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HPB

ORIGINAL ARTICLE

Predicting the risks of venous thromboembolism versus post-pancreatectomy haemorrhage: analysis of 13 771 NSQIP patients

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Abstract

Background: The fear of an early post-pancreatectomy haemorrhage (PPH) may prevent surgeons from prescribing post-operative venous thromboembolism (VTE) chemoprophylaxis. The primary hypothesis of this study was that the national post-pancreatectomy early PPH rate was lower than the rate of VTE. The secondary hypothesis was that patients at high risk for post-discharge VTE could be identified, potentially facilitating the selective use of extended chemoprophylaxis.

Patients and methods: All elective pancreatectomies were identified in the 2005 to 2010 American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) database. Factors associated with 30-day rates of (pre- versus post-discharge) VTE, early PPH (transfusions > 4 units within 72 h) and return to the operating room (ROR) with PPH were analysed.

Results: Pancreaticoduodenectomies (PD) and distal pancreatectomies (DP) numbered 9140 (66.4%) and 4631 (33.6%) out of 13 771 pancreatectomies, respectively. Event rates included: VTE (3.1%), PPH (1.1%) and ROR+PPH (0.7%). PD and DP had similar VTE rates ($P > 0.05$) with 31.9% of VTE occurring post-discharge. Independent risk factors for late VTE included obesity [odds ratio (OR), 1.5], age ≥ 75 years (OR, 1.8), DP (OR, 2.4) and organ space infection (OR, 2.1) (all $P < 0.02$).

Conclusions: Within current practice patterns, post-pancreatectomy VTE outnumber early haemorrhagic complications, which are rare. The fear of PPH should not prevent routine and timely post-pancreatectomy VTE chemoprophylaxis. Because one-third of VTE occur post-discharge, high-risk patients may benefit from post-discharge chemoprophylaxis.

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Introduction

For most major abdominal operations, routine post-operative venous thromboembolism (VTE) chemoprophylaxis has been proven to be both safe and effective, and is now considered the international standard of care, especially for cancer surgery.[1–7] Post-operative VTE chemoprophylaxis in the form of low-dose unfractionated heparin or low-molecular-weight heparin is a Grade 1B recommendation from the most recent American College of Chest Physicians (ACCP) guidelines, for all moderate- to high-VTE-risk patients undergoing major abdominal surgery, as long as there is no significant bleeding risk.[1,2,8] In spite of this recommendation, hepatopancreatobiliary (HPB) surgeons have frequently withheld VTE chemoprophylaxis owing to the perceived risk of peri-operative haemorrhage in liver and pancreatic surgery. This traditional mentality has placed surgical HPB patients, most of whom have cancer, at risk for the significant morbidity and mortality associated with VTE.[9,10]

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ACS-NSQIP Disclaimer for Participant Use File Research:The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

As with all major abdominal surgery, pancreatic surgeons must maintain a balance between the risk of intra- or post-operative bleeding and the risk of VTE. In addition, pancreatic cancer patients, who make up the majority of patients undergoing pancreatic surgery, have an intrinsically high risk of VTE.[11,12] With regard to bleeding risk, the true incidence of an early post-pancreatectomy haemorrhage (PPH)[13] has not been delineated except in institutional studies.[14] Nor has it been compared with VTE event rates. In the absence of large-scale comparative data regarding the incidence of bleeding and thrombosis,[14] pancreatic surgery patients have been treated based on the surgeon's discretion, with a variety of approaches to the initiation, timing and duration of post-operative VTE chemoprophylaxis. We recently reported that in liver surgery patients, the risk of VTE outweighed the risk of early post-hepatectomy bleeding events.[15] In the present study, we sought to determine whether this paradigm held true for pancreatectomies as well.

A second set of issues to address is the timing of post-pancreatectomy VTE and the potential benefit of extended, post-discharge, chemoprophylaxis.[16] Several previous studies of abdominal surgery patients have shown the value of extended chemoprophylaxis in high-risk patients.[8,17,18] Thus, in high-VTE-risk cancer patients undergoing abdominal surgery, the ACCP currently recommends 4 weeks of extended duration chemoprophylaxis if the risk of bleeding is not high (Grade 1B recommendation).[1] However, longer-term prescriptions of extended chemoprophylaxis are associated with problems related to patient quality of life, financial costs and potential bleeding risk. The most tailored strategy would, therefore, be to focus extended chemoprophylaxis on only patients who are truly high risk and thus would benefit most from the prescription. Before developing post-discharge VTE prophylaxis recommendations, there is a need to demonstrate that post-discharge VTE is a separate entity from pre-discharge VTE and that post-discharge VTE comprises a clinically relevant proportion of all post-operative VTE. Then there must be identifiable risk factors (and a large enough study cohort with sufficient events) to stratify patients into a high-risk group who would potentially benefit the most from extended chemoprophylaxis.

The primary hypothesis of the present study was that the national post-pancreatectomy VTE rate was greater than the rates of early PPH events. The secondary hypothesis was that a certain subset of pancreatectomy patients was at high risk for post-discharge VTE and that there were clinical factors that could be used to select patients for extended chemoprophylaxis. To test these hypotheses, this study was designed to evaluate the rates, timing and risk factors for pre- and post-discharge VTE after a pancreaticoduodenectomy (PD) and a distal pancreatectomy (DP).

Patients and methods

Data acquisition, patients, and definitions

From the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) participant use file for 2005 to 2010, all pancreatectomy procedures were selected. After excluding emergency cases, enucleations, necrosectomies, pancreatic biopsies, hyperthermic intraperitoneal chemotherapy cases, islet cell transplants and ampullectomies, all remaining pancreatectomies were included for analysis. For PD, this included current procedural terminology (CPT) codes 48150, 48152, 48153 and 48154. For the purposes of the analysis, total pancreatectomies (CPT 48155) were grouped with PD. A distal pancreatectomy included CPT codes 48140, 48145 and 48146. CPT codes were analysed from the primary CPT column as well as from any of the concurrent procedure columns. CPT coding did not differentiate between open and laparoscopic cases.

For thrombotic events within 30 days of a pancreatectomy, the analysis focused on three post-operative NSQIP variables: deep vein thrombosis (DVT), pulmonary embolism (PE) or a combination of the two. VTE was defined as a clinically detected DVT or PE. When both DVT and PE occurred, the first instance of either was considered the presenting VTE. The timing of VTE was compared with discharge date and labelled as 'early' (pre-discharge) versus 'late' (post-discharge).

For post-operative haemorrhagic events, the analysis focused on two post-operative variables: post-operative 'bleeding transfusion' which was defined by NSQIP as a transfusion of > 4 units packed red blood cells (PRBC) within 72 h of surgery (early PPH) and unplanned return to the operating room (ROR) combined with bleeding transfusion (ROR with PPH). Risk factors for pre- and post-discharge VTE were derived from analysis of all NSQIP-collected clinical factors.

The pre-operative NSQIP risk factors that were assessed included race, age, gender, performance status, weight/body mass index, haematocrit, platelets, blood urea nitrogen, creatinine, albumin, partial thrombin time, international normalized ratio, bilirubin, white blood cell count, alkaline phosphatase, aspartate aminotransferase, American Society of Anesthesiologists (ASA) class, smoking, chronic obstructive pulmonary disease (COPD), pneumonia, ascites, sepsis, disseminated cancer, diabetes, bleeding disorder, pre-operative radiation therapy, pre-operative chemotherapy, pre-operative transfusion, pre-operative hospitalization and a previous operation within 30 days.

Intra-operative variables included operative time, intra-operative transfusion, type of pancreatectomy and concurrent major operation. Concurrent major operations were defined as adrenalectomy, gastrectomy, oesophagectomy, intestinal resection, colorectal resection, retroperitoneal tumor resection, nephrectomy and/or hepatectomy. The definition of major concurrent operations did not include splenectomy, cholecystectomy, liver wedge resection/biopsy, radiofrequency ablation, feeding tube placement and abdominal wall hernia repair.

Thirty-day post-operative outcomes included a post-operative transfusion, bleeding transfusion (early PPH), ROR, renal insufficiency or failure, respiratory failure, myocardial infarction, cardiac arrest, surgical site infection, organ space infection (OSI, including abscess or pancreatic leak), fascial dehiscence,

post-operative sepsis or septic shock, length of stay and mortality. As a result of the defined limitations of NSQIP data, post-pancreatectomy mortality was defined as death within 30 postoperative days or death at a later date if the patient had a continuous hospitalization from surgery to the death date.

Statistical analysis

The association of clinical factors with VTE, bleeding complications and mortality, was analysed using the chi-squared test or Fisher's exact test for non-parametric categorical data and the Mann–Whitney *U*-test for non-parametric continuous data. Significant univariate risk factors were entered into a multivariate logistic regression model to determine independent associations. Analyses were performed using SPSS Statistics 19 (IBM, Armonk, NY, USA). All tests were two-sided. Statistical significance was defined as $P < 0.05$.

Results

Patients and pancreatectomies analysed

From 2005 to 2010, 13 771 patients met the inclusion criteria with a median age 64 years (range 16–90), 51.7% female gender and 78.6% Caucasian race. Rates of common pre-operative risk factors included 66.5% with ASA class ≥3, 19.7% with age ≥ 75 years and 26.9% with obesity [body mass index (BMI) ≥ 30 kg/m^2]. The case distribution included 9140 (66.4%) PD (including 306 (2.2%) total pancreatectomies) and 4631 (33.6%) DP. Indications for surgery included malignant diagnoses in 81.7% of patients with no difference in VTE rates between malignant and benign indications (3.2% versus 2.9%, $P = 0.451$). Other clinically relevant pre-, intra- and post-operative factors are described in Table 1.

VTE, bleeding, and transfusions in relation to type of pancreatectomy

Overall complication rates included the following: DVT (2.2%), PE (1.2%), VTE (3.1%), PPH (1.1%) and ROR with PPH (0.6%). There were only 5 (0.04%) patients who experienced both VTE and PPH after a pancreatectomy. VTE event rates were more frequent than PPH rates and/or ROR with PPH rates for both PD (3.0%, 1.1%, 0.7%) and DP (3.3%, 1.0%, 0.5%, $P < 0.001$, Fig. 1). Analysis of the association between the type of pancreatectomy and complication rates showed no differences in bleeding or VTE events, $P = 0.362$, Fig. 1. Intra-operative transfusions ≥ 1 unit PRBC were common (28.7%), as were intra-operative transfusions ≥ 2 units PRBC (21.6%), with PD transfusion rates (31.5%, 23.4%) higher than for DP (23.5%, 18.2%, respectively, $P < 0.001$).

Factors associated with early PPH

The univariate analysis of peri-operative factors associated with early PPH, or bleeding transfusion, is detailed in Table 1. On multivariate analysis, independent pre- and intra-operative factors associated with early PPH included the following: ASA class ≥ 3 [odds ratio (OR) 1.74, 95% confidence interval (CI) 1.08–2.79, $P = 0.023$], a lack of independent functional status (OR 2.10, 95% CI, 1.11–3.95, $P = 0.023$) and an intra-operative transfusion ≥ 4 units PRBC (OR 6.16, 95% CI, 4.12–9.21, $P < 0.001$, Table 2).

Factors associated with ROR with early PPH

The univariate analysis of peri-operative factors associated with ROR with early PPH is detailed in Table 3. On multivariate analysis, independent pre- and intra-operative predictors of ROR with early PPH included the following: pre-operative sepsis (OR 2.77, 95% CI, 1.23–6.25, $P = 0.014$), a pre-operative bleeding disorder (OR 2.83, 95% CI, 1.25–6.44, $P = 0.013$) and an intra-operative transfusion ≥ 4 units PRBC (OR 6.09, 95% CI, 3.64–10.21, $P < 0.001$, Table 2).

Factors associated with 30-day mortality

The 30-day postoperative mortality rate was 2.6%. Comparisons of risk factors for 30-day mortality are provided in Table 4. Independent risk factors for 30-day mortality included age ≥ 80 years (OR 2.56, 95% CI 1.723–3.79), pre-operative dyspnoea (OR 1.57, 95% CI 1.03–2.40), a lack of independent function (OR 2.14, 95% CI 1.28–3.57), albumin <3.5 g/dl (OR 1.47, 95% CI 1.07–2.03), an intra-operative transfusion ≥ 4 units PRBC (OR 2.65, 95% CI 1.81–3.88), PD (vs. DP, OR 1.87, 95% CI 1.26–2.77), unplanned ROR (OR 4.35, 95% CI 3.00–6.29), post-operative acute renal insufficiency/failure (OR 6.33, 95% CI 3.86–10.40), post-operative pneumonia (OR 2.35, 95% CI 1.56–3.54), ventilator need/failure to wean >48 h (OR 2.13, 95% CI 1.38–3.28) and early PPH (OR 2.05, 95% CI 1.11–3.81). VTE was not an independent factor for death.

Risk factors and timing of post-pancreatectomy VTE

Comparisons of risk factors for VTE are provided in Table 5. Independent risk factors for any (either pre- or post-discharge) VTE within 30 days of surgery are listed in Table 2. Major post-operative complications associated with any VTE included OSI (OR 1.72, 95% CI, 1.26–2.34, $P = 0.001$) and post-operative ventilator requirement >48 h (OR 3.55, 95% CI 2.57–4.91). For PD, the median date of diagnosis of OSI was post-operative day (POD) 11, whereas for DP, it was POD 14. Relative to the median discharge dates of POD 9 for PD and POD 7 for DP, the median date of any VTE was POD 11, whereas it was POD13 for DP. Late thromboembolic events accounted for 33.7%, 35.7% and 31.9% of all observed DVT, PE, and VTE, respectively (Fig. 2). Among patients with early VTE, the median date of VTE was POD 8 with a median discharge date of POD 20. Among patients with late VTE, the median date of VTE was POD 19 with a median discharge date of POD 8.

Post-pancreatectomy VTE pre-discharge risk factors

Univariate factors associated with early VTE are detailed in Table 6. Independent risk factors included a lack of independent functional status (OR 1.78, 95% CI 1.05–2.99, $P = 0.031$),

Table 1 Factors associated with early post-pancreatectomy haemorrhage (PPH, > 4 units blood in first 72 h after surgery)

Clinical Characteristic	All patients (*n* = 13771)		No early PPH > 4 units		Early PPH > 4 units		*P*
	n or median	% or range	*n* or median	% or range	*n* or median	% or range	
N	13771		13623		148		
Pre-operative factors							
BMI ≥ 40 kg/m^2	537	3.9%	526	3.9%	11	7.4%	0.026
Dyspnoea	1210	8.8%	1189	8.7%	21	14.2%	0.020
Diabetes	3063	22.2%	3019	22.2%	44	29.7%	0.028
Lack of independent function	380	2.8%	366	2.7%	14	9.5%	<0.001
Alcohol use	417	3.0%	417	3.1%	0	0%	0.031
Haematocrit <39%	7189	53.6%	7098	53.5%	91	65.0%	0.007
AST > 46 IU/l	3066	25.4%	3023	25.3%	43	34.1%	0.023
Albumin < 3.5 g/dl	3129	26.5%	3082	26.4%	47	38.2%	0.003
ASA class ≥ 3	9161	66.5%	9045	66.4%	116	78.4%	0.002
Disseminated cancer	495	3.6%	479	3.5%	16	10.8%	<0.001
Bleeding disorder	382	2.8%	373	2.7%	9	6.1%	0.014
Intra-operative							
Operative time, min	314	12–1146	246	12–892	313	12–1146	0.004
Operative time ≥ 360 min	5069	36.8%	5000	36.7%	69	46.6%	0.013
Any intra-operative transfusion	3002	28.7%	2910	28.3%	92	62.6%	<0.001
RBC ≥4	718	6.9%	669	6.5%	49	33.3%	<0.001
Concurrent Major GI/GU	990	7.2%	969	7.1%	21	14.2%	0.001
PD/total versus distal pancreatectomy							0.628
PD/total	9140	66.4%	9039	66.4%	101	68.2%	
Distal	4631	33.6%	4584	33.6%	47	31.8%	
Post-operative							
Return to OR	921	6.7%	832	6.1%	89	60.1%	<0.001
Sepsis/septic shock	1899	13.8%	1838	13.5%	61	41.2%	<0.001
Acute renal insufficiency/failure	238	1.7%	217	1.6%	21	14.2%	<0.001
Failure to wean ventilator 48 h	694	5.0%	633	4.6%	61	41.2%	<0.001
Post-operative pneumonia	706	5.1%	674	4.9%	32	21.6%	<0.001
Any SSI or organ space infection	2759	20.0%	2715	19.9%	44	29.7%	0.003
Organ space infection	1451	10.5%	1421	10.4%	30	20.3%	<0.001
Cardiac arrest	151	1.1%	137	1.0%	14	9.5%	<0.001
Severe complications	3436	25.0%	3313	24.3%	123	83.1%	<0.001
Post-operative LOS	8	1–215	8	1–215	14	1–119	<0.001
Death within 30 days	357	2.6%	323	2.4%	34	23.0%	<0.001

ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; BMI, body mass index; LOS, length of stay; OR, operating room; RBC, (units) red blood cells; SSI, surgical site infection.

- Not significant: age, gender, race, platelets, sodium, blood urea nitrogen, creatinine, partial thrombin time, international normalized ratio, total bilirubin, alkaline phosphatase, white blood cells, steroid use; chronic obstructive pulmonary disease; previous coronary stent; previous cardiac surgery; medical hypertension; pre-operative sepsis; surgical peripheral vascular disease; smoking, pre-operative stroke, pre-operative radiation therapy, operation in the preceding 30 days; pre-operative chemotherapy within 30 days; pre-operative weight loss ≥ 10%; dehiscence; superficial SSI, deep SSI, venous thromboembolism.
- Not evaluated with < 1%: pre-operative pneumonia; ascites; varices; congestive heart failure; recent myocardial infarction; angina; rest pain, pre-operative acute renal failure or dialysis; altered mental status; pre-operative open wound; pre-operative transfusion > 4 units; post-operative MI, post-operative coma, post-operative stroke.

Severe complications include: pneumonia, reintubation, ventilator >48 h, renal insufficiency/failure, cardiac arrest, myocardial infarction, coma, stroke, sepsis, septic shock, return to OR, wound dehiscence and organ space infection.

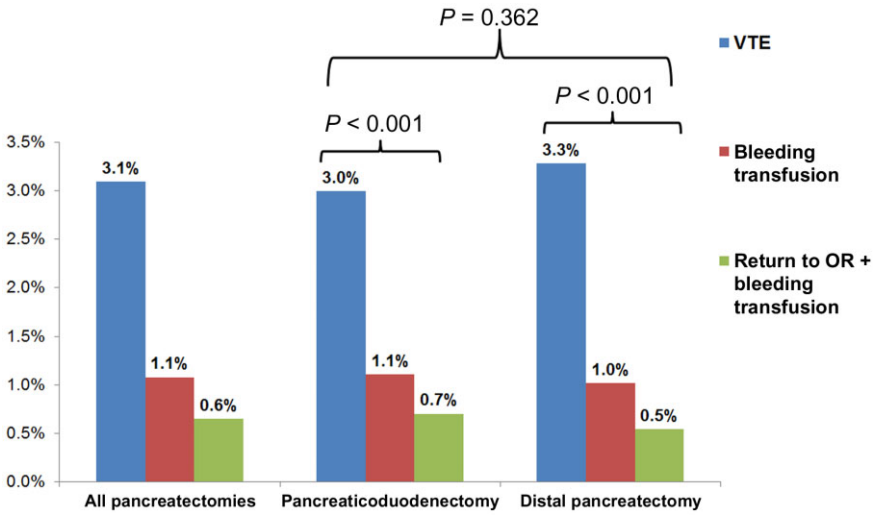

Figure 1 Venous thromboembolism (VTE) events outnumber post-operative bleeding transfusions (post-pancreatectomy haemorrhage > 4 units in first 72 h after surgery) and returns to the operating room (ROR) with bleeding transfusions. There is no difference in the rates of bleeding or thrombotic events between a pancreaticoduodenectomy and a distal pancreatectomy

Table 2 Independent factors associated with venous thromboembolism (VTE) and bleeding events after a pancreatectomy

Risk factor	VTE			Early PPH > 4 units			ROR with early PPH		
	OR	95% CI	*P*	OR	95% CI	*p*	OR	95% CI	*P*
Pre-operative									
Haematocrit < 39%	1.46	1.13–1.88	0.003						
Age ≥ 70 years	1.47	1.15–1.88	0.002						
BMI ≥ 30 kg/m^2	1.47	1.14–1.90	0.003						
Bleeding disorder	1.93	1.17–3.18	0.010				2.77	1.23–6.25	0.014
Pre-operative sepsis	1.98	1.19–3.29	0.008				2.83	1.25–6.44	0.013
Disseminated cancer	2.12	1.36–3.32	0.001						
ASA class ≥ 3				1.74	1.08–2.79	0.023			
Lack independent function				2.10	1.11–3.95	0.023			
Intra-operative									
Operative time ≥ 360 min	1.30	1.02–1.65	0.048						
Transfusion ≥ 4 units				6.16	4.12–9.21	<0.001	6.09	3.64–10.21	<0.001
Post-operative									
Organ space infection	1.72	1.26–2.34	0.001						
Ventilator > 48 h	3.55	2.57–4.91	<0.001						

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; OR, odds ratio; PPH, post-pancreatectomy haemorrhage; ROR, return to operating room; VTE, venous thromboembolism.

pre-operative haematocrit < 39% (OR 1.69, 95% CI 1.17–2.43, P = 0.005), chronic obstructive lung disease (OR 1.74, 95% CI 1.01–2.99, P = 0.046), pre-operative leukocytosis (OR 2.12, 95% CI 1.43–3.16, P < 0.001), disseminated cancer (OR 2.50, 95% CI 1.02–3.32, P = 0.040), bleeding disorder (OR 2.56, 95% CI 1.47–4.44, P = 0.001), an intra-operative transfusion ≥ 2 units (OR 1.53, 95% CI 1.09–2.16, P = 0.014), operative time ≥300 min (OR 1.44, 95% CI 1.02–2.03, P = 0.039), ventilator need/failure to wean > 48 h (OR 3.74, 95% CI 2.42–5.77, P < 0.001) and OSI (OR1.64, 95% CI 1.10–2.45, P = 0.016). Patients with early VTE experienced a 30-day mortality rate of 9.0% (versus 2.6% overall baseline mortality rate, P < 0.001).

Post-pancreatectomy post-discharge VTE risk factors

Univariate factors associated with late VTE are detailed in Table 6. Multivariate analysis identified the following independent risk factors associated with post-discharge VTE: obesity (OR 1.53, 95% CI, 1.08–2.19, P = 0.018) and age ≥ 75 years (OR 1.76, 95%

Table 3 Factors associated with return to the operating room (ROR) and a post-pancreatectomy haemorrhage (PPH) > 4 units blood in the first 72 h after surgery

Clinical characteristic	All patients (*n* = 13771)		No ROR with PPH >4 units		ROR with PPH >4 units		*P*
	n or median	% or range	*n* or median	% or range	*n* or median	% or range	
n	13771		13682		89		
Pre-operative factors							
Lack of independent function	380	2.8%	373	2.7%	7	7.9%	0.003
AST > 46 IU/l	3066	25.4%	3035	25.3%	31	39.7%	0.003
Alkaline phosphatase ≥ 126 IU/l	4411	36.6%	4376	36.6%	35	48.6%	0.035
Albumin < 3.5 g/dl	3129	26.5%	3097	26.4%	32	42.7%	0.002
ASA class ≥ 3	9161	66.5%	9091	66.4%	70	78.7%	0.015
Disseminated cancer	495	3.6%	487	3.6%	8	9.0%	0.006
Pre-operative sepsis	467	3.4%	459	3.4%	8	9.0%	0.003
Bleeding disorder	382	2.8%	375	2.7%	7	7.9%	0.003
Intra-operative							
Operative time, min	314	12–1146	313	12–1146	358	81–892	0.021
Operative time ≥ 360 min	5069	36.8%	5026	36.7%	43	48.3%	0.024
Any intra-operative transfusion	3002	28.7%	2949	28.5%	53	59.6%	<0.001
RBC ≥ 4	718	6.9%	689	6.7%	29	32.6%	<0.001
Concurrent major GI/GU	990	7.2%	376	7.1%	14	15.7%	0.002
PD/total versus distal pancreatectomy							0.267
PD/total	9140	66.4%	9076	66.3%	64	71.9%	
Distal	4631	33.6%	4606	33.7%	25	28.1%	
Post-operative							
Sepsis/septic shock	1899	13.8%	1858	13.6%	41	46.1%	<0.001
Acute renal insufficiency/failure	238	1.7%	222	1.6%	16	18.0%	<0.001
Failure to wean ventilator 48 h	694	5.0%	649	4.7%	45	50.6%	<0.001
Post-operative pneumonia	706	5.1%	682	5.0%	24	27.0%	<0.001
Organ space infection	1451	10.5%	1431	10.5%	20	22.5%	<0.001
Cardiac arrest	151	1.1%	141	1.0%	10	11.2%	<0.001
Post-operative LOS	8	1–215	8	1–215	13	1–73	<0.001
Death within 30 days	357	2.6%	334	2.4%	23	25.8%	<0.001

ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; GI, gastrointestinal; GU, genitourinary; LOS, length of stay; PD, pancreaticoduodenectomy; RBC, (units) red blood cells.

- Not significant: age, gender, race, body mass index, platelets, sodium, blood urea nitrogen, creatinine, partial thrombin time, international normalized ratio, total bilirubin, white blood cells, steroid use; lung disease, dyspnoea, diabetes, previous coronary stent; previous cardiac surgery; medical hypertension, alcohol use, smoking, pre-operative stroke, pre-operative radiation therapy, operation in preceding 30 days, pre-operative chemotherapy, pre-operative weight loss ≥ 10%, dehiscence; superficial or deep surgical site infection, venous thromboembolism.

CI 1.20–2.58, $P = 0.004$), distal pancreatectomy (OR 2.41, 95% CI 1.71–3.39) and OSI (OR 2.14, 95% CI 1.39–3.28, $P < 0.001$). Of the 136 patients with late VTE, 89 (65.4%) had at least one of these 4 risk factors. Patients with late VTE experienced a 30-day mortality rate of 2.9% (versus 2.6% overall baseline mortality rate, $P = 0.579$).

Discussion

The primary aims of this study were to compare the post-operative rates of thromboembolic and bleeding events after pancreatectomy and to identify risk factors for VTE, early PPH and ROR with PPH, in patients undergoing PD and DP. Based on standardized definitions and the presence of trained reviewers for data collection, the ACS-NSQIP database was well-suited to address each of these aims.[15,19,20] This analysis determined that, within the context of current national practice patterns, the risk of VTE outweighs the risk of haemorrhagic events for both PD and DP. In addition, the study identified unique risk factors for both pre- and post-discharge VTE after pancreatic surgery. These data suggest that late VTE is a clinically relevant complication after a pancreatectomy with one-third of post-operative VTE occurring

Table 4 Factors associated with 30-day mortality after a pancreatectomy

Clinical characteristic	All patients (n = 13771)		No death		Death		P
	n or median	% or range	n or median	% or range	n or median	% or range	
N	13771		13414		357		
Pre-operative factors							
Age ≥ 80 years	1120	8.1%	1058	7.9%	62	17.4%	<0.001
Male	6650	48.3%	6459	48.2%	191	53.5%	0.046
Dyspnoea	1210	8.8%	1150	8.6%	60	16.8%	<0.001
Diabetes	3063	22.2%	2953	22.0%	110	30.8%	<0.001
COPD	598	4.3%	569	4.2%	29	8.1%	<0.001
Previous coronary stent	852	6.2%	809	6.0%	43	12.0%	<0.001
Medical hypertension	7145	51.9%	6888	51.3%	257	72.0%	<0.001
Lack of independent function	380	2.8%	342	2.5%	38	10.6%	<0.001
> 10% weight loss	2186	15.9%	2103	15.7%	83	23.2%	<0.001
Haematocrit <39%	7189	53.6%	6972	53.4%	217	62.7%	0.001
Alkaline phosphatase ≥126 IU/l	4411	36.6%	4270	36.4%	141	43.9%	0.006
AST > 46 IU/l	3066	25.4%	2952	25.1%	114	35.4%	<0.001
PTT > 27 s	6806	67.5%	6606	67.4%	200	73.5%	0.032
BUN ≥ 20 mg/dl	2426	18.6%	2339	18.4%	87	25.1%	0.002
Creatinine ≥ 1.3 mg/dl	1129	8.5%	1068	8.2%	61	17.7%	<0.001
Albumin < 3.5 g/dl	3129	26.5%	2982	26.0%	147	46.4%	<0.001
Bilirubin > 1.0 mg/dl	3490	29.4%	3377	29.2%	113	37.3%	0.002
Steroid use	270	2.0%	257	1.9%	13	3.6%	0.020
ASA class ≥ 3	9161	66.5%	8848	66.0%	313	87.7%	<0.001
INR ≥ 1.1	3920	34.0%	3776	33.7%	144	46.9%	<0.001
Platelets < 150 000/μl	804	6.0%	772	5.9%	32	9.2%	0.012
Pre-operative sepsis	467	3.4%	436	3.3%	31	8.7%	<0.001
Disseminated cancer	495	3.6%	472	3.5%	23	6.4%	0.003
Bleeding disorder	382	2.8%	366	2.7%	16	4.5%	0.046
Pre-operative radiation therapy	304	2.2%	289	2.2%	15	4.2%	0.009
Intra-operative							
Operative time ≥ 360 min	5069	36.8%	4886	36.4%	183	51.3%	<0.001
Any intra-operative transfusion	3002	28.7%	2863	28.1%	139	55.6%	<0.001
RBC ≥ 4	718	6.9%	645	6.3%	73	29.2%	<0.001
Concurrent major GI/GU	990	7.2%	946	7.1%	44	12.3%	<0.001
PD/total versus distal pancreatectomy							<0.001
Distal	4632	33.6%	4566	34.0%	66	18.5%	
Post-operative							
Early VTE	290	2.1%	264	2.0%	26	7.3%	<0.001
Late VTE	136	1.0%	132	1.0%	4	1.1%	0.782
Any VTE	426	3.1%	396	3.0%	30	8.4%	<0.001
Bleeding transfusion	148	1.1%	114	0.8%	34	9.5%	<0.001
Any post-operative transfusion	916	6.7%	835	6.2%	81	22.7%	<0.001
Return to OR	921	6.7%	769	5.7%	152	42.6%	<0.001
Sepsis/septic shock	1899	13.8%	1714	12.8%	185	51.8%	<0.001
Acute renal insufficiency/failure	238	1.7%	158	1.2%	80	22.4%	<0.001
Failure to wean ventilator 48 h	694	5.0%	544	4.1%	150	42.0%	<0.001
Post-operative pneumonia	706	5.1%	616	4.6%	90	25.2%	<0.001
Dehiscence	224	1.6%	211	1.6%	13	3.6%	0.002
Organ space infection	1451	10.5%	1376	10.3%	75	21.0%	<0.001
Cardiac arrest	151	1.1%	36	0.3%	115	32.2%	<0.001
Severe complications (not VTE)	3436	25.0%	3130	23.3%	306	85.7%	<0.001

ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; GU, genitourinary; INR, international normalized ratio; OR, operating room; PD, pancreaticoduodenectomy; PTT, partial thrombin time; RBC, (units) red blood cells; VTE, venous thromboembolism.

- Not significant: body mass index; race, alcohol use; white blood cells, smoking, pre-operative stroke, operation in preceding 30 days; pre-operative chemotherapy within 30 days; superficial and deep surgical site infections.

Table 5 Factors associated with no venous thromboembolism (VTE) compared with VTE

Clinical characteristic	All patients (*n* = 13771)		No VTE (DVT or PE)		VTE (DVT or PE)		*P*
	n or median	% or range	*n* or median	% or range	*n* or median	% or range	
N	13771		13345		426		
Preoperative factors							
Median age (range), years	64	16–90	64	16–90	66	20–90	0.004
Age ≥70 years	4572	33.2%	4407	33.0%	165	38.7%	0.014
BMI ≥ 30 kg/m^2	3703	26.9%	3566	26.7%	137	32.2%	0.013
Dyspnoea	1210	8.8%	1156	8.7%	54	12.7%	0.004
COPD	598	4.3%	567	4.2%	31	7.3%	0.003
Steroid use	270	2.0%	256	1.9%	14	3.3%	0.045
Medical hypertension	7145	51.9%	6892	51.6%	253	59.4%	0.002
Lack of independent function	380	2.8%	349	2.6%	31	7.3%	<0.001
Pre-operative sepsis	467	3.4%	441	3.3%	26	6.1%	0.002
INR > 1.0	5235	45.5%	5045	45.2	190	52.6%	0.005
Haematocrit < 39%	7189	53.6%	6928	53.3%	261	62.7%	<0.001
WBC > 11 000/μl	1060	7.9%	1005	7.7%	55	13.2%	<0.001
Albumin < 3.5 g/dl	3129	26.5%	2989	26.2%	140	38.3%	<0.001
Disseminated cancer	495	3.6%	459	3.4%	36	8.5%	<0.001
Bleeding disorder	382	2.8%	354	2.7%	28	6.6%	<0.001
Neoplasm (versus benign)	8618	81.7%	8339	81.7%	279	83.3%	0.451
Intra-operative							
Operative time, min	314	12–1146	313	12–1146	346	72–981	<0.001
Operative time ≥ 360 min	5069	36.8%	4872	36.5%	197	46.2%	<0.001
Any intra-operative transfusion	3002	28.7%	2864	28.3%	138	41.1%	<0.001
RBC ≥ 4	718	6.9%	671	6.6%	47	14.0%	<0.001
Concurrent major operation	990	7.2%	945	7.1%	45	10.6%	0.006
PD/total versus distal pancreatectomy							0.362
PD/total	9140	66.4%	8866	66.4%	274	64.3%	
Distal	4631	33.6%	4479	33.6%	152	35.7%	
Post-operative							
Any post-operative transfusion (<72 h)	916	6.7%	873	6.5%	43	10.1%	0.004
Return to OR (ROR)	921	6.7%	854	6.4%	67	15.7%	<0.001
Sepsis/septic shock	1899	13.8%	1747	13.1%	152	35.7%	<0.001
Acute renal insufficiency/failure	238	1.7%	223	1.7%	15	3.5%	0.004
Failure to wean ventilator 48 h	694	5.0%	613	4.6%	81	19.0%	<0.001
Post-operative pneumonia	706	5.1%	644	4.8%	62	14.6%	<0.001
Deep SSI	268	1.9%	253	1.9%	15	3.5%	0.017
Any SSI or organ space infection	2759	20.0%	2606	19.5%	153	35.9%	<0.001
Organ space infection	1451	10.5%	1357	10.2%	94	22.1%	<0.001
Fascial dehiscence	224	1.6%	208	1.6%	16	3.8%	<0.001
Severe complications	3436	25.0%	3209	24.0%	227	53.3%	<0.001
Post-operative LOS	8	1–215	8	1–215	14	1–98	<0.001
Death within 30 days	357	2.6%	327	2.5%	30	7.0%	<0.001

BMI, body mass index; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; INR international normalized ratio; LOS, length of stay; OR, operating room; PD, pancreaticoduodenectomy; PE, pulmonary embolus; RBC, (units) red blood cells; SSI, surgical site infection; WBC, white blood cells.

- Not significant: race, gender, American Society of Anesthesiologists score, platelets, sodium, blood urea nitrogen, creatinine, partial thrombin time, total bilirubin, aspartate aminotransferase, alkaline phosphatase, previous coronary stent, previous cardiac surgery, alcohol use, smoking, diabetes, pre-operative radiation therapy, operation in preceding 30 days, pre-operative chemotherapy; pre-operative weight loss ≥ 10%; post-operative bleeding transfusion; superficial SSI.

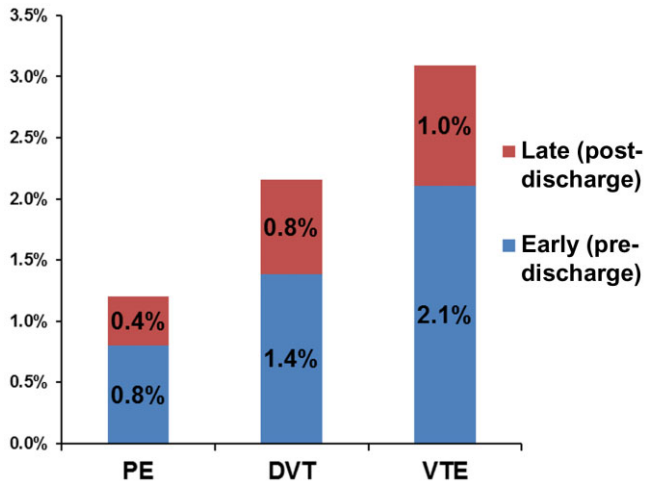

Figure 2 Approximately 1 in 3 post-pancreatectomy VTE events are recognized post-discharge. (PE, pulmonary embolus; DVT, deep venous thrombosis; VTE, venous thromboembolism)

post-discharge. Finally, by isolating the risk factors for late VTE, including obesity, age ≥75 years, DP and/or OSI, the results of this study provide a basis for identifying high-risk patients for selective use of extended chemoprophylaxis.

There is general consensus that post-operative VTE chemoprophylaxis should be prescribed for all patients undergoing major abdominal surgery if the patient's acute bleeding risk is acceptably lower than the thrombotic risk.[1,2] The transferability of these recommendations to complex HPB surgery, in which intra-operative bleeding and intra-operative transfusions are common, is less clear. To disprove or to corroborate historical fears of early PPH, an accurate comparison of VTE and bleeding event rates after a pancreatectomy is needed to determine the safety and practicality of recommending routine post-operative VTE chemoprophylaxis.

It is estimated that as many as 30% of pancreatic resections in the United States are currently being performed at NSQIP member institutions. By analysing a large national sampling of patients, this study showed that early post-operative haemorrhagic events, although traditionally feared, are quite rare (<1% event rate). Unlike early PPH which is likely related to intra-operative technical issues,[14] ongoing surgical bleeding, or uncorrected coagulopathy (all of which are contraindications for immediately starting post-operative VTE chemoprophylaxis), late PPH is generally related to abdominal sepsis, undrained pancreatic leaks and vascular pseudoaneurysms. Therefore, these unpredictable late bleeding events may not represent a barrier to the routine use of chemoprophylaxis. The number of patients who experienced both VTE and PPH was extremely low (5 of 13 771), to the point that detailed analysis of risk factors for this difficult clinical scenario was not feasible.

The comparative rarity of early haemorrhagic events combined with the higher risk of post-operative VTE in both PD and DP make a very strong argument for routine and timely post-operative chemoprophylaxis in all pancreatectomy patients. Although early PPH is an independent risk factor for 30-day mortality, its very low event rate is associated with the defined risk factor of a major intra-operative transfusion (≥4 units pRBC). As the most significant independent risk factor for early PPH or ROR with PPH was an intra-operative transfusion ≥ 4 units PRBC, the main exception to the regimented delivery of immediate post-operative VTE chemoprophylaxis would be patients with ongoing signs of active bleeding in the immediate post-operative period. For these rare patients, haemostasis should be confirmed before initiating VTE chemoprophylaxis.

There is ample evidence that institutional protocols for post-operative (and even pre-induction dosing)[21] have led to reduced rates of post-operative VTE. However, there remains no consensus on the length of post-operative therapy, even although extended chemoprophylaxis is recommended for high-VTE-risk cancer patients.[1,2,8] Thus, many, if not most, surgeons subjectively discontinue VTE chemoprophylaxis when patients meet discharge criteria and leave the hospital. In order to comment on this practice, an additional aim of this study was to examine the rates of and risk factors for post-discharge VTE. The data from this analysis provide a rationale for recommending extended chemoprophylaxis at least to obese and elderly patients, and those who experience significant post-operative complications such as OSI. In addition, the analysis suggests that DP patients are more susceptible to post-discharge VTE. There are a number of explanations for this observation, but the most plausible is that pancreatic fistulae are often identified later in the post-operative period after DP compared with PD, and with the national trend of earlier discharge of DP patients, more of these patients may develop this important risk factor after leaving the hospital.[22] Finally, malignant diagnoses are typically associated with more post-operative VTE compared with benign diseases, leading the ACCP to recommend extended chemoprophylaxis for 30 days after major abdominal cancer surgery in patients with a high VTE risk. However, our data showed no difference among surgical patients within 30 post-operative days, indicating that even patients undergoing a pancreatectomy for non-malignant diagnoses may benefit from extended VTE chemoprophylaxis.

A limitation of this study was that VTE chemoprophylaxis usage was not a recorded variable in NSQIP.[15,23] An assumption can be made that many, but not all, patients received some amount of inpatient post-operative chemoprophylaxis. The timing of initiation would have been inconsistent. In contrast, it is likely that post-discharge chemoprophylaxis was uncommonly utilized, as it is not yet a current standard quality measure for hospitalized or surgical patients, in spite of the ACCP recommendations. NSQIP does not proactively screen asymptomatic patients for VTE, and thus only clinically apparent VTE are recorded. Another potential weakness is the limitation of the study period to 30 days after surgery, which does not capture the full post-operative risk of patients, especially cancer patients requiring

Table 6 Factors associated with no venous thromboembolism (VTE), early VTE, and late VTE, after a pancreatectomy

Clinical characteristic	All patients (n = 13 771)		No VTE (DVT or PE)		Early (pre-discharge) VTE		Late (post-discharge) VTE		Early versus none	Late versus none	Early versus late
	n or median	% or range	*n* or median	% or range	*n* or median	% or range	*n* or median	% or range	*P*	*P*	*P*
n	13771	100%	13345	96.9%	290	2.1	136	1.0%			
Pre-operative factors											
Median age (range), years	64	16–90	64	16–90	66	25–90	66	20–90	**0.033**	**0.041**	0.586
Age ≥ 75 years	2715	19.7%	2618	19.6%	60	20.7%	37	27.2%	0.649	**0.027**	0.135
BMI ≥ 30 kg/m^2	3703	26.9%	3566	26.7%	86	29.7%	51	37.5%	0.264	**0.005**	0.106
Dyspnoea	1210	8.8%	1156	8.7%	34	11.7%	20	14.7%	0.068	**0.013**	0.389
COPD	598	4.3%	567	4.2%	25	8.6%	6	4.4%	**<0.001**	0.925	0.119
Medical hypertension	7145	51.9%	6892	51.6%	169	58.3%	84	61.8%	**0.025**	**0.019**	0.494
Lack of independent function	380	2.8%	349	2.6%	26	9.0%	5	3.7%	**<0.001**	0.410	0.050
Pre-operative sepsis	467	3.4%	441	3.3%	19	6.6%	7	5.1%	**0.002**	0.233	0.572
INR > 1.0	5235	45.5%	5045	45.2%	133	52.0%	57	54.3%	**0.032**	0.063	0.687
Haematocrit < 39%	7189	53.6%	6928	53.3%	193	68.7%	68	50.4%	**<0.001**	0.494	**<0.001**
WBC > 11 000/μl	1060	7.9%	1005	7.7%	46	16.4%	9	6.7%	**<0.001**	0.641	**0.006**
Albumin < 3.5 g/dl	3129	26.5%	2989	26.2%	117	46.8%	23	19.8%	**<0.001**	0.122	**<0.001**
ASA class ≥ 3	9161	66.5%	8859	66.4%	212	73.1%	90	66.2%	**0.016**	0.959	0.142
Disseminated cancer	495	3.6%	459	3.4%	27	9.3%	9	6.6%	**<0.001**	**0.044**	0.352
Bleeding disorder	382	2.8%	354	2.7%	23	7.9%	5	3.7%	**<0.001**	0.415	0.099
Malignant (versus benign)	8618	81.7%	8339	81.7%	191	82.0%	88	86.3%	0.905	0.231	0.332
Intra-operative											
Operative time, min	314	12–1146	313	12–1146	362	81–981	291	72–872	**<0.001**	0.160	**<0.001**
Operative time ≥ 300 min	7492	54.4%	7224	54.1%	206	71.0%	62	45.6%	**<0.001**	**0.047**	**<0.001**
Any intra-operative transfusion	3002	28.7%	2864	28.3%	115	48.9%	23	22.8%	**<0.001**	0.217	**<0.001**
RBC ≥ 2	2256	21.6%	2138	21.2%	101	43.0%	17	16.8%	**<0.001**	0.290	**<0.001**
RBC ≥ 4	718	6.9%	671	6.6%	41	17.4%	6	5.9%	**<0.001**	0.779	**0.005**
Concurrent major operation	990	7.2%	945	7.1%	30	10.3%	15	11.0%	**0.033**	0.075	0.830
PD/total versus distal pancreatectomy									**0.017**	**<0.001**	**<0.001**
PD/total	9140	66.4%	8866	66.4%	212	73.1%	62	45.6%			
Distal	4631	33.6%	4479	33.6%	78	26.9%	74	54.4%			
Post-operative											
Any post-operative transfusion (72 h)	916	6.7%	873	6.5%	36	12.4%	7	5.1%	**<0.001**	0.512	0.020
Return to OR (ROR)	921	6.7%	854	6.4%	55	19.0%	12	8.8%	**<0.001**	0.251	**0.007**
Sepsis/septic shock	1899	13.8%	1747	13.1%	117	40.3%	35	25.7%	**<0.001**	**<0.001**	**0.003**
Acute renal insufficiency/ failure	238	1.7%	223	1.7%	15	5.2%	0	0%	**<0.001**	0.178	**0.007**
Failure to wean ventilator 48 h	694	5.0%	613	4.6%	78	26.9%	3	2.2%	**<0.001**	0.296	**<0.001**
Post-operative pneumonia	706	5.1%	644	4.8%	52	17.9%	10	7.4%	**<0.001**	0.172	**0.004**
Superficial SSI	1141	8.3%	1095	8.2%	35	12.1%	11	8.1%	**0.018**	0.961	0.217
Deep SSI	268	1.9%	253	1.9%	12	4.1%	3	2.2%	**0.006**	0.746	0.406
Any SSI or OSI	2759	20.0%	2606	19.5%	111	38.3%	42	30.9%	**<0.001**	**0.001**	0.138
OSI	1451	10.5%	1357	10.2%	67	23.1%	27	19.9%	**<0.001**	**<0.001**	0.451
Fascial dehiscence	224	1.6%	208	1.6%	13	4.5%	3	2.2%	**<0.001**	0.474	0.290
Severe complications	3436	25.0%	3209	24.0%	174	60.0%	53	39.0%	**<0.001**	**<0.001**	**<0.001**
Post-operative LOS	8	1–215	8	1–215	20	7–98	8	3–24	**0.001**	**0.017**	**<0.001**
Death within 30 days	357	2.6%	327	2.5%	26	9.0%	4	2.9%	**<0.001**	0.579	**0.025**

ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; INR, international normalized ratio; LOS, length of stay; OR, operating room; OSI, organ space infection; PD, pancreaticoduodenectomy; PE, pulmonary embolus; RBC, (units) red blood cells; SSI, surgical site infection; WBC, white blood cells.

- Not significant: race, gender, platelets, sodium, blood urea nitrogen, creatinine, partial thrombin time, total bilirubin, aspartate aminotransferase, alkaline phosphatase, previous coronary stent; previous cardiac surgery; surgical peripheral vascular disease; alcohol use, smoking, diabetes, steroid use, pre-operative radiation therapy, operation in preceding 30 days, pre-operative chemotherapy; pre-operative weight loss ≥ 10%; post-operative bleeding transfusion.

Bold type highlights univariate comparisons with $P < 0.05$.

adjuvant chemotherapy. This specific risk would argue for extended chemoprophylaxis for all cancer patients regardless of the aforementioned risk factors, as a VTE can derail planned adjuvant therapy. In spite of the weaknesses of NSQIP analyses, the size of the cohort provided an event rate that powered a multivariate analysis of VTE risk factors, which would be difficult to accomplish with a smaller institutional sample or dataset.[19,20] As this is the first study to describe a subset of high-risk pancreatectomy patients who might benefit from chemoprophylaxis beyond discharge, further prospective studies are required to study the clinical effectiveness and cost effectiveness of extended chemoprophylaxis after a pancreatectomy.

In conclusion, within current national practice patterns, post-pancreatectomy VTE events outnumber major bleeding complications, which rarely occur. With the exception of patients with overt ongoing bleeding, the fear of early PPH should not prevent the timely administration of routine post-operative VTE for all pancreatectomy patients. One-third of post-pancreatectomy VTE occur post-discharge with clearly identifiable risk factors, potentially providing a rationale for selective use of post-discharge VTE chemoprophylaxis in high-risk patients.

Conflicts of interest

None declared.

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