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Corinne Frere, Barbara Bournet, Sophie Gourgou, Julien Fraisse, Cindy Canivet, et al.. Incidence of Venous Thromboembolism in Patients With Newly Diagnosed Pancreatic Cancer and Factors Associated With Outcomes. *Gastroenterology*, 2020, 158 (5), pp.1346-1358.e4. 10.1053/j.gastro.2019.12.009 . hal-02860957

HAL Id: hal-02860957

<https://hal.science/hal-02860957>

Submitted on 20 May 2022

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Title: Incidence of Venous Thromboembolism in Patients with Newly Diagnosed Pancreatic Cancer and Factors Associated With Outcomes

Short Title: Venous Thromboembolism and Pancreatic Cancer

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Grants and financial supports: The BACAP cohort and the BACAP-VTE study were funded by the French National Cancer Institute (Grant INCa_6294) and the BACAP-VTE study by the Groupe Francophone Thrombose et Cancer (GFTC).

Abbreviations : BMI, Body Mass Index; CI, confidence interval; CRT, catheter-related thrombosis; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group Performance Status; GEM, gemcitabine ; VTE, venous thromboembolism ; DVT, deep-vein thrombosis; OS, overall survival; PC, Pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PE, pulmonary embolism; PFS, progression free survival; RCT, randomized controlled trials; VVT, visceral vein thrombosis.

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Disclosure: The authors declare they have no conflict of interest regarding the content of this manuscript.

Authors contribution: Study concept: CF, BB, CC, LB, and DF; Study design: CF, BB, CC, LB and DF; Analysis and interpretation of data: CF, BB, CC, JF, SG, JC, LB and DF; Drafting of the manuscript: CF, JC and DF; Critical revision for important intellectual content: All authors

Abstract:

Background & Aims: Pancreatic ductal adenocarcinoma (PDAC) is associated with the highest incidence of venous thromboembolism (VTE) of any cancer type. However, little is known about risk factors for VTE or its outcomes in patients with PDAC.

Methods: We collected data from a prospective, observational study performed at multiple centers in France from May 2014 through November 2018 (the Base Clinico-Biologique de l'Adénocarcinome Pancréatique [BACAP] study) linked to a database of patients with a new diagnosis of PDAC of any stage. Data were collected from 731 patients at baseline and during clinical follow-up or in the event of symptoms. The primary endpoint was the onset of VTE during follow up. The secondary end points were progression-free survival (PFS) and overall survival (OS) times.

Results: During a median follow-up of 19.3 months, 152 patients (20.79%) developed a VTE. The median time from PDAC diagnosis to the onset of VTE was 4.49 months. Cumulative incidence values of VTE were 8.07% (95% CI, 6.31–10.29) at 3 months and 19.21% (95% CI, 16.27–22.62) at 12 months. In multivariate analysis, PDAC primary tumor location (isthmus vs head, hazard ratio [HR], 2.06; 95% CI, 1.09–3.91; $P=.027$) and stage (locally advanced vs resectable or borderline HR, 1.66; 95% CI 1.10–2.51, $P=.016$ and metastatic vs resectable or borderline HR, 2.50; 95% CI, 1.64–3.79; $P<.001$) were independent risk factors for onset of VTE. Patients who developed VTE during follow up had shorter times of PFS (HR, 1.74; 95% CI, 1.19–2.54; $P=.004$) and OS (HR, 2.02; 95% CI, 1.57–2.60; $P<.001$).

Conclusion: In an analysis of data from the BACAP study, we found that frequent and early onset of VTE after diagnoses of PDAC are associated with significant decreases in times of PFS and OS. Studies are needed to determine whether primary prophylaxis of VTE in patients with PDAC will improve morbidity and mortality related to VTE.

KEY WORDS: pancreatic cancer, blood clot, prognostic factor, complication

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of death in USA¹ and carries the highest mortality rate amongst all solid organ cancers.^{2,3} Its prevalence is expected to increase by around 40 percent over the next decade in North America and in Europe,⁴ and this devastating disease is projected to become the second cause of cancer-related death by 2020.⁵ Surgical resection offers a chance for cure, but only 15 to 20 percent of the patients have a resectable tumor at diagnosis³ and less than 4 percent of these patients are still alive after 10 years.⁶ Palliative chemotherapy is warranted for the majority of PDAC patients and the use of FOLFIRINOX, which improves survival, has become the standard of care in the metastatic setting.⁷ Patients with unresectable tumor have a 5-year survival rate less than 8 percent.³

Cancer is an independent and major risk factor for venous thromboembolism (VTE),^{8,9} defined as deep-vein thrombosis (DVT), including catheter-related thrombosis (CRT), and pulmonary embolism (PE). VTE occurs in 15% to 20% of all cancer patients¹⁰ and accounts for increased mortality,⁸ although it is a potentially preventable complication.¹¹ PDAC carries the highest risk of VTE amongst all cancers,¹²⁻¹⁶ with VTE rates from 5% to 41% in retrospective cohorts,¹⁷⁻²⁹ and up to 67% in postmortem series.³⁰ However, no study has yet prospectively assessed the relative importance of patients and tumor characteristics, cancer treatments, and the biological markers on the risk of VTE in PDAC. Whether the onset of VTE is associated with decreased survival in PDAC patients remains unknown, with only few retrospective studies and conflicting results.^{18,20,21,25,29,31,32} We therefore designed the prospective, multicenter BACAP-VTE (Base Clinico-Biologique de l'Adénocarcinome Pancréatique-Venous Thromboembolism) study to investigate the incidence and risk factors for the onset of VTE in all patients with newly diagnosed PDAC, regardless of the stage or treatment, and to further assessed their clinical outcomes.

