Review

Primary Thromboprophylaxis in Pancreatic Cancer Patients: Why Clinical Practice Guidelines Should Be Implemented

Dominique Farge 1,2,3, *, Barbara Bournet 4,5, Thierry Conroy 6, Eric Vicaut 7,8, Janusz Rak 9, George Zogoulous 9, Jeffrey Barkun 9, Mehdi Ouaisi 10, Louis Buscail 4,5 and Corinne Frere 11,12

1 Institut Universitaire d’Hématologie, Université de Paris, EA 3518, F-75010 Paris, France
2 Assistance Publique Hôpitaux de Paris, Saint-Louis Hospital, Internal Medicine, Autoimmune and Vascular Disease Unit, F-75010 Paris, France
3 Department of Medicine, McGill University, Montreal, Québec, QC H4A 3J1, Canada
4 University of Toulouse, F-31059 Toulouse, France; bournet.b@chu-toulouse.fr (B.B.); buscail.l@chu-toulouse.fr (L.B.)
5 CHU de Toulouse, Department of Gastroenterology and Pancreatology, F-31059 Toulouse, France
6 Institut de Cancérologie de Lorraine, Department of Medical Oncology, Université de Lorraine, APEMAC, EA4360, F-54519 Vandoeuvre-les-Nancy, France; t.conroy@nancy.unicancer.fr
7 Department of Biostatistics, Université de Paris, F-75010 Paris, France; eric.vicaut@aphp.fr
8 Assistance Publique Hôpitaux de Paris, Department of Biostatistics, Fernand Widal Hospital, F-75010 Paris, France
9 McGill University and the Research Institute of the McGill University Health Centre, Montreal, Québec, QC H4A 3J1, Canada; janusz.rak@mcgill.ca (J.R.); george.zogoulous@mcgill.ca (G.Z.); jeffrey.barkun@mcgill.ca (J.B.)
10 Department of Digestive, Oncological, Endocrine, and Hepatic Surgery, and Hepatic Transplantation, Trousseau Hospital, CHRU Trousseau, F-37170 Chambray-les-Tours, France; m.ouaisi@chu-tours.fr
11 Institut of Cardiometabolism and Nutrition, Sorbonne Université, INSERM UMRS_1166, GRC 27 GRECO, F-75013 Paris, France; corinne.frere@aphp.fr
12 Assistance Publique Hôpitaux de Paris, Department of Haematology, Pitié-Salpêtrière Hospital, F-75013 Paris, France
* Correspondence: dominique.farge-bancel@aphp.fr

Received: 12 February 2020; Accepted: 4 March 2020; Published: 6 March 2020

Abstract: Exocrine pancreatic ductal adenocarcinoma, simply referred to as pancreatic cancer (PC) has the worst prognosis of any malignancy. Despite recent advances in the use of adjuvant chemotherapy in PC, the prognosis remains poor, with fewer than 8% of patients being alive at 5 years after diagnosis. The prevalence of PC has steadily increased over the past decades, and it is projected to become the second-leading cause of cancer-related death by 2030. In this context, optimizing and integrating supportive care is important to improve quality of life and survival. Venous thromboembolism (VTE) is a common but preventable complication in PC patients. VTE occurs in one out of five PC patients and is associated with significantly reduced progression-free survival and overall survival. The appropriate use of primary thromboprophylaxis can drastically and safely reduce the rates of VTE in PC patients as shown from subgroup analysis of non-PC targeted placebo-controlled randomized trials of cancer patients and from two dedicated controlled randomized trials in locally advanced PC patients receiving chemotherapy. Therefore, primary thromboprophylaxis with a Grade 1B evidence level is recommended in locally advanced PC patients receiving chemotherapy by the International Initiative on Cancer and Thrombosis clinical practice guidelines since 2013. However, its use and potential significant clinical benefit continues to be underrecognized worldwide. This narrative review aims to summarize the main recent advances in the field including on the use of individualized risk assessment models to stratify the risk of VTE in each patient with individual available treatment options.
Keywords: pancreatic cancer; venous thromboembolism; thromboprophylaxis; low-molecular weight heparin; direct oral anticoagulant; survival

