outcome was mainly because of a lower rate of asymptomatic distal DVT in the enoxaparin group. Less symptomatic venous thromboembolic events, including PEs, were observed in nadroparin-treated patients. Thus, on the basis of the composite endpoint currently recommended in non-inferiority trials, that is, asymptomatic proximal DVT or symptomatic non-fatal VTE or VTE-related death [16], non-inferiority of nadroparin relative to enoxaparin was close to significance, the upper limit of the RR being 1.56 to be compared with 1.43. The fact that non-inferiority was not statistically demonstrated may reflect a lack of power. It should also be noted that the non-inferiority margin was very conservative; in a recent trial in high-risk abdominal surgery patients, this margin was set at 1.70 [17]. Of note, using the superiority analysis, the incidence of VTE between the two study groups was not statistically different ($P = 0.134$).

The 14.2% overall rate of VTE at day 12 is consistent with the 8–18% rates observed in most recent trials on patients undergoing general surgery for cancer receiving an appropriate dose of UH or LMWHs [12,13,17,18]. Likewise, the 9.4% overall rate of major bleeding is consistent with the 8.1% rate reported in a meta-analysis of studies on abdominal surgery for cancer with UH [9]. Of note, the definition of major bleeding used in this trial was especially broad and included in particular surgical bleeds of ≥ 1200 mL, which overall represented 42% of major bleeding events. Data on perioperative bleeds, blood loss and transfusion requirements were comparable to those reported in previous similar trials [12,13]. Importantly, nadroparin 2850 IU was safer in terms of bleeding risk than enoxaparin 4000 IU, regardless of the type of major bleeding considered.

Once-daily nadroparin 2850 IU was shown to be more effective than and as safe as thrice-daily 5000 IU of UH in general surgery patients [11]. In an initial trial, enoxaparin 2000 IU tended to be less effective than thrice-daily 5000 IU of UH in the subpopulation of general surgery patients operated

for cancer [19]. In two other trials, enoxaparin 4000 IU was as effective as UH but at the cost of a trend towards an increased risk of major bleeding [12,13]. Few studies have compared two different recommended regimens of LMWHs. In the study reported by Bergqvist *et al*. [6] in abdominal surgery (66.4% of patients with cancer), dalteparin 5000 IU was more effective than dalteparin 2500 IU, but at the cost of a greater risk of major bleeding. In the study performed by Bounameaux *et al*. [5] in high-risk general surgery, nadroparin 2850 IU was more effective than dalteparin 2500 IU; in a subsequent open series in patients treated with dalteparin 5000 IU, the incidence of VTE was comparable with that observed with nadroparin 2850 IU [20]. Overall, these studies confirm that LMWHs do not form a homogeneous group and cannot be compared solely on the basis of anti-FXa IU. The benefit-to-risk ratio of each LMWH must be examined separately on the basis of appropriate clinical trials [21]. In practice, various dosage regimens are proposed by manufacturers, depending on the drug and the thrombotic risk.

Both nadroparin and enoxaparin were initiated 2–4 h before surgery, as in the majority of thromboprophylaxis trials performed in general surgery and as recommended by the manufacturers of the respective study drugs when the trial was conducted. The benefit of initiating drugs earlier therefore remains largely unknown. Of note, the difference in bleeding events between the treatment groups in our study was observed with regard to both perioperative and postoperative bleeds. The two fatal bleeds observed in the enoxaparin group occurred on days 3 and 6, respectively.

Extended thromboprophylaxis with LMWHs after general surgery for cancer is now recommended in order to reduce late thrombotic events [2,22,23]. In our study, the rate of delayed symptomatic VTE occurring between days 12 and 60 after surgery was 0.6%. None of these events was fatal. However, these results should be interpreted with caution, as the incidence of symptomatic events after day 12 may have been influenced by the administration of anticoagulant therapy to patients diagnosed with asymptomatic DVT in the first part of the study. Although the study drugs were given for short-term duration, we believe that the bleeding data are relevant to the contemporary management of patients undergoing abdominal surgery for cancer and receiving extended prophylaxis, bearing in mind that bleeding events are most likely to occur within the first 10 days following surgery [12,23].

In conclusion, this study represents the first large study comparing two dosage regimens of two LMWHs in patients undergoing surgery for cancer. Non-inferiority of nadroparin 2850 IU relative to enoxaparin 4000 IU with regard to total VTE was not statistically demonstrated. Patients allocated to nadroparin 2850 IU showed a higher incidence of asymptomatic distal DVT, but a lower incidence of symptomatic VTE, including PE. Nadroparin treatment was safer in terms of bleeding risk. A once-daily dose of 2850 IU of nadroparin may therefore represent an attractive thromboprophylactic strategy for patients undergoing surgery for colorectal cancer.

Disclosure of conflicts of interest

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G. Simonneau reports having consulting and lecture fees as well as research grants from Actelion, Pfizer, Schering, Myogen, Glaxo-Wellcom, Sanofi–Aventis, Encysive and Mondobiotech. The other authors declare no conflicts of interest.

Appendix

The members of the FX140 Study group were as follows.

Steering Committee: G. Simonneau (Chair), F. Bonnet, Y. Chapuis, H. Decousus, A. Derlon, C. M. Samama, K. Samii, B. Boutin, I. Richard.

Blind-Review Committee: J.-F. Bergmann, S. Laporte, C. M. Samama, G. Simonneau.

Central Reading Committee: D. Musset, P. Lacombe.

Critical Event Committee: F. Bonnet, J. Belghiti, J.-N. Fiessinger.

Data Safety Monitoring Committee: J.-F. Bergmann, C. Conseiller.

Non-inferiority Limit Committee: M. Cucherat, P. Mismetti.

Participating centers: Dr Allantaz (Annecy, 10 patients), Dr Angelvin (Avignon, 92 patients), Dr Arnaud (Angers, 38 patients), Dr Atthar (Cabestany, 4 patients), Dr Atthar (Perpignan, 21 patients), Dr Balique (Saint-Etienne, 6 patients), Dr Bazin (Elbeuf, 19 patients), Dr Belliard (Bruges, 16 patients), Dr Bougain (Villejuif, 48 patients), Dr Bur (Metz, 45 patients), Dr de Calan (Tours, 20 patients), Dr Casteux (Valence, 11 patients), Dr Cougard (Dijon, 14 patients), Dr Degroote (Boulogne-sur-Mer, 17 patients), Dr Deleuze (Alès, 24 patients), Dr Deleplanque (Niort, 4 patients), Dr Elhomsy (Troyes, 56 patients), Dr Escat (Toulouse, 10 patients), Dr Estenne (Le Chesnay, 4 patients), Dr Favre (Dijon, 72 patients), Dr Fontaumard (Lyon, 6 patients), Dr Ghisbain (Maubeuge, 51 patients), Dr Gilly (Pierre Benite, 1 patient), Dr Grall (Soissons, 52 patients), Dr Grosdidier (Nancy, 12 patients), Dr Gstach (Dunkerque, 8 patients), Dr Kostiukova (Poissy, 21 patients), Dr Kraimps (Poitiers, 38 patients), Dr Lambert (Villeneuve-Saint-Georges, 14 patients), Dr Laurent (Paris, 18 patients), Dr Lazorthes (Toulouse, 10 patients), Dr Leroux (Cesson-Sevigne, 2 patients), Dr Letoquart (Quimper, 49 patients), Dr Letoublon (Grenoble, 11 patients), Dr Leynaud (Desertines, 18 patients), Dr L'Hegaret (Brest, 40 patients), Dr Lointier (Beaumont, 26 patients), Dr Loriferne (Bry-sur-Marne, 21 patients), Dr Lorimier (Angers, 7 patients), Dr Mambrini (Rennes, 7 patients), Dr Marescaux (Strasbourg, 26 patients), Dr Meyer (Strasbourg, 134 patients), Dr Nouira (Créteil, 17 patients), Dr Perrin (Saint-Doulchard, 5 patients), Dr Regairaz (Saint Etienne, 3 patients), Dr Richelme (Nice, 31 patients), Dr Robial (Brive, 3 patients), Dr Roques (Toulouse, 8 patients), Dr Sage (Auxerre, 16 patients), Dr Siriser (Caen, 6 patients), Dr Taccoen (Lille, 14 patients), Dr Teniere (Rouen, 10 patients), Dr Vazel (Saint-Brieuc, 4 patients), Dr Vergos (Saint-Mande, 29 patients), Dr Voitellier (Vichy, 37 patients).

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