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## Chapter 5

# Outcomes following pancreatic surgery using three different thromboprophylaxis regimens

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## Abstract

**Background:** Postpancreatectomy haemorrhage (PPH) and venous thromboembolism (VTE) are serious complications following pancreatic surgery. The aim was to assess the timing, occurrence and predictors of PPH and VTE.

**Methods:** Elective pancreatic resections in a single university hospital between November 2013 and September 2017 were assessed. Three intervals were reviewed, each with a different routine regimen of nadroparin: 2850 units once daily (single dose) administered in hospital only, or 5700 units once daily (double dose) or 2850 units twice daily (split dose) administered in hospital and continued for 6 weeks after surgery. Clinically relevant PPH (CR-PPH) was classified according to International Study Group of Pancreatic Surgery criteria. VTE was defined according to a number of key diagnostic criteria within 6 weeks of surgery. Cox regression analyses were performed to test the hypotheses that the double-dose group experienced more PPH than the other two groups, the single-dose group experienced more VTE than the other two groups, and the split-dose group experienced the fewest adverse events (PPH or VTE).

**Results:** In total, 240 patients were included, 80 per group. The double-dose group experienced significantly more CR-PPH (hazard ratio (HR) 2.14, 95% CI; 1.16 to 3.94;  $P = 0.015$ ). More relaparotomies due to CR-PPH were performed in the double-dose group (16 versus 3.8%;  $P = 0.002$ ). The single-dose group did not experience more VTE (HR 1.41, 0.43 to 4.62;  $P = 0.570$ ). The split dose was not associated with fewer adverse events (HR 0.77, 0.41 to 1.46;  $P = 0.422$ ). Double-dose LMWH, high BMI and pancreatic fistula were independent predictors of CR-PPH.

**Conclusion:** A double dose of LMWH prophylaxis continued for 6 weeks after pancreatic resection was associated with a twofold higher rate of CR-PPH, resulting in four times more relaparotomies. Patients receiving a single daily dose of LMWH in hospital only did not experience a higher rate of VTE.

## **Introduction**

Pancreatic surgery is associated with high morbidity rates.<sup>1-3</sup> Postpancreatectomy haemorrhage (PPH) occurs in 1–8 per cent of all pancreatic resections and is considered one of the most severe complications of pancreatic surgery, with a mortality rate of 16 – 60 per cent.<sup>3-5</sup> Early PPH (24 h or less after surgery) usually results from technical failure of appropriate haemostasis during the index operation or an underlying perioperative coagulopathy, whereas late PPH (more than 24 h after surgery) is often related to pancreatic fistula or intra-abdominal abscess.<sup>6</sup> PPH in patients with postoperative pancreatic fistula (POPF) is usually caused by erosion of peripancreatic vessels by (activated) pancreatic juices<sup>5,7-9</sup>.

Venous thromboembolism (VTE) is a common complication and a major source of postoperative morbidity and mortality.<sup>10,11</sup> Thromboprophylaxis is indicated in patients with pancreatic cancer because cancer is associated with a state of hypercoagulability.<sup>12</sup> In one study<sup>13</sup>, patients with pancreatic cancer had a 60-fold increased risk of developing VTE compared with the general population. Another study<sup>14</sup> of patients with cancer receiving thromboprophylaxis showed that pancreatic cancer was associated with a higher risk of recurrent VTE than most other cancers. The UK National Institute for Health and Care Excellence<sup>15</sup> recommends low molecular weight heparins (LMWHs) up to 28 days after surgery for primary thromboprophylaxis following abdominal cancer surgery. Until January 2015, the Dutch guideline for thromboprophylaxis after major abdominal surgery<sup>16</sup> recommended a single daily dose of 2850 units LMWH during the hospital stay, based on the American College of Clinical Pharmacy thromboprophylaxis guideline.<sup>17</sup> Thereafter, the national and in-hospital guidelines<sup>18</sup> were adjusted to a daily double dose of 5700 units LMWH for 6 weeks after surgery. An increase in occurrence of PPH was noted in the hospital after adoption of the revised guideline. After internal evaluation and benchmarking with other tertiary referral centres, an increase in PPH was evident. The correlation between change of guideline and the increase in PPH led to consultation with the Department of Thrombosis and Haemostasis at Leiden University Medical Centre (LUMC). In an effort to maintain adequate thromboprophylaxis and lower the peak dose of LMWH, an adjustment to the thromboprophylaxis regimen was made: to a twice-daily dose of 2850 units LMWH (split dose of 5700 units) for 6 weeks after surgery. This adjustment was pragmatic and not related to the present study.

The aim of the present cohort study was to investigate the incidence and timing of PPH and VTE in three different LMWH regimens: dose of 2850 units once daily (single dose), dose of 5700 units once daily (double dose) and dose of 2850 units twice daily (split dose) after pancreatic surgery. The study hypotheses were: that the double-dose group would have a higher incidence of clinically relevant PPH (CR-PPH) than the single-dose and split-dose groups combined; that the single-dose group would have

a higher incidence of VTE than the double-dose and split-dose groups combined; and that the split-dose group would have a lower incidence of adverse events than the single-dose and double-dose groups combined.

## Methods

This cohort study was approved by the Medical Ethics Committee of LUMC, which waived the need for informed consent owing to its retrospective design. All elective pancreatic resections carried out at LUMC, a tertiary referral centre, between November 2013 and September 2017 were reviewed for inclusion in this study. Patients were excluded if they had already received LMWH before surgery, or did not start LMWH after operation. Patients were admitted on the day of surgery and therefore did not receive thromboprophylaxis before operation. Thrombocyte aggregation inhibitors were continued during the perioperative period, whereas oral anticoagulants were stopped before surgery. Two investigators collected data independently from the medical charts; a third independent investigator was consulted in the event of dispute. In case of postoperative death, patient and autopsy records were searched for the cause of death. Since 2013, the surgical technique and perioperative care protocols have not changed.

### *Heparin regimens*

The study cohort comprised three LMWH dosage groups. The single-dose group received 2850 units nadroparin injected subcutaneously once daily between 17.00 and 18.00 hours, during the hospital admission; the double-dose group received 5700 units nadroparin injected subcutaneously once daily between 17.00 and 18.00 hours, for up to 6 weeks after surgery; and the split-dose group received 2850 units nadroparin subcutaneously twice daily injected between 05.00 and 06.00 hours and between 17.00 and 18.00 hours, for up to 6 weeks after surgery. In all groups, the first postoperative dose was administered 4–6h after surgery.

### *Definitions*

PPH was classified according to the International Study Group of Pancreatic Surgery (ISGPS) criteria.<sup>5</sup> PPH was graded from A to C depending on the timing (24h or less, or more than 24h after surgery), severity (mild or severe depending on clinical consequence) and site (intraluminal or extraluminal) of bleeding. Grade A has no impact on the clinical course, grade B makes specific therapy and prolonged hospital stay necessary, and grade C is potentially life-threatening. Grades B and C were considered as clinically relevant in this study. When PPH was suspected, diagnosis and treatment were undertaken in a step-up approach: CT and/or angiography of the abdomen; attempted embolization of any CR-PPH by an interventional radiologist; and relaparotomy if embolization was not possible or unsuccessful. If a patient had multiple therapeutic consequences, the most severe was included in the analysis. Complications

of pancreatic surgery (clinically relevant POPF (CR-POPF), bile leakage and delayed gastric emptying) were defined according to ISGPS criteria.<sup>4,9,19</sup> For each of these complications, grades B and C were regarded as clinically relevant.

For VTE, the analyses focused on: objective VTE, comprising deep venous thrombosis (DVT) or pulmonary embolism (PE) on imaging; fatal PE, defined by otherwise unexplained death or confirmed by autopsy; and VTE in unusual locations, such as abdominal veins. Diagnostic tests were undertaken where there was clinical suspicion of VTE. CT pulmonary angiography was performed for suspected PE, which was defined by the presence of filling defects up to the subsegmental level. DVT was confirmed by ultrasonography. Formal VTE risk assessment is not carried out before surgery at LUMC. Abdominal vein thrombosis was identified as filling defects on contrast-enhanced CT. If multiple types of VTE occurred, only the first was counted in the analysis. An adverse event (composite endpoint) was defined as any CR-PPH or VTE within 6 weeks of surgery.

### **Outcomes**

The main outcomes were the timing and occurrence of CR-PPH, VTE and adverse events. Secondary outcomes were the identification of independent predictors of CR-PPH and VTE, and other postoperative outcomes.

### **Statistical analysis**

Comparisons of patient and intraoperative characteristics, other postoperative outcomes and details of CR-PPH were performed by testing differences between the three dosage groups. Depending on the distribution, continuous variables are presented as mean(s.d.) or median (i.q.r.), with evaluation of differences between groups using one-way ANOVA or Kruskal – Wallis test. Categorical variables, presented as absolute numbers with percentages, were evaluated by means of the  $\chi^2$  test.

For the main outcomes, time-to-event analyses were undertaken, comprising construction of cumulative incidence curves and Cox regression analyses. Patients were censored for the other primary endpoint at the moment either a CR-PPH or VTE occurred. For the time-to-event analysis, patients were followed until the end of follow-up or the first adverse event. DVT and PE are two presentations of the same disease and are treated identically, so were analysed as one. Patients who did not complete the 6 weeks of thromboprophylaxis after surgery (those who died or restarted therapeutic oral anticoagulants) were censored from cumulative incidence curves and Cox regression analyses on the day of discontinuation. Follow-up ended after 43 days (duration of thromboprophylaxis plus five times the half-life of nadroparin (3 – 6 h)).<sup>20</sup> Analyses of the total (uncensored) incidences of CR-PPH, VTE and adverse events were performed in accordance with the study hypotheses and conducted using logistic regression analysis.

Baseline and intraoperative characteristics were used in univariable Cox regression analyses to identify additional predictors of the main outcomes. Variables with  $P < 0.100$  were included in multivariable Cox regression analyses. All tests were two-sided. Statistical significance was defined as  $P < 0.050$ . Statistical analyses were done using SPSS® for Windows® version 23.0 (IBM, Armonk, New York, USA).

## Results

During the study interval, 244 patients underwent elective pancreatic resection. Four patients were excluded owing to preoperative LMWH use (2) and because thromboprophylaxis was withheld after surgery (2). In total, 240 patients were included (*Table 1*). Overall, 160 patients (66.7 per cent) underwent pancreatoduodenectomy with invaginating pancreatojejunostomy and 57 (23.8 per cent) had distal pancreatectomy. Patient and intraoperative characteristics were distributed evenly over the dosage groups, except for sex ratio, vascular resection and blood loss.

### **Main outcomes**

Some 38 patients (15.8 per cent) developed CR-PPH as a first event: nine (11 per cent) in the single-dose, 18 (23 per cent) in the double-dose and 11 (14 per cent) in the split-dose group. Time-to-event analysis for CR-PPH showed that the double-dose group did worse than the other groups (hazard ratio (HR) 2.14, 95 per cent c.i. 1.16 to 3.94;  $P = 0.015$ ) (*Fig. 1a*).

Nine patients (3.8 per cent) developed a VTE as a first event: three (4 per cent) in the single-dose, four (5 per cent) in the double-dose and two (3 per cent) in the split-dose group. The single-dose group did not do worse than the other groups (HR 1.41, 0.43 to 4.62;  $P = 0.570$ ) (*Fig. 1b*).

In total, 47 patients (19.6 per cent) had any adverse event: 12 (15 per cent) in the single-dose, 22 (28 per cent) in the double-dose and 13 (16 per cent) in the split-dose group. Time-to-event analysis for an adverse event showed that patients who received a split dose did not do better than those in the other groups (HR 0.77, 0.41 to 1.46;  $P = 0.422$ ) (*Fig. 1c*).

*Fig. S1* (supporting information) shows the total (uncensored) incidences of CR-PPH, VTE and adverse events in the three dosage groups. Five patients who developed both CR-PPH and VTE were included in this analysis. Three patients developed VTE first (2 in the double-dose and 1 in the single-dose group) and two patients developed CR-PPH first (both in the single-dose group). In total, 29 of 41 CR-PPHs occurred within 10 days after surgery. VTE occurred within 10 days after surgery in only four of 11 patients.

### **Other postoperative outcomes**

The rates of most pancreas-specific and other complications were not significantly different between the dosage groups (*Table 2*). More CR-PPH-related relaparotomies were performed in the double-dose group compared with the other groups combined (16.3 versus 3.8 per cent; odds ratio (OR) 4.98, 95 per cent c.i. 1.82 to 13.66;  $P = 0.002$ ). In total, eight patients (3.3 per cent) died within 90 days. In one patient autopsy showed active (extraluminal) CR-PPH as the immediate cause of death (single-dose group), and four patients died from abdominal sepsis/CR-POPF (1 also developed CR-PPH, and 1 also developed CR-PPH and VTE during the postoperative course). One patient died from pulmonary sepsis (also developed VTE), one owing to a complicated postoperative course and refusal of further treatment (also developed VTE), and one patient from intracerebral haemorrhage 70 days after surgery.

### **Details of postpancreatectomy haemorrhage and venous thromboembolism**

There were significant differences between the groups concerning the ISGPS criteria for CR-PPH (*Table 3*). CR-PPHs were more likely to be extraluminal in the double-dose group than in the other groups (12 of 20 versus 8 of 21;  $P = 0.160$ ). All radiological interventions in the single- and split-dose groups were successful. One radiological intervention in the double-dose group was unsuccessful and the patient required a relaparotomy 5 days later. CT or angiography was performed before relaparotomy in one three patients in the single-dose group, eight of 13 in the double-dose group and one of three in the split-dose group to see whether it was possible to embolize the bleeding ( $P = 0.519$ ).

Of 11 patients with a VTE, four developed pulmonary embolism, four had portal vein thrombosis (in 2 after segmental/patch resection of the portal vein/superior mesenteric vein), two developed jugular vein thrombosis (both after central venous catheter placement) and one had a thrombosis in the left gastric vein. VTE was symptomatic in nine patients, whereas two cases were diagnosed incidentally during CT for other indications.

### **Univariable and multivariable analyses**

Univariable analyses identified LMWH regimen, high BMI, type of resection and CR-POPF as predictors of CR-PPH. Independent predictors in multivariable analysis were double dose of LMWH (HR 2.20, 95 per cent c.i. 1.18 to 4.11;  $P = 0.013$ ), high BMI (HR 1.02, 1.00 to 1.03;  $P = 0.013$ ) and CR-POPF (HR 3.10, 1.59 to 6.02;  $P = 0.001$ ) (*Table 4*). Type of resection was not significant in multivariable analysis.

Univariable and multivariable analysis of VTE was not possible because of the small number of events. Univariable analyses for any adverse event identified high BMI, preoperative non-steroidal anti-inflammatory drug use, type of resection, duration

of operation and CR-POPF as predictive factors. In multivariable analysis, LMWH regimen was not an independent predictor of any adverse event (HR 1.52, 0.78 to 2.97;  $P = 0.217$ ), whereas high BMI (HR 1.02, 1.01 to 1.03;  $P = 0.009$ ) and CR-POPF (HR 3.27, 1.76 to 6.04;  $P < 0.001$ ) were (*Table S1*, supporting information).

## Discussion

This study investigated the timing and incidence of CR-PPH and VTE after pancreatic resection between three different LMWH regimens. Time-to-event analysis showed that almost three-quarters of CR-PPHs occurred within 10 days after surgery. In contrast, only one-third of the cases of VTE occurred within 10 days. CR-PPH developed more often in the double-dose group than in the other groups, and more relaparotomies for CR-PPH were performed in this group. The increase in relaparotomies owing to CR-PPH in the double-dose group was not caused by less adherence to the step-up approach, because a similar proportion of patients in all three groups underwent CT angiography before relaparotomy. The VTE rate was low and did not differ between groups. The adverse event rate in the split-dose group was no lower than that in the other two groups combined. Double-dose LMWH, high BMI and CR-POPF were identified as independent predictors of CR-PPH.

A few other studies have reported the association between postoperative bleeding and VTE and thromboprophylaxis after major abdominal surgery. Most<sup>22-25</sup> included patients on chronic oral anticoagulation receiving perioperative bridging therapy. One study<sup>26</sup> investigated once- versus twice-daily LMWH thromboprophylaxis. In this RCT, 111 patients were assigned to 4100 units nadroparin once or twice daily following oesophagectomy in a Chinese population. The once-daily group had significantly more VTE (5 versus 0 in twice-daily group); there were no postoperative haemorrhages. Another study<sup>27</sup> investigated the safety and efficacy of 4100 units enoxaparin in 150 patients undergoing pancreatic surgery. The primary outcome was objective evidence of PE, whereas secondary outcomes were major postoperative bleeding (requiring blood transfusion, radiological or surgical intervention) or minor bleeding (ecchymosis or bloody discharge from the drainage tube not requiring treatment). No PEs and a small number of bleeds (4 major, 1 minor) were identified in that study. Objective comparison with the present results is difficult as all kinds of VTE were reviewed and ISPGS criteria for PPH were used to score postoperative bleeding in the present analysis.

This study has several limitations owing to its retrospective nature and the limited cohort size, which hampered propensity score matching. One limitation is the difference in duration of LMWH treatment in the single-dose group (in hospital only) compared with the other groups (for 6 weeks after surgery). It is known that both a longer duration of LMWH and higher dose can increase the chance of developing PPH. However, this study aimed to compare different LMWH strategies used over the past

couple of years. Ideally, all patients should have been randomized into one of the three dosage groups, but this was not possible in a retrospective study. Asymptomatic DVT may have been missed during the 6-week postoperative phase. There was minimal overlap between the dosage groups and consecutive patients were included, thereby minimizing selection bias. There was a violation of the protocol for two patients (reasons unknown), and treatment deviated from the protocol in seven patients over a period of 2 weeks after the first regimen change (from single dose to double dose). Baseline and operative characteristics that differed between the dosage groups (sex ratio, vascular resection and blood loss) did not show statistically significant associations with the main outcomes in univariable analyses.

Double-dose LMWH thromboprophylaxis should be used with caution in patients undergoing pancreatic surgery to balance the effect on postoperative haemorrhage and VTE. In particular, after a CR-POPF has developed, continuation of LMWH thromboprophylaxis and the dose should be reconsidered carefully. Further research is needed to validate the present results. An RCT comparing single- *versus* split-dose LMWH, both for 6 weeks after operation, would be the design of choice. In the authors' centre, the present results have led to a change in local practice; the current routine thromboprophylaxis is a single dose of 2850 units LMWH for up to 6 weeks after operation.

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## **Disclosure**

The authors declare no conflict of interest.

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**Table 1.** Patient and intraoperative characteristics

	Low molecular weight heparin regimen			P#
	Single dose 2850 units (n = 80)	Double dose 5700 units (n = 80)	Split dose 2 × 2850 units (n = 80)	
<b>Age (years)*</b>	65 (57–75)	65 (57–72)	65 (57–73)	0.886**
<b>Sex ratio (M : F)</b>	30 : 50	46 : 34	47 : 33	0.011
<b>BMI (kg/m<sup>2</sup>)*</b>	25 (22–28)	24 (22–29)	25 (24–28)	0.137**
<b>ASA fitness grade</b>				0.315
I–II	69 (86)	63 (79)	62 (78)	
III–IV	11 (14)	17 (21)	18 (23)	
<b>Preoperative NSAID use</b>				0.148
No	67 (84)	72 (70)	63 (79)	
Yes	13 (16)	8 (10)	17 (21)	
<b>Preoperative oral anticoagulant use</b>				0.077
No	79 (99)	73 (91)	73 (91)	
Yes	1 (1)	7 (9)	7 (9)	
<b>Pathology</b>				0.881
Adenocarcinoma	51 (64)	50 (63)	53 (66)	
Other	29 (36)	30 (38)	27 (34)	
<b>Type of resection</b>				0.392
Pancreatoduodenectomy	56 (70)	52 (65)	52 (65)	
Distal pancreatectomy	18 (23)	17 (21)	22 (28)	
Total pancreatectomy	2 (3)	8 (10)	5 (6)	
Partial pancreatectomy‡	4 (5)	3 (4)	1 (1)	
<b>Vascular resection§</b>				0.036
No	75 (94)	64 (80)	67 (84)	
Yes	5 (6)	16 (20)	13 (16)	
<b>Multivisceral resection¶</b>				0.395
No	68 (85)	63 (79)	69 (86)	
Yes	12 (15)	17 (21)	11 (14)	
<b>Blood loss (ml)*</b>	620 (450– 1000)	975 (500– 1475)	875 (550– 1375)	0.020**
<b>Duration of operation (min)†</b>	244(65)	256(79)	270(80)	0.100††

Values in parentheses are percentages unless indicated otherwise; values are \*median (i.q.r.) and †mean(s.d.). ‡Includes tumour enucleations and central pancreatectomies. §Includes patch and segmental resections of the portomesenteric vein. ¶Includes resection of the stomach, small bowel, colon and adrenal glands(s); splenectomy in distal and total pancreatectomy was not considered as multivisceral resection. NSAID, non-steroidal anti-inflammatory drug. #c<sup>2</sup> test, except \*\*Kruskal–Wallis test and ††one-way ANOVA.

**Table 2.** Postoperative outcomes

	Low molecular weight heparin regimen			P‡
	Single dose 2850 units (n = 80)	Double dose 5700 units (n = 80)	Split dose 2 × 2850 units (n = 80)	
<b>Postoperative pancreatic fistula†</b>				0.676
No	68 (85)	66 (83)	70 (88)	
Yes	12 (15)	14 (18)	10 (13)	
<b>Bile leakage†</b>				0.213
No	76 (95)	73 (91)	78 (98)	
Yes	4 (5)	7 (9)	2 (3)	
<b>Delayed gastric emptying†</b>				0.012
No	73 (91)	60 (75)	70 (88)	
Yes	7 (9)	20 (25)	10 (13)	
<b>ICU admission</b>				0.917
No	66 (83)	65 (81)	67 (84)	
Yes	14 (18)	15 (19)	13 (16)	
<b>Relaparotomy</b>				0.021
No	73 (91)	64 (80)	74 (93)	
Not CR-PPH-related	4 (5)	3 (4)	3 (4)	
CR-PPH-related	3 (4)	13 (16)	3 (4)	
<b>Radiological reintervention</b>				0.541
No	63 (79)	57 (71)	64 (80)	
Not CR-PPH-related	15 (19)	22 (28)	14 (18)	
CR-PPH-related	2 (3)	1 (1)	2 (3)	
<b>Clavien–Dindo grade of complication</b>				0.336
No complication	30 (38)	21 (26)	28 (35)	
I–II	25 (31)	29 (36)	32 (40)	
III–V	25 (31)	30 (38)	20 (25)	
<b>Death within 90 days</b>				0.126
No	76 (95)	76 (95)	80 (100)	
Yes	4 (5)	4 (5)	0 (0)	
<b>Postoperative duration of hospital stay (days)*</b>	9 (8–13)	11 (8–18)	9 (7–13)	0.076§

Values in parentheses are percentages unless indicated otherwise; \*values are median (i.q.r.). †Grade B or C as defined by International Study Group of Pancreatic Surgery criteria. CR-PPH, clinically relevant postpancreatectomy haemorrhage. ‡c<sup>2</sup> test, except §Kruskal–Wallis test.

**Table 3.** Details of clinically relevant postpancreatectomy haemorrhage

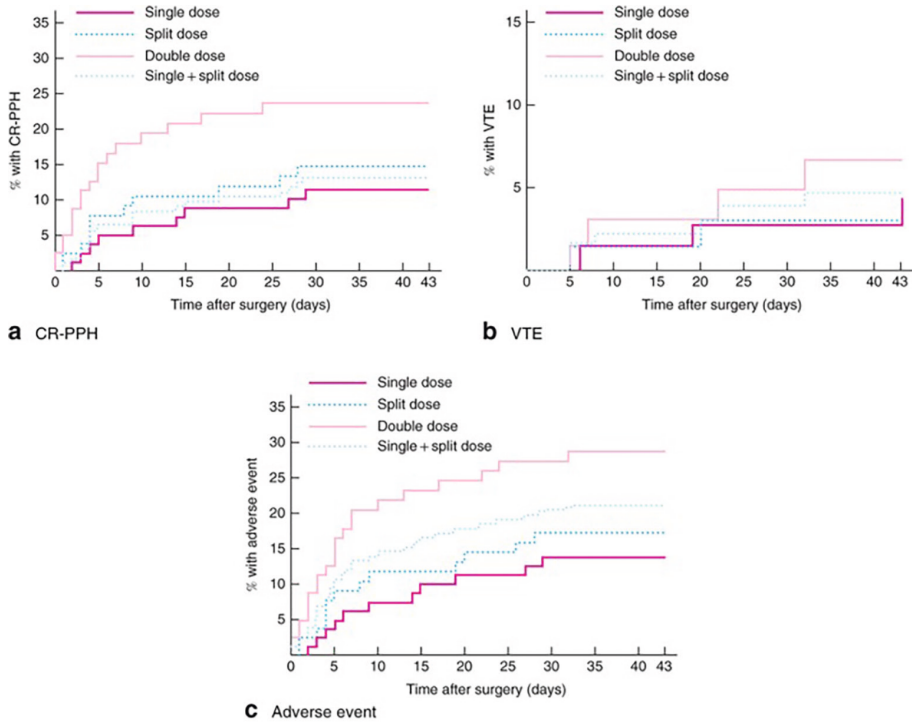
	Low molecular weight heparin regimen			P§
	Single dose 2850 units	Double dose 5700 units	Split dose 2 × 2850 units	
<b>CR-PPH*</b>	10	20	11	0.789
Grade B	6	11	5	
Grade C	4	9	6	
<b>Time of onset</b>				0.425
Early (≤ 24 h)	0	3	1	
Late (> 24 h)	10	17	10	
<b>Location</b>				0.218
Extraluminal	5	12	3	
Intraluminal	5	8	8	
<b>Clinical impact</b>				0.848
Mild	4	6	4	
Severe	6	14	7	
<b>Therapeutic consequence†</b>				0.290
Medication	0	1	0	
Transfusion	4	5	5	
MCU/ICU admission	0	1	1	
Endoscopic treatment	0	0	0	
Embolisation	2	0	2	
Relaparotomy	3	13	3	
<b>Death in presence of CR-PPH</b>	1	2	0	0.552

\*Defined by the International Study Group of Pancreatic Surgery criteria. †The most severe treatment is reported for each patient. Data are shown for only nine patients in the single-dose group because one patient died shortly after readmission in shock without starting therapy; autopsy showed extraluminal bleeding. CR-PPH, clinically relevant postpancreatectomy haemorrhage; MCU, medium care unit. ‡ $\chi^2$  test.

**Table 4.** Results of multivariable Cox regression analysis to identify predictors of clinically relevant postpancreatectomy haemorrhage

	Hazard ratio	P
<b>LMWH regimen</b>		
Single + split dose	1.00 (reference)	
Double dose	2.20 (1.18, 4.11)	0.013
<b>BMI (per kg/m<sup>2</sup>)</b>	1.02 (1.00, 1.03)	0.013
<b>Type of resection</b>		
Pancreatoduodenectomy	1.00 (reference)	
Distal pancreatectomy	0.58 (0.24, 1.41)	0.229
Total pancreatectomy	0.37 (0.05, 2.75)	0.330
Partial pancreatectomy	-	0.974
<b>Postoperative pancreatic fistula*</b>		
No	1.00 (reference)	
Yes	3.10 (1.59, 6.02)	0.001

Values in parentheses are 95 per cent confidence intervals. \*Grade B or C as defined by International Study Group of Pancreatic Surgery criteria. LMWH, low molecular weight heparin.



**Figure 1. Time-to-event analyses for clinically relevant postpancreatectomy haemorrhage, venous thromboembolism and adverse events**

**a** Clinically relevant postpancreatectomy haemorrhage (CR-PPH), **b** venous thromboembolism (VTE) and **c** adverse events. **a**  $P = 0.015$ , **b**  $P = 0.570$ , **c**  $P = 0.422$  (Cox regression analysis).

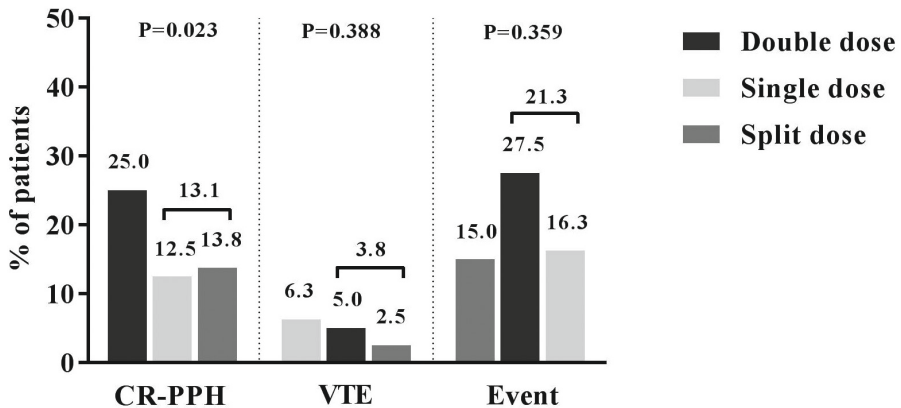
## Supplementary information

**Table S1** - Multivariable Cox regression analysis for an adverse events (CR-PPH or VTE)

		Multivariable analysis		
		HR	95% CI	p-value
Dosage LMWH	Split dose	1	Reference	-
	Single + double dose	1.52	0.78-2.97	0.217
BMI (kg/m <sup>2</sup> )		1.02	1.01-1.03	0.009
Preoperative NSAID usage	No	1	Reference	-
	Yes	1.83	0.94-3.56	0.076
Type of resection	Pancreaticoduodenectomy	1	Reference	-
	Distal pancreatectomy	0.55	0.21-1.48	0.196
	Total pancreatectomy	0.34	0.05-2.55	0.295
	Partial pancreatectomy	-	-	0.974
Operative time (min)		1.00	0.99-1.01	0.520
POPF*	No	1	Reference	-
	Yes	3.27	1.76-6.04	<0.001

HR, hazard ratio; CI, confidence interval; LMWH, Low Molecular Weight Heparin; BMI, Body Mass Index; NSAID, non-steroidal anti-inflammatory drugs; POPF, postoperative pancreatic fistula  
 \* Grade B & grade C as defined by the International Study Groups of Pancreatic Surgery criteria.

### Main outcomes



**Figure S1** - Total (uncensored) incidences of CR-PPH, VTE, and adverse events within the dosage groups, tested by logistic regression analyses

Forty-one patients developed CR-PPH: 10 (12.5%) patients in the single-dose, 20 (25.0%) patients in the double-dose and 11 (13.8%) patients in the split-dose group. The double-dose group experienced significantly more CR-PPH than the other 2 groups combined, (OR= 2.21, 95% CI=1.11-4.37). The single-dose group did not experience more VTE than the other 2 groups combined (OR= 1.71, 95 CI%=0.51-5.79). In total, 47 (19.6%). The split-dose group did not experience less adverse events than the other 2 groups combined (OR= 0.72, 95 CI%=0.36-1.46).