1. Introduction

Exocrine pancreatic ductal adenocarcinoma (PDAC), often referred to simply as pancreatic cancer (PC) is a malignancy with the highest mortality rate of any solid cancer and with a growing incidence, partly due to aging of the population and improvements in diagnostic techniques [1,2]. The global burden of PC as reported by the Global Burden of Disease 2017 PC collaborators showed a 2.3-fold increase in incidence between 1990 and 2017, with 441,000 documented cases in 2017 compared to 196,000 in 1990, and this rise is expected to continue [3]. The prevalence of PC is projected to increase by approximately 40% over the next decade in North America and Europe [4], and it is predicted to become the second-leading cause of cancer-related death by 2030 [5]. However, the factors contributing to the current increasing rate of incidence are not fully understood.

Only 15–20% of PC patients have a potentially resectable tumor at diagnosis, while most patients have locally advanced tumors and over 50% have metastatic disease, due to a lack of early symptoms or available biological markers, with a life expectancy of less than one year [2,6]. Patients undergoing curative resection for PC mostly develop recurrent disease; 69–75% of patients relapse within 2 years and 80–90% relapse within 5 years [7]. Palliative and adjuvant chemotherapy remains the appropriate therapeutic option in unresectable cases and the 5-year survival rate for patients with unresectable tumor is less than 8% [8–10]. FOLFIRINOX, which was demonstrated to improve clinical status and survival by Conroy et al. in 2011, is now the current treatment standard for metastatic PC [9]. More recently, Conroy et al. also showed that adjuvant therapy with a modified FOLFIRINOX regimen led to significantly longer survival than gemcitabine (GEM) monotherapy among patients with resected PC [11]. However, despite recent advancements, prognosis remains poor, with few patients surviving to 10 years [7]. In this context, there is a need for optimizing and integrating supportive care in the management of PC patients to improve survival and quality of life. The importance of taking charge of the main physical symptoms related to disease evolution, which include pain, anorexia, depression, duodenal obstruction, ascites and venous thromboembolism (VTE) is well recognized and advocated by disease specialist experts [7]. Although recommended by the International Thrombosis and Cancer Initiative (ITAC) clinical practice guidelines (CPGs) since 2013 [12–14] and more recently by the American Society of Clinical Oncology (ASCO) guidelines [15], the use of primary thromboprophylaxis, a supportive treatment with potential significant clinical benefit, continues to be underrecognized [16].