Patients and Methods

Study design and patients

The BACAP-VTE study was conducted from May 2014 until November 2018, as part of the BACAP (Base Clinico-Biologique de l'Adénocarcinome Pancréatique) prospective, multicenter, observational French cohort study linked to biological clinical database of patients with newly diagnosed PDAC. The BACAP cohort is supported by the French National Cancer Institute (INCa) and detailed study design was previously reported.³³ Briefly, since May 2014, all consecutive patients with suspected diagnosis of PDAC were prospectively screened in all participating oncology centers in France. Eligible patients to be included in the BACAP prospective cohort had to be older than 18 years, with an established diagnosis of PDAC based on a solid pancreatic mass on computed tomography (CT) or endoscopic ultrasonography, and histologically or cytologically proven PDAC confirmed by biopsy or fine-needle aspiration. The exclusion criteria were as follows: not histologically nor cytologically confirmed PDAC, pregnancy, or inability to provide a written informed consent. Patients with presence of VTE at time of PDAC diagnosis and enrollment in the BACAP cohort or within the previous 3 months and those with a follow-up duration less than 3 months after inclusion in the cohort were excluded from the BACAP-VTE study. PDAC diagnosed patients included in the BACAP-VTE cohort were allowed to take aspirin, P₂Y₁₂ ADP receptor antagonists, or Low-Molecular-Weight Heparin (LMWH) for any reason, including for VTE prophylaxis. The BACAP cohort was conducted in compliance with the Helsinki Declaration and approved by: i) the National Committee for Data Processing related to health research (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé, CCTIRS, September 2013, Folder 13.490); ii) the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL, – March 2014, Authorization N°913,462); iii) the Ethics Committee (Comité de Protection des Personnes pour la recherche biomédicale Sud-ouest et Outre-Mer I, CPP, March 2014). All voluntary participating patients provided a written informed consent. The BACAP project, including the BACAP-VTE study, was registered on www.clinicaltrials.gov as #NCT02818829. PDAC newly diagnosed patients were managed according to the ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of pancreatic cancer³⁴ until last follow-up or death. During routine clinical follow-up and in the

event of clinical symptoms, all venous VTE events, including visceral venous thrombosis (VVT), were objectively confirmed and independently validated by trained experts, based on imaging results. The diagnosis of the index VTE -including DVT, VVT, CRT, or PE- was established by the referring physician and was based on the following objective standard routine clinical practice criteria: i) for DVT: a non-compressible proximal or distal vein on compression ultrasonography; ii) for VVT: a thrombus detected on a (staging) abdominal or pelvic CT; a bland thrombus was defined as a filling defect in an otherwise well-opacified vein while a tumor in the vein was defined by the presence of unequivocal enhancing soft tissue in the vein, regardless of visualization of parenchymal mass, or other imaging features suggesting tumor in the vein, such as an occluded vein with ill-defined walls or with restricted diffusion, an occluded or obscured vein in contiguity with malignant parenchymal mass, a heterogeneous vein enhancement not attributable to artifact;³⁵ iii) for PE: an intraluminal filling defect in one or more subsegmental or proximal pulmonary arteries on spiral CT scan; an intraluminal filling defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram; a perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy.

Data collection

Patient's characteristics (age, gender, alcohol and tobacco consumption, Body Mass Index [BMI], Eastern Cooperative Oncology Group [ECOG] Performance Status) and PDAC primary tumor location, stage and grade according to NCCN guidelines,³⁶ as well as clinical (medical history, comorbidities, including classical risk factors for VTE) and laboratory (CA 19-9, CAE, blood count, liver enzymes, bilirubin, creatinine) data were collected at BACAP cohort study enrollment or during the diagnosis process using an e-observation system with the Clinsight® software and a centralized data center located at Montpellier Cancer Institute. All cancer treatments, including type of chemotherapy, surgery and supportive care, were collected through the entire duration of patient's follow-up from time of enrollment until last follow-up visit or death. All surgical patients were treated with LMWH during hospitalization and discharged with LMWH for a total duration of 4 weeks to prevent

postoperative VTE, as recommended in published Clinical Practice Guidelines since 2013.³⁷ The Khorana VTE risk score was prospectively calculated as previously described and used in cancer patients.³⁸ This score assigns different points to five clinical and pre-chemotherapy laboratory parameters, namely: primary tumor site (+2 points for all these PDAC patients), platelet count $\geq 350 \times 10^9 \cdot \text{dL}^{-1}$ (+1 point), hemoglobin concentration $\leq 10 \text{ g} \cdot \text{dL}^{-1}$ or use of red cell growth factors (+1 point), leukocyte count $\geq 11 \times 10^9 \cdot \text{L}^{-1}$ (+1 point), and a BMI $\geq 35 \text{ kg/m}^2$ (+1 point). According to a sum score of 0, 1 or 2, or ≥ 3 points, cancer patients are classified as being at low, intermediate or high risk of onset of VTE, respectively.³⁸ All VTE events were objectively confirmed and independently validated by trained experts, based on imaging results (compression ultrasonography, venography perfusion–ventilation scan, pulmonary angiography, spiral CT). Arterial thrombotic events were excluded. Data quality control was performed using automatic data consistency check, data management control through regular queries and e-control of entered data by the project manager, with on-site data monitoring of at least 10% of the entered data.

Outcomes measures

The BACAP-VTE study primary endpoint was the onset of VTE occurring during the entire follow-up period, defined as a composite of symptomatic distal or proximal DVT, symptomatic or incidental proximal and distal PE, CRT and symptomatic or incidental VVT. The secondary end points were the progression free survival (PFS), defined as the time from enrollment to documented PDAC tumor progression or death, and the overall survival (OS), defined as the time from enrollment to death.

Statistical Analysis

Statistical Analysis was performed using Stata version 13.0 (StataCorp LP, College Station, TX, USA) and R version 3.1.3 (The R Foundation for Statistical Computing, Vienna, Austria) statistical packages. Continuous variables were expressed as median and interquartile range (IQR), and categorical variables as numbers and percentages. The Kruskal-Wallis or Wilcoxon signed-rank tests, as appropriate, were used for comparison of continuous variables. The chi-square test or Fisher's exact tests, as appropriate, were used for comparison of categorical variables. The cumulative incidence of VTE was

estimated using the Kaplan–Meier method. A multivariate Cox’s proportional hazards model with a time-dependent covariate was developed to identify prognostic factors for the onset of VTE using a stepwise selection process. Variables associated with a p -value < 0.20 in univariate analysis as well as variables selected a priori based on known relevance were included in the pool of variables for the forward stepwise model. To test the effect of new onset of VTE on the PFS and the OS, the same Cox’s proportional hazards model was used including VTE as time-dependent covariable. To analyze the predictive value of the Khorana score a cause specific hazard approach was used. To model death in addition to VTE and to consider factors which appeared closely related with the risk of onset of VTE or death independently, we fitted a three unidirectional illness-death models (Schematic representation: **Supplementary Figure 1.**). The multistate model used for the primary analysis included 3 different states: alive without presence of VTE at time of initial staging or enrollment (State 1) which was experienced by all patients, alive with VTE (State 2) which occurred as a transient state for some patients, and death (State 3) as an absorbing state. This model accounted for three potential transitions: PDAC patients alive without VTE may experience either onset of VTE (transition#1) or die (transition#2); PDAC patients alive with VTE may die (transition#3). To study the impact of the time point of onset of VTE on mortality, we extended the multi-state model by including the time-to-onset of VTE as a covariate for transition#3 (State arrival extended model). The multi-state analyses were performed in R, using the mstate library.³⁹ All P -values and 95% confidence intervals (CI) were two-sided, and a P -value $< .05$ was considered statistically significant.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patients

From May 2014 to November 2018, 1331 patients were screened for eligibility at 15 participating centers in France; 1147 newly diagnosed PDAC patients meeting the inclusion criteria were prospectively enrolled in the BACAP cohort. Four hundred sixteen patients (31.2%) of these BACAP patients were excluded from the BACAP-VTE study due to the presence of VTE at time of enrollment

in the BACAP cohort or within the previous 3 months (n=91, **Supplementary Table 1** for the characteristics of the patients with VTE at enrollment) or a follow-up duration shorter than 3 months (n=325). The BACAP-VTE final study cohort consisted of 731 PDAC patients with a median follow-up duration of 19.3 months (95% CI 17.45-22.54) after diagnosis (**Supplementary Figure 2** for the BACAP-VTE consort diagram).

Baseline PDAC patients and tumor characteristics are shown in **Table 1**. At inclusion, their median age was 69 years (range, 34–92), and 386 (52.8%) were men. The most frequent primary tumor location was the pancreas head (n=410, 57.99%), followed by the body (n= 92, 13.01%) or the tail (n= 60, 8.49%), with also overlapping lesions (n= 111, 15.70%). Overall, 208 patients (28.97%) had resectable PDAC tumor, 105 patients (14.62%) had borderline PDAC tumor, 212 patients (29.53%) had locally advanced PDAC and 193 patients (26.88%) had metastatic disease. Most patients (n=622, 99%) had an ECOG performance status ≤ 2 at time of diagnosis with the presence of various comorbidities, including hypertension (n=307, 42.05%), diabetes mellitus (n=188, 25.79%), and hyperlipemia (n=172, n=23.59%). Seventy-two (9.89%) patients had new-onset diabetes. The median time from new-onset diabetes diagnosis to inclusion in BACAP was 2.69 months (range, 0.39-13.93 months). One or more preexisting classical risk factors for VTE were present in 208 patients (28.53%) at study entry, namely a previous history of DVT (n=35) or PE (n=6), obesity (BMI ≥ 35 Kg/m²) (n=33), recent acute medical illness (n=14) or surgery (n=19), presence of lower limb varicosities (n=88), previous thoracic central venous catheter or trauma (n=10), and inherited thrombophilia (n=3). First line PDAC treatment consisted of tumor resection in 229 (31.33%) patients. Thirty-four out of the 105 (32.4%) patients with borderline resectable tumor were treated with chemotherapy followed by surgery. Overall, chemotherapy was administered to 432 patients (**Table 1**). The various types of first-line chemotherapy are detailed in **Table 1**. During the first 3 months of follow-up after BACAP-VTE study entry, 204 patients (17.79%) received hematopoietic growth factors, including red blood cell growth factors (n=57) or granulocyte colony-stimulating factors (n=163). According to the

Khorana VTE risk score calculated at study entry, 492 PDAC patients (67%) were categorized at intermediate-risk (score 2) and 183 patients (33%) at high-risk of VTE (score 3).

Incidence and risk factors for VTE

During a median follow-up of 19.3 months (95% CI 17.45-22.54), 152 out the 731 VTE-BACAP study patients (20.79%) developed a VTE event, with either VVT (n=45, 29.61%), DVT (n=40, 26.32%), PE (n=26, 17.11%) or combined events (n=32, 21.05%). Overall, 70 (46.0%) VTE events were symptomatic vs 82 (54.0%) asymptomatic VTE events (**Table 2**). The median duration between diagnosis of PDAC and onset of VTE was 4.49 months (range 0.8–38.26). The cumulative probabilities of onset of VTE were 8.07% (95% CI 6.31-10.29) at 3-months, 13.19% (95% CI 10.89-15.93) at 6 months, 19.21% (95% CI 16.27-22.62) at 12 months and 24.7% (95% CI 20.85-29.12) at 18 months (**Figure 1**). There was no statistical difference in age, sex, ECOG performance status, comorbidities, established risk factors for VTE or the Khorana risk score between patients who did or did not develop VTE during follow-up (**Table 1**). Onset of VTE during follow-up was more frequently observed in patients with locally advanced or metastatic PDAC at study entry than in those with resectable or borderline disease ($P=.002$). Chemotherapy as first-line cancer treatment ($P<.001$) and hematopoietic growth factors within the first 3 months of PDAC treatment ($P<.001$) were more frequently administered in patients who developed VTE during follow-up compared to those patients who did not.

Univariable modeling of prognostic factors for VTE identified 12 variables, namely sex, age, primary tumor location, stage, platelet count $>450 \times 10^9 \text{.mL}^{-1}$, abnormal levels of ALAT, abnormal levels of ASAT abnormal levels of bilirubin, abnormal levels of alkaline phosphatases, previous VTE, obesity, chemotherapy as first line treatment, and use of hematopoietic growth factors (including both red blood cell growth factors and granulocyte colony-stimulating factors) within the first 3 months of treatment (**Supplementary Table 2**). Surgery within the first 3 months after PDAC diagnosis was not associated with the onset of VTE during follow-up (HR 1.16, 95% CI 0.47-2.82, $P=.751$). In the multivariate model, PDAC primary tumor location (isthmus vs head, HR 2.06 95% CI 1.09-3.91,

$P=.027$) and stage (locally advanced vs resectable or borderline, HR 1.66, 95% CI 1.10-2.51, $P=.016$ and metastatic vs resectable or borderline, HR 2.50, 95% CI 1.64-3.79, $P<.001$) were independent predictors for the onset of VTE (**Figure 2**). After adjusting for confounding factors, the multivariate analysis confirmed that the development of VTE was significantly associated with the tumor primary location (regression coefficient=0.84, $P=.021$) and stage (regression coefficient=0.94, $P<.0001$).

VTE risk prediction

Patients having either an isthmus location or an unresectable tumor had cumulative probabilities for onset of VTE after newly diagnosed PDAC of 11.51 % (95% CI 8.72-15.11) at 3-months, 23.71 % (95% CI 19.40-28.81) at 12 months, and 29.62 % (95% CI 24.17-35.98) at 18 months. Patients with both isthmus location and unresectable tumor had respective cumulative probabilities for the development of VTE after newly diagnosed PDAC of 14.29 % (95% CI 4.84-38.03) at 3-months, 28.79 % (95% CI 12.64-57.38) at 12 months, and 43.03 % (95% CI 19.44-76.89) at 18 months (**Figure 3**). In this PDAC study population, the development of VTE did not differ between patients with intermediate and high-risk Khorana score did not differ between those with and without the development of VTE (intermediate vs high risk, HR 0.83, 95% CI 0.56-1.23, $P=.363$).

Progression and survival

The overall median PFS was 9.13 months (95% CI 8.51-9.69) for the 731 PDAC patients. Patients who developed VTE had significantly shorter median PFS compared to those without VTE (6.66 months, 95% CI 4.33–8.60 vs 9.56 months, 95% CI 8.87–10.38, **Figure 4A**). After adjustment for cancer stage and other risk factors for decreased PFS identified by univariate analysis, the development of VTE remained significantly associated with decreased PFS (HR 1.74, 95%CI 1.19-2.54, $P=.004$). The impact of VTE on PFS did not differ between asymptomatic and symptomatic VTE ($P=.301$, Supplementary Table 3). The development of VTE also remained significantly associated with decreased PFS even after excluding VVT from the analysis (Supplementary Table 4).

The median OS was 13.93 months (95% CI 12.85-14.62) for the entire cohort and 452 out of 731 (61.83%) PDAC patients died during the follow-up. The median OS was significantly decreased in

patients with VTE compared to those without VTE (9.13 months, 95% CI 7.98–10.97 vs 14.55 months, 95% CI 13.93–16.39, **Figure 4B**). After adjustment for age, cancer stage and other risk factors for decreased OS, the onset of VTE after newly diagnosed PDAC remained significantly associated with a shorter OS (HR 2.02, 95%CI 1.57-2.60, $P<.001$). The impact of VTE on OS did not differ between asymptomatic and symptomatic VTE ($P=.797$, Supplementary Table 5). The development of VTE remained significantly associated with decreased OS even after excluding VVT from the analysis (Supplementary Table 6).

The impact of VTE on OS was confirmed using the three unidirectional illness-death model. **Figure 5** shows that PDAC patients with onset of VTE after study entry rapidly transitioned to death compared to patients who did not develop VTE: among 732 patients included in the BACAP-VTE study, 343 patients without VTE (46.92%) died (transition#2) during the follow-up compared to 109 out of 152 patients with VTE (71.71%; transition#3; odds ratio 2.88, 95% CI 1.96-4.21, $P<.0001$).

Discussion

The BACAP-VTE study is the largest prospective, multicenter cohort analyzing the incidence, risk factors and outcomes of VTE events in PDAC patients. While the national prospective BACAP cohort effectively collected data on newly diagnosed PDAC patients in all participating centers, the rate of resectable or borderline resectable PDAC patients in the BACAP-VTE study population was 43.6% and higher than expected, when compared to approximately 20% in real-life practice.⁴⁰ Two reasons may explain this discrepancy. First, most of the centers involved in the BACAP project are tertiary referral centers with specialized surgical oncology departments devoted to pancreatic surgery, which may have introduced a selection bias in the BACAP cohort study with a higher proportion of patients referred for surgery with earlier stages. Second, a number of metastatic patients ($n=164$) enrolled in the BACAP cohort were further excluded from the BACAP-VTE study analysis due to either the presence of VTE at time of enrollment ($n=52$) or a follow-up duration shorter than 3 months ($n=112$).

The cumulative incidence of VTE at 6 months was 13.19 percent in newly diagnosed PDAC patients. More than 20 percent of patients experienced a VTE event within a median 19.3 months follow-up after PDAC diagnosis. This result is in line with the most recent retrospective cohort study among 150 advanced PDAC patients where the prevalence of incidental or symptomatic VTE was 25 percent.²⁹ The very wide VTE ranges previously reported in PDAC patients reflect the heterogeneity between studies in terms of patients population, VTE definition and follow-up duration,^{17–29,41} therefore comparison of the VTE event rates across prospective and retrospective studies in PDAC patients is difficult.

BACAP-VTE patients were treated in accordance with the ESMO guidelines³⁴ and 432 of them (59.1%) received adjuvant chemotherapy. Therefore, the present BACAP-VTE results can be compared to those from previous pivotal randomized controlled trials (RCT) in pancreatic cancer, namely PRODIGE 4/ACCORD 11⁷ and PRODIGE 24/ACCORD 24,⁴² which showed the survival benefits from adjuvant chemotherapy with FOLFIRINOX compared to gemcitabine (GEM) alone in metastatic⁷ and in resected PDAC patients.⁴² The reported cumulative incidence of VTE at 6 months in PRODIGE 4/ACCORD 11 were 6.6 percent in the FOLFIRINOX arm and 4.1 percent in the GEM arm.⁷ Similarly, in PRODIGE 24/ACCORD 24, the reported rates of VTE at 6 months were 6.6 percent in the FOLFIRINOX arm and 7.9 percent in the GEM arm.⁴² Both RCT reported only symptomatic Common Terminology Criteria for Adverse Events (CTCAE)⁴³ grade 3 and 4 VTE, underestimating the total rate of VTE, as incidental VTE were not reported. In the BACAP-VTE study, approximately 50 percent of the VTE events were incidentally diagnosed. This finding is similar to previous studies where incidental VTE accounted for 30 to 50 percent of VTE events among PDAC patients.^{27–29} In a recent study on the incidence, management, and implications of VVT in PDAC patients, VVT was a common thrombotic event in PDAC patients, predominantly discovered by CT imaging, and a marker for poor prognosis.⁴⁴ Importantly, it has been now well established that the risk of recurrent VTE and VTE-related mortality did not differ between symptomatic and incidental VTE in cancer patients.^{45–47}

The median duration between PDAC diagnosis and onset of VTE was 4.49 months, supporting that the VTE risk is higher during the first month after diagnosis.^{21,22,29} Selection of patients at high risk for development of VTE and who may benefit from thromboprophylaxis is of importance and adequate risk assessment models are needed to guide clinical decision.⁴⁸⁻⁵⁰

Because the Khorana score assigns +2 points for PDAC, all PDAC patients per definition have a score of two or more points and consequently classified as at least at intermediate-risk for the onset of VTE. In our study, the Khorana risk assessment score did not discriminate between patients with intermediate vs high VTE risk scores; 21% of patients with score 2 and 18% of those with score 3 or higher developed VTE. Our results are consistent with previous small retrospective studies in PDAC patients undergoing chemotherapy, where no difference was found in the rates of VTE between intermediate and high-risk patients, as estimated by the Khorana score.^{23,28,29} These results might be partly explained by the poor predictive value of several other items in the presence of PDAC, such as “BMI \geq 35k/m²” and “haemoglobin level < 10 g/dL or use of red cell growth factors”, which were not associated with onset of VTE by multivariate analysis in the BACAP-VTE study. In addition, the Khorana score has been developed to predict the VTE risk in patients with various cancer types and the number of pancreatic cancer patients was less than 2 percent of all cancers in the original cohort used to develop the score, as well as in the external validation cohorts.³⁸ Supportive of our findings, Pabinger et al. demonstrated that only tumor-type in the Khorana score was significantly associated with the 6-month cumulative incidence of VTE, suggesting no additional predictive value from the other items.⁵¹

In the BACAP-VTE study, multivariate Cox’s proportional hazards and multistate statistical models identified only two clinical variables that independently predicted the onset of VTE, the PDAC tumor location (isthmus) and a locally advanced or metastatic tumor stage. However, after excluding the VVT from the analysis, patients with isthmus PDAC had only a non-significant trend toward higher risk for VTE compared to patients with non-isthmus PDAC (HR 1.88; 95% CI 0.907-3.878; P=.09). This loss of significance may be related to the small number of patients with an isthmus location included

in the BACAP cohort study. Further larger studies are needed to specifically evaluate the effect of isthmic tumors on the occurrence of VTE in PDAC patients.

PDAC patients with either one or these two risk factors (isthmus location or locally advanced or metastatic tumor stage) had cumulative probabilities of VTE greater than 10% at 3 months from diagnosis, raising important issues regarding the use of primary thromboprophylaxis in pancreatic cancer patients. Although the international clinical practice guidelines recommended primary thromboprophylaxis with LMWH in surgical hospitalized and ambulatory patients with advanced or metastatic pancreatic cancer undergoing chemotherapy,^{37,48-50,52,53} thromboprophylaxis remains largely underused.⁵⁴ The bleeding risk and the quality of life due to LMWH subcutaneous injections are two major concerns in PDAC patients, although we recently showed that quality of life (QOL) does improve in cancer patients under LMWH for treatment of a VTE event.⁵⁵ The efficacy and safety of LMWH in patients with advanced PDAC receiving chemotherapy has been demonstrated in two dedicated RCT, respectively the FRAGEM⁵⁶ and the PROSPECT-CONKO 004 studies⁵⁷ and in a recent meta-analysis.⁵⁸ In the CASSINI trial, 841 cancer patients initiating chemotherapy with a Khorana score ≥ 2 were randomized to receive either the direct oral anticoagulant rivaroxaban (10 mg once daily) or placebo for 6 months.⁵⁹ In a prespecified subgroup analysis of the pancreatic cancer patients (n=273), the primary composite endpoint of symptomatic DVT, asymptomatic proximal DVT, any PE and VTE-related death occurred in 5 out of 135 (3.7%) in the rivaroxaban arm compared to 14 out of 138 (10.1%) in the placebo arm (HR 0.35, 95% CI 0.13-0.97) during intervention.⁶⁰ All together, these data indicate that appropriate use of primary thromboprophylaxis can effectively reduce the rate of VTE onset in PDAC patients.

In the BACAP-VTE study, the onset of VTE was associated with significant decrease in both the PFS and the OS and remained significantly associated with decreased PFS and OS even after excluding asymptomatic VTE or VVT from the analysis. Previous pancreatic cancer studies assessing the impact of VTE onset on OS were heterogenous and reported conflicting results^{18,20,21,25,29,31,32} One retrospective study in 227 patients with unresectable PDAC reported that symptomatic VTE occurring

during chemotherapy was significantly associated with decreased PFS (HR 1.95, 95% CI 1.32-2.87).¹⁸ Several earlier prospective studies evaluated the hypothesis that targeted inhibition of the coagulation cascade might improve survival in cancer patients using LMWH.⁶¹⁻⁶³ Few data were obtained in PDAC patients due to their short life expectancy, but these studies indicated that in addition to reducing VTE occurrence, prophylactic anticoagulation might improve PFS in this setting. Limitations of our study include that not all outcomes were centrally adjudicated by independent reviewers and that the time from study entry to time of reporting VTE was driven by scheduled follow-up visits in accordance with the ESMO and NCCN Clinical Practice Guidelines for the management of PDAC.^{34,36} The strengths of BACAP-VTE study include a prospective observational design, large sample size, long follow-up duration, and use of a validated multistate statistical model. In conclusion, the development of VTE in one out of five PDAC patients, which occurred early after diagnosis, was associated with significant decreases in PFS and in OS. Future research focusing on the benefit of prophylactic anticoagulants in pancreatic cancer is warranted.

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Figure legends

Figure 1. Cumulative incidence rate of new onset of venous thromboembolism in the BACAP-VTE study population.

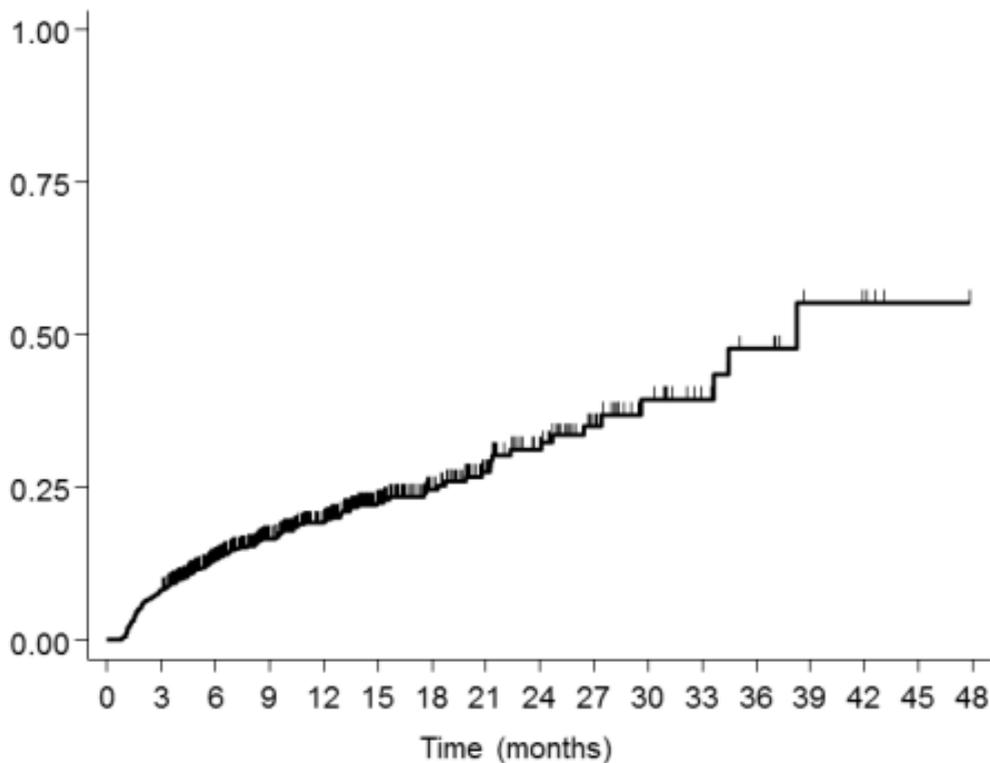
Figure 2. Risk factors for venous thromboembolism (VTE) identified by multivariate analysis. HR (95% CI): Hazard ratios and corresponding 95% confidence intervals (CI). Factors with a hazard ratio <1 are protective and those with a hazard ratio of >1 are risk factors.

Figure 3. Venous thromboembolism (VTE) free event survival in patients having 0, 1 or 2 risk factors (isthmus location or/and locally advanced or metastatic disease) as identified by multivariate analysis.

Figure 4. Progression free survival (**A**) and overall survival (**B**) in newly diagnosed pancreatic ductal adenocarcinoma cancer patients with or without onset of venous thromboembolism (VTE).

Figure 5. The clinical course of cancer patients at risk for venous thromboembolism (VTE) and death: Multi-state model of state occupation probabilities during the entire follow-up period. Transition #1: patients without VTE transiting to VTE; transition #2: patients without VTE transiting to death; transition #3: patients without VTE transiting to death.

VTE Cumulative incidence rate



Number at risk

731 672 521 380 283 177 121 83 61 39 24 16 11 5 4 1 0

Risk factors**HR (95% CI)****Women** (vs. Men)**0.75 (0.53-1.04)****Previous VTE** (vs. non previous VTE)**1.73 (0.89-3.33)****Tumor Location** (vs. Head as reference)

Isthmus

2.06 (1.09-3.91)

Body

0.97 (0.57-1.64)

Tail

1.35(0.78-2.35)

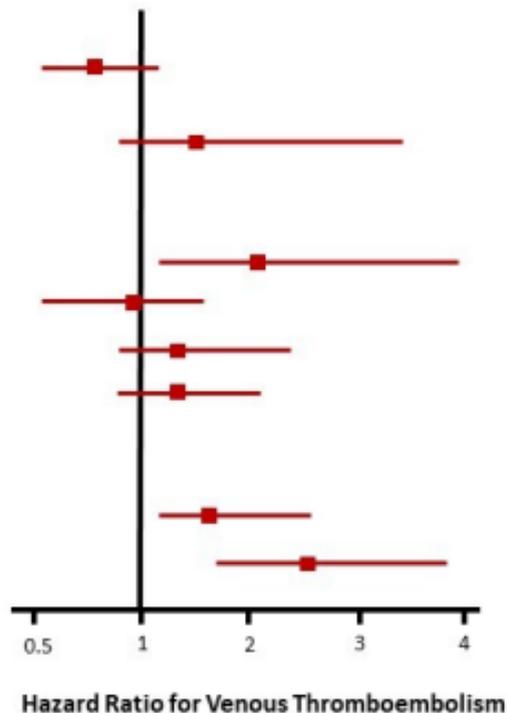
Overlapping lesion

1.29(0.81-2.04)**Tumor stage** (vs. resectable as reference)

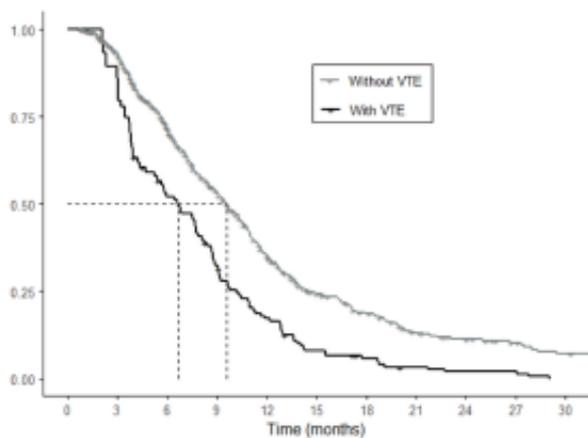
Locally advanced

1.66 (1.10-2.51)

Metastatic

2.5 (1.64-3.79)

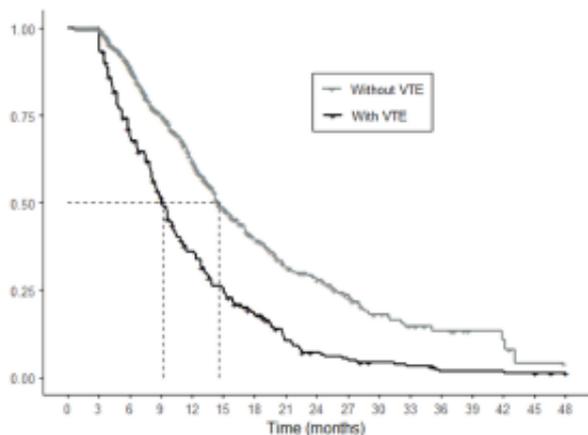
A. Progression free survival



Number at risk

Without VTE	731	624	427	277	167	95	64	36	26	17	11
With VTE	0	52	48	36	21	11	7	4	3	3	0
	0	3	6	9	12	15	18	21	24	27	30

B. Overall survival



Number at risk

Without VTE	731	672	521	379	279	175	119	80	59	38	23	16	11	5	4	1	0
With VTE	0	59	65	57	44	37	24	13	10	10	8	6	3	4	4	3	1
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48

Cumulative hazard

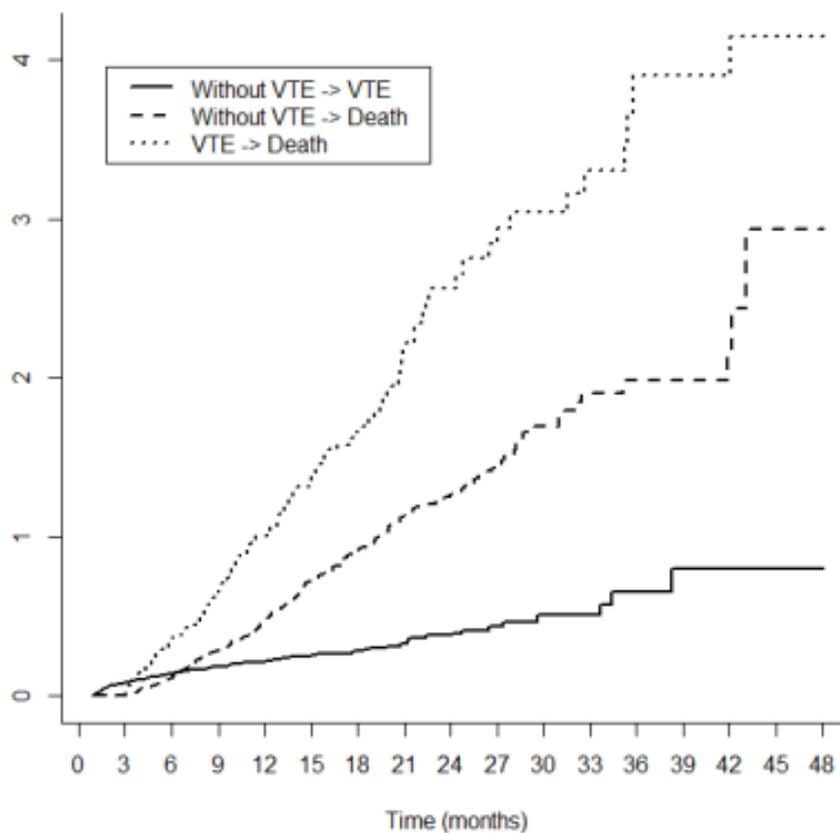


Table 1. Baseline characteristics of the BACAP-VTE study population.

Variable	All patients (n=731)	Patients without VTE (n=579)	Patients with VTE (n=152)	P- value
Age (years)	69(34-92)	69(34-92)	68(34-84)	0.053
Male	386 (52.80)	298 (51.47)	88 (57.89)	0.171
Body mass index (Kg/m ²)	23.9(14.2-52.04)	23.8(14.2-52.04)	24.2(15.82-38.97)	0.215
Missing	16	13	3	
ECOG Performance status				0.388
0	274 (43.63)	221 (44.65)	53 (39.85)	
1	288 (45.86)	223 (45.05)	65 (48.87)	
2	60 (9.55)	47 (9.49)	13 (9.77)	
3	5 (0.80)	4 (0.81)	1 (0.75)	
4	1 (0.16)	0 (0.0)	1 (0.75)	
Missing	103	84	19	
Primary PDAC location				0.201
Head	410 (57.99)	334 (59.64)	76 (51.70)	
Isthmus	34 (4.81)	23 (4.11)	11 (7.48)	
Body	92 (13.01)	74 (13.21)	18 (12.24)	
Tail	60 (8.49)	44 (7.86)	16 (10.88)	
Overlapping lesion	111 (15.70)	85 (15.18)	26 (17.69)	
Missing	24	19	5	
Stage				0.002
Resectable	208 (28.97)	177 (31.22)	31 (20.53)	
Borderline	105 (14.62)	88 (15.52)	17 (11.26)	
Locally advanced	212 (29.53)	163 (28.75)	49 (32.45)	
Metastatic	193 (26.88)	139 (24.51)	54 (35.76)	
Missing	13	12	1	
Tumor Grade				0.807
Gx	214 (29.93)	166 (29.33)	48 (32.21)	
G1	194 (27.13)	158 (27.92)	36 (24.16)	
G2	268 (37.48)	211 (37.28)	57 (38.26)	
G3/G4	39 (5.45)	31 (5.48)	8 (5.37)	
Missing	16	13	3	
Alcohol consumption	191 (26.64)	155 (27.24)	36 (24.32)	0.445
Tobacco consumption	142 (19.62)	119 (20.77)	23 (15.44)	0.338
Biological Parameters				
CA 19.9 5IU/mL)	229.9(0-679070)	243.1(0-240000)	215.9(.03-679070)	0.861
CEA (ng/mL)	4(.19-3862)	4(.19-3862)	4.4(.8-2130.5)	0.341
Hemoglobin (g/dL)	13(7.1-17.1)	13(8.2-17.1)	13.2(7.1-17)	0.336
Leucocytes (x10 ⁹ /l)	7.5(1.06-35.66)	7.4(1.08-35.66)	7.8(1.06-33.33)	0.539
Platelets (x10 ⁹ /l)	255(.25-1267)	255.5(.25-1267)	253(1.77-554)	0.127
ALAT (IU/L)	52(6-1365)	55.5(6-1289)	47(9-1365)	0.328
ASAT (IU/L)	36(9-825)	39(9-758)	30.5(13-825)	0.184
γ-GT (IU/L)	157(5-5599)	173.5(5-4388)	118.5(8-5599)	0.290
Bilirubin (μmol/L)	20.7(1.71-647)	25(1.71-647)	17(3.8-525)	0.745
Albumin (g/L)	38.8(20.3-164.34)	38(20.3-164.34)	40(26-98)	0.090
Creatinine (μmol/L)	67(0-71000)	67.2(28.8-71000)	66(0-200)	0.483
Glycemia (g/L)	1.2(.55-4.24)	1.2(.55-4.24)	1.1(.76-3.71)	0.290
Alkaline Phosphatase (IU/L)	162(28-1684)	178(28-1684)	122(34-1560)	0.527

Comorbidities				
Hypertension	307 (42.05)	248 (42.83)	59 (39.07)	0.459
Hyperlipidemia	172 (23.59)	134 (23.18)	38 (25.17)	0.593
Diabetes	188 (25.79)	154 (26.64)	34 (22.52)	0.347
New-onset diabetes	72 (9.86)	60 (10.38)	12 (8.00)	0.826
Chronic respiratory failure	12 (1.65)	11 (1.90)	1 (0.66)	0.476
Cardiac failure	26 (3.57)	20 (3.46)	6 (3.97)	0.805
Risk factors for VTE				
≥1 risk factor for DVT	208 (28.53)	168 (29.07)	40 (26.49)	0.613
Previous DVT	35 (4.80)	25 (4.33)	10 (6.62)	0.283
Previous PE	6 (0.82)	4 (0.69)	2 (1.32)	0.609
Obesity (BMI > 30 kg/m ²)	33 (4.53)	27 (4.67)	6 (3.97)	0.829
Acute medical illness	14 (1.92)	11 (1.90)	3 (1.99)	1.000
Recent surgery (<3 months)	19 (2.61)	14 (2.42)	5 (3.31)	0.566
bedridden patient	18 (2.47)	16 (2.77)	2 (1.32)	0.392
Lower limbs varicose	88 (12.07)	73 (12.63)	15 (9.93)	0.403
Previous thoracic central venous catheter or trauma	10 (1.37)	9 (1.56)	1 (0.66)	0.696
Known thrombophilia	3 (0.41)	2 (0.35)	1 (0.66)	0.502
Khorana VTE risk score at study entry	492 (72.89)	384 (71.91)	108 (76.60)	0.288
Intermediate-risk (2)	183 (27.11)	150 (28.09)	33 (23.40)	
High-risk (≥3)				
Missing	56	45	11	
Cancer Treatment within the first 3 months after diagnosis				<.001
Surgery	229 (31.33)	191 (32.99)	38 (25.00)	
Chemotherapy	432 (59.1)	318 (54.92)	114 (75.00)	
5FU	7 (1.62)	5 (1.57)	2 (1.75)	1.000
Gemcitabine	169 (39.12)	128 (40.25)	41 (35.96)	0.436
Folfirinox	232 (53.70)	164 (51.57)	68 (59.65)	0.155
Folfiri	6 (1.39)	5 (1.57)	1 (0.88)	1.000
Capecitabine	2 (0.46)	1 (0.31)	1 (0.88)	0.459
Taxanes	2 (0.46)	1 (0.31)	1 (0.88)	0.459
Radiotherapy + Chemotherapy	6 (1.39)	5 (1.57)	1 (0.88)	1.000
Palliative care	70 (9.58)	70 (12.09)	0 (0.00)	
Hematopoietic growth factors within the first 3 months	204 (17.79)	127 (14.16)	77 (30.80)	<.001
Red blood cell growth factors	57 (27.94)	39 (30.71)	18 (23.38)	0.334
G-CSFs	163 (79.90)	96 (75.59)	67 (87.01)	0.071

Values are median (range) or n (%)

Abbreviations: VTE, venous thromboembolism; BMI, body mass index; ECOG, eastern cooperative oncology group; PDAC, pancreatic ductal adenocarcinoma; DVT, deep vein thrombosis; PE, pulmonary embolism; CA 19.9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; G-CSFs, Granulocyte colony-stimulating factors

Table 2. Types of venous thromboembolism events (n=152) in the BACAP-VTE study.

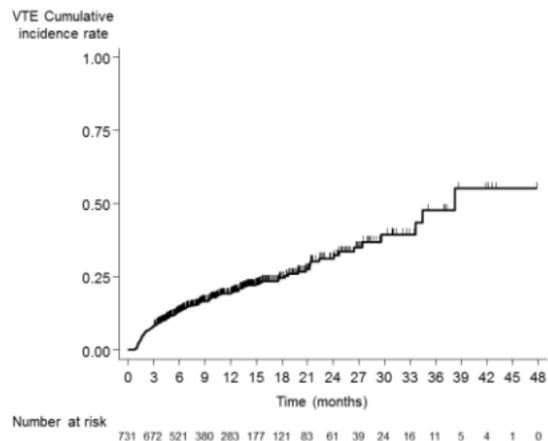
Location of Venous thrombosis	Overall	Symptomatic	Asymptomatic
Visceral venous thrombosis	45 (29.61)	0 (0)	45 (54.88)
Portal Vein	14 (9.21)	0 (0)	14 (17.08)
Splenic Vein	12 (7.90)	0 (0)	12 (14.63)
Mesenteric vein	11 (7.25)	0 (0)	11 (13.42)
Both splenic Vein and Mesenteric vein	5 (3.27)	0 (0)	5 (6.10)
Hepatic veins	3 (1.68)	0 (0)	3 (3.65)
Deep vein thrombosis	40 (26.32)	30 (42.86)	10 (12.19)
Combined venous thrombosis events	32 (21.05)	20 (28.57)	12 (14.63)
Pulmonary embolism	26 (17.11)	14 (20)	12 (14.63)
Central venous catheter-related thrombosis	9 (5.92)	6 (8.57)	3 (3.67)
Total	152 (100)	70 (46.00)	82 (54.00)

Values are n (%); event types are sorted by decreasing proportion

Venous Thromboembolism and Pancreatic Cancer

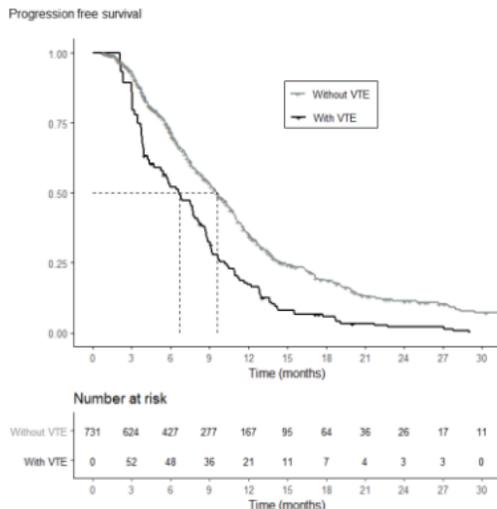
The BACAP-VTE Study : 731 pancreatic cancer patients prospectively followed-up from time of enrollment until last visit or death

Cumulative incidence of VTE



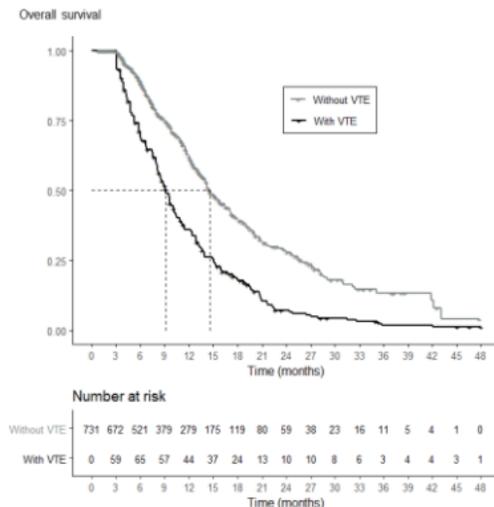
152 patients (20.79%) developed a VTE during a median follow-up of 19.3 months

Progression Free Survival



Patients developing VTE during follow-up had lower PFS (HR 1.74, 95%CI 1.19-2.54, $P=0.004$)

Overall Survival



Patients developing VTE during follow-up had lower OS (HR 2.02, 95%CI 1.57-2.60, $P<.001$).

Abbreviations : VTE, Venous Thromboembolism; PFS, progression free survival; OS, overall survival; HR, Hazard Ratio

Gastroenterology