2. Pancreatic Cancer and Venous Thromboembolism

2.1. Burden of Venous Thromboembolism (VTE) in Pancreatic Cancer: the Highest Incidence of VTE Among All Cancer Types

Cancer is an independent major risk factor for VTE [17,18], the latter occurring in 4% to 20% of all cancer patients [19,20]. The extent of VTE risk is determined by the type of cancer, the stage of the disease, and the location of the tumor [17,21]. PC is the malignancy associated with the highest rate of VTE [19,22]. A strong association between VTE and PC was first reported in an autopsy study of 4258 consecutive necropsies, which documented a VTE event in 56.2% of pancreatic patients compared to 15–25% in other cancer patients [23]. The reported incidence of VTE in PC patients varies from 5% to 41% in retrospective cohorts, depending on the diagnostic methods used (Table 1) [24–42]. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the most common VTE events observed [43], but visceral vein thrombosis (VVT), including portal vein thrombosis, splenic vein thrombosis, mesenteric vein thrombosis and hepatic veins thrombosis, accounts for approximatively 30–50% of all reported VTE events [31,38,41,44]. The main risk factors for the onset of VTE in PC
patients are advanced or metastatic disease, surgery, or use of chemotherapy [35,39]. The highest incidence of VTE has been reported in a retrospective cohort of PC patients receiving palliative chemotherapy, with a VTE diagnosis in 41.3% of patients [36]. In this study, symptomatic VTE (12.2%) was identified as an independent risk factor for death by multivariate analysis (hazard ratio [HR]: 2.22, 95% CI: 1.05–2.60, \( p < 0.05 \)). We recently investigated the incidence and risk factors for VTE in the BACAP-VTE study, a large prospective multicenter cohort of patients with histologically proven PC. Diagnosis of the index VTE, including DVT, VVT, Catheter-Related Thrombosis (CRT), or PE, was established by the referring physician and based on objective standard routine clinical practice criteria, as previously detailed [41]. During a median follow-up of 19.3 months (95% CI 17.45–22.54), 152 out of 731 (20.79%) patients developed a VTE event. In competing-risk analysis, the cumulative probabilities 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. The median time from PC diagnosis to VTE was 4.49 months (range 0.8–38.26). The rates of VTE did not differ between patients treated with GEM and those treated with FOLFIRINOX. In a multivariate analysis, primary pancreatic tumor location (isthmus versus head, HR 2.06, 95% CI 1.09–3.91, \( p = 0.027 \)) and tumor stage (locally advanced versus resectable or borderline, HR 1.66, 95% CI 1.10–2.51, \( p = 0.016 \) and metastatic versus resectable or borderline, HR 2.50, 95% CI 1.64–3.79, \( p < 0.001 \)) were independent predictors for onset of VTE [41]. The PRODIGE 4/ACCORD 11 [9] and PRODIGE 24/ACCORD 24 [11] randomized controlled trials (RCT) reported lower rates of VTE both in metastatic patients (cumulative incidence of grade 3–4 VTE at 6 months, 6.6% in the FOLFIRINOX arm vs. 4.1% in the GEM arm) [9] and in resected pancreatic patients (cumulative incidence of any grade VTE at 6 months, 5.9% in the FOLFIRINOX arm vs. 7.9% in the GEM arm) [11]. Of note, only Common Terminology Criteria for Adverse Events (CTCAE) [45] grade 3 and 4 VTE events were reported in the PRODIGE 24/ACCORD study [11], leading to an underestimate of the overall rate of VTE. In a recent retrospective cohort of 150 PC patients receiving either GEM-based chemotherapy or FOLFIRINOX, there was a 21.4% incidence of incidental and symptomatic VTE (grade 2 or higher) in the FOLFIRINOX group vs. 29.5% in the GEM group, suggesting that patients treated with FOLFIRINOX carry the same risk for VTE as patients treated with GEM-based therapy [38].

2.2. Association of VTE with Progression Free Survival and Overall Survival in Pancreatic Cancer

VTE is the second-leading cause of death after metastasis in cancer patients [46,47]. Patients with cancer who develop VTE have a shorter overall survival compared to those without VTE who have a similar tumor stage and anti-cancer treatment [19]. In a study of 235-149 cancer patients (with 6712 patients with PC) included in the California Cancer Registry, adjusted for age, race, and stage, VTE was a significant predictor of decreased survival during the first year for all cancer types (hazard ratios, 1.6–4.2; \( p < 0.01 \)) and when measured in person-time, the incidence of VTE during the first year after cancer diagnosis, was the highest among patients with metastatic PC (20.0 events per 100 patient-years) [21]. Early retrospective studies assessing the association of VTE with progression-free survival (PFS) and overall survival (OS) in PC patients reported conflicting results. Two monocentric cohorts of PC patients found no difference in OS between patients who developed VTE and those who did not [29,35]. The lack of difference in survival between patients with and without VTE might be explained by patient short life expectancy, since most patients included in both studies had stage III-IV disease. In contrast, several studies have found an association between the onset of VTE and poorer prognosis. In an early monocentric retrospective cohort of 227 patients with unresectable PC, the onset of VTE during chemotherapy was associated with decreased PFS (HR 2.59, 95% CI 1.69–3.97, \( p < 0.0001 \)) and OS (HR 1.64, 95% CI 1.04–2.58, \( p = 0.032 \)) [25]. Similarly, VTE, including VVT, was associated with increased mortality in a small cohort of 135 PC patients. [31] Of note, anticoagulant therapy improved survival in those patients with VTE (HR 0.30, 95% CI 0.12–0.74, \( p = 0.009 \)) [31]. Two retrospective studies focusing on the association of VVT with survival also found an association between the onset of VVT and increased mortality [44,48]. Few studies have investigated the association between early VTE (defined by a VTE at diagnosis or within 30 days after the beginning of palliative chemotherapy) and survival.
Table 1. Main studies reporting the rates of venous thromboembolism in pancreatic cancer (PC) patients.

| Reference         | Study Type   | n   | Study Period or Duration of Follow-Up | Rates of VTE                                                                 | Type of VTE                                                                 | Risk Factors for VTE/Survival                                                                 |
|-------------------|--------------|-----|--------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Blom et al. 2006  | Cohort Study | 202 | From January 1990 to December 2000   | Incidence rate of VTE: 108.3 per 1000 patient-year (95% CI 64.4–163.8)       | Early VTE: 15 out of 19 cases of VTE occurred in the first 6 months after cancer diagnosis | Risk factors for VTE: Tumor of the corpus (HR 1.9, 95% CI 0.5–6.7) and of the cauda (HR 2.9, 95% CI 1.0–8.5) Chemo-therapy (HR 4.8, 95% CI 1.1–20.8) Postoperative period of 30 days (HR 4.5, 95% CI 0.5–40.9) Distant metastases (HR 1.9, 95% CI 0.7–5.1) |
| Mandala et al. 2007 | Retrospective | 227 | From December 2001 to December 2004 | VTE = 26% (n = 59) VTE occurring during chemotherapy in 15 patients (6.6%) |                                                                       | Risk factors for VTE: Use of thromboprophylaxis (HR 0.03, 95% CI 0.003–0.27) Biological inflammatory syndrome (HR 9.0, 95% CI 2.30–34.4) Metastatic disease (HR 4.4, 95% CI 1.1–17.9) |
| Mitry et al. 2007 | Retrospective | 90  | -                                    | 26.7% (n = 24) 4 PE, 2 fatal PE                                           |                                                                       |                                                                                             |
| Oh et al. 2008    | Retrospective | 75  | From June 2003 to December 2005       | 5.3% (n = 4) Incidence rate of VTE 157 per 1000 patient-year (95% CI 59–418) |                                                                       |                                                                                             |
| Poruk et al. 2010 | Retrospective | 133 | -                                    | 20% Incidence rate of VTE 169 per 1000 patient-year (95% CI 109–263)        | Multiple thrombosis: 17.2% (n = 10)                                       |                                                                                             |
| Shaib et al. 2010 | Retrospective | 201 | From July 2003 to December 2008       | 28.9% (n = 58) Multiple thrombosis: 17.2% (n = 10)                          |                                                                       |                                                                                             |
| Epstein et al. 2012 | Retrospective | 1915 | From January 2000 to December 2009 | 32% (n = 650) Arterial Thrombosis in 1.5% patients (n = 30)                |                                                                       |                                                                                             |
| Menapace et al. 2011 | Retrospective | 135 | From 2006 to 2009                     | 34.8% patients (n = 47) Incidental events: 33.3% PE, 21.4% DVT and 100% VVT | 12 PE, 28 DVT and 47 VVT                                              | Anticoagulants reduced the risk of death by 70% (95% CI 26–88%, p = 0.009)                       |
| Afsar et al. 2014 | Retrospective | 77  | From 2007 to 2012                     | 18.1% (n = 14) Multiple thrombosis: 7.1% (n = 68) 66% of the events diagnosed during the first 6 months after diagnosis. |                                                                       |                                                                                             |
| Munoz-Martin et al. 2014 | Retrospective | 84  | From 2008 to 2011                     | 35.7% (n = 30)                                                             |                                                                       |                                                                                             |
| Reference                  | Study Type | n     | Study Period or Duration of Follow-Up                  | Rates of VTE | Type of VTE | Risk Factors for VTE/Survival |
|----------------------------|------------|-------|-------------------------------------------------------|--------------|-------------|------------------------------|
| Larsen et al. 2015 [49]    | Prospective | 121   | Duration of follow-up: 24 months                      | At the time of cancer diagnosis: 12.4% (n = 15)       | VTE associated with shorter survival (HR 1.995, 95% CI 1.209–3.292) |
| Ouisi et al. 2015 [42]     | Retrospective | 162   | Median follow-up of 15 months after diagnosis         | 17.3% (n = 26)                                      |                          |
| Krepline et al. 2016 [34]  | Retrospective | 260   | From 2009 to 2014                                     | 10% (n = 26)                                        | All VTE events were incident events: 9 (35%) PE, 9 (35%) DVT, and 8 (31%) VVT |
| Lee et al. 2016 [35]       | Retrospective | 1115  | From 2005 to 2010                                     | 11.8% (n = 132)                                     | Major risk factors associated with VTE events: advanced cancer stage, major surgery, and poor performance status |
| Kruger et al. 2017 [36]    | Retrospective | 172   | From 2002 to 2017                                     | 41.3%                                                 | 50.2% of asymptomatic VTE |
| Van Es et al. 2017 [37]    | Retrospective | 178   | Median of follow-up of 234 days                       | 12.4% (n = 22)                                       | 50% of incidental VTE    |
| Berger et al. 2017 [38]    | Retrospective | 150   | From initiation of first-line treatment until last follow-up or death | 25% (n = 37)                                         | 43.2% of incidental VTE |
| Chen et al. 2018 [39]      | Retrospective | 816   | From 2010 to 2016                                     | 8.0% (n = 67)                                        | Risk factors for VTE: Low serum sodium (OR 10.30; 95% CI 1.04–102.47; p = 0.047) |
| Kim et al. 2018 [40]       | Retrospective | 216   | From 2005 to 2015                                     | 23.6% (n = 51)                                       |                              |
| Frere et al. 2019 [41]     | Prospective | 731   | From study entry until last follow-up or death       | 20.79% (n = 152)                                     | Risk factors for VTE:PC tumor location (isthmus versus head, HR 2.06, 95% CI 1.09–3.91, p = 0.027) |

Abbreviations: CI, Confidence interval; DVT, deep vein thrombosis; HR, Hazard ratio; OR, odds ratio; PC, pancreatic cancer; PE, pulmonary embolism; VTE, venous thromboembolism; VVT, visceral vein thrombosis.
In 227 unresectable PC patients, Mandala et al. reported that presence of synchronous VTE at cancer diagnosis was associated with a higher probability of not responding to treatment (odds ratio [OR] 2.98, 95% CI 1.42–6.27, \(p = 0.004\)), but were not associated with PFS or OS on multivariate analysis, while the occurrence of a VTE during chemotherapy was associated with significant shorter PFS (HR 2.59, 95% CI 1.69–3.97, \(p < 0.0001\)) and OS (HR 1.64, 95% CI 1.04–2.58, \(p = 0.032\)) [25].

In another monocentric retrospective cohort of 216 metastatic PC patients receiving GEM-based palliative chemotherapy, early VTE occurred in 10.6% patients and was associated with a significantly shorter OS (3.7 months vs. 6.4 months in patients with late VTE or without VTE, \(p = 0.005\)) [40].

Only two prospective studies have investigated the impact of VTE on survival in PC patients. A small cohort of 121 PC patients reported a significant association between the onset of VTE within the study and shorter OS (median OS 4.4 months vs. 11.9 months in patients without VTE; HR 2.15, 95% CI 1.28–3.60, \(p = 0.004\)) [49]. In the BACAP-VTE study, patients developing VTE during follow-up had shorter PFS even after adjustment for cancer stage and other risk factors for decreased PFS (6.66 months vs. 9.56 months in patients without VTE; HR 1.74, 95% CI 1.19–2.54, \(p = 0.004\)). The onset of VTE was also associated with shorter OS, even after adjustment for age, cancer stage and other risk factors for decreased OS (9.13 months vs. 14.55 months in patients without VTE; HR 2.02, 95% CI 1.57–2.60, \(p = 0.004\)). PC patients who developed VTE after study entry had a higher mortality rate compared to patients who did not develop VTE: 109 out of 152 (72%) patients with VTE died vs. 343 out 531 (65%) patients without VTE (OR 2.88, 95% CI 1.96–4.21, \(p < 0.0001\)) [41]. These results deserve attention since this association between VTE and mortality suggests that preventing VTE might improve survival in PC patients.

2.3. VTE in Pancreatic Cancer: A Model of Hypercoagulability and the Effects of Heparins

Cancer leads to a hypercoagulable state which confers advantages to cancer cells. This hypercoagulable state is attributed to high expression of tissue factor (TF) and transmembrane proteins (e.g.: PSGL-1, Muc1) by cancer cells [50], leading to thrombin generation and platelet activation and aggregation [51]. Aggregation of blood platelets around cancer cells provides protection from immune responses, and also facilitates circulation of cancer cells in the blood stream and their adhesion at potential sites of metastasis [52–54]. In cancer multiple oncogenic events including activation of proto-oncogenes KRAS [55], EGFR, and inactivation of tumor suppressor genes such as P53 and PTEN, promote TF expression and contribute to other procoagulant changes in the tumor microenvironment [56]. Of note is the fact that in sporadic PC/PDAC over 90% of lesions carry an activating KRAS mutation [57] and elevated TF expression is common in advanced stages [58]. Moreover, cancer cells spontaneously release TF-positive microvesicles (MVs) in the circulation [59–61]. TF-positive MVs bind to Factor VII (FVII), promoting the activation of the extrinsic pathway and thrombin generation. An additional mechanism of thrombin generation is related to Factor XII activation, which initiates the intrinsic coagulation pathway. Moreover, Plasminogen Activator Inhibitor 1 (PAI-1) can be released by pancreatic tumor cells, as well as by activated platelets [62]. TF initiates angiogenesis via both a) a clotting-dependent mechanism where thrombin formation and fibrin deposition support angiogenesis, and TF induces VEGF expression, and b) a clotting-independent mechanism in which TF-FVIIa complex activates pro-angiogenic protease-activated receptor 2 (PAR-2). In addition, an alternatively spliced TF (asTF, soluble variant of TF) is expressed in PDAC as opposed to normal pancreas, and stimulates angiogenesis independently of FVIIa [63,64]. Unruh et al. demonstrated that asTF binds \(\beta_1\)-integrins on the surface of PDAC cells and also on microvascular endothelial cells [63,64], thereby promoting tumor growth, metastatic dissemination, and monocyte recruitment to the stroma through an autocrine paracrine manner [64]. Overall, TF overexpression by the PC cells which induces thrombin generation and platelet activation all directly contribute to cancer progression and dissemination [65]. Whether and how preceding intermittent inflammation and PC-associated desmoplasia contribute to these events remain of great interest [57].
Circulating extracellular MVs derived from cancer-cells contribute to hypercoagulability and to metastatic invasion. Experimental data have shown that MVs released by cultured PC cells exhibit TF-dependent procoagulant activity [66]. In a mouse model of PC, cancer cell-derived MVs expressing TF accumulate at sites of endothelial injury in a $p$-selectin-dependent manner [67].

Several publications demonstrate the presence of TF-bearing MVs in patients with cancer [68–75]. In PC patients specifically, around 50% of TF-positive MVs detected in platelet-poor plasma are also positive for MUC-1 antigen, suggesting that they are derived from the underlying malignancy. TF-positive MVs are highly procoagulant [69]. A retrospective study of 117 patients with pancreatic or biliary cancer (68% of PC) reported a 44.4% rate of VTE. In these patients, elevated TF levels were significantly associated with VTE events ($p = 0.04$), and with decreased overall survival (HR 1.05; $p = 0.01$) [70]. A first prospective study suggested that MVs-TF activity may be predictive of VTE in PC patients [71]. In a cohort study of 73 PDAC patients, elevated MVs-TF activity was present only in patients with poorly differentiated metastatic, unresectable tumors and correlated with CA 19–9 and D-dimer levels [73]. In a prospective cohort study on 79 PDAC patients, MVs-TF activity did not correlate with the intensity of TF expression in adenocarcinoma cells but to the number of TF-positive macrophages in the surrounding stroma [74]. More recently, Faille et al. showed that MVs-TF activity was predictive of VTE in 48 PDAC patients [75]. Both D-dimers and MVs-TF activity were associated with the occurrence of VTE [75].

Many studies have analyzed the effect of heparins and of low molecular weight heparin (LMWH) on tumor progression, metastasis formation, and angiogenesis [76,77]. In addition to its action on the coagulation cascade, heparin also inhibits the binding of $P$-selectin to its ligands [78], which is involved in hypercoagulability and metastasis process. Heparins as well as heparan sulfate (HS) belong to the glycosaminoglycan family and bind antithrombin via a pentasaccharide sequence. HS are key components of the extracellular matrix (ECM). Heparanase, which is overexpressed in PC, acts by cleaving heparan sulfate side chains from proteoglycans, contributing to ECM disruption and vascular endothelial growth factor A (VEGF-A) and fibroblast growth factor 2 (FGF-2) release [51]. In addition, heparanase has a non-enzymatic pro-coagulant activity in which removal of glycocalyces containing tissue factor pathway inhibitor (TFPI) enhances TF activity [79]. By inhibiting heparanase, heparins may potentially inhibit tumor growth [80].

LMWHs can also contribute to the inhibition of cancer progression. LMWHs were shown to inhibit P-and L-selectin as well as integrin-mediated formation of tumor thrombi, and to alter tumor neo-angiogenesis. This effect is primarily based on their ability to induce the prolonged release of TFPI from binding sites on endothelial cells [81,82]. TFPI acts by inhibiting TF-FVIIa complex, leading to activation of Factor X, inhibition of thrombin generation and PAR-2 activation, and disruption of pro-angiogenic signaling [83,84]. Thus, anticoagulants could possess both biological and antithrombotic activities in cancer albeit possibly exerted through different mechanisms.

3. Risk Assessment Models (RAM) for Prediction of VTE in Patients with PC

Risk assessment models (RAM) have been developed to help identify cancer patients at high risk of VTE who may benefit from primary thromboprophylaxis (Table 2). Nonetheless, VTE risk factors vary according to cancer type and during the course of malignancy, from diagnosis through treatment, metastasis, and end-of-life care. Therefore, repeated individual risk assessments are important.

The most widely used RAM for VTE prediction in ambulatory cancer patients is the Khorana score (KS). This score was developed in a prospective derivation cohort of 2701 cancer outpatients in the United States more than ten years ago and validated in an independent cohort of 1365 patients from the same study [85]. The KS assigns different points to five clinical and pre-chemotherapy laboratory parameters, namely: primary tumor site (+2 points for PC and gastric cancer), platelet count $\geq 350 \times 10^9 \cdot \text{dL}^{-1}$ (+1 point), hemoglobin concentration $\leq 10 \text{g.dL}^{-1}$ or use of erythropoiesis-stimulating agents (+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). The KS discriminates three groups of patients according to risk of VTE: a low-risk group (score of 0),
an intermediate-risk group (score of 1–2) and a high-risk group (score ≥3). Several small retrospective studies in PC patients undergoing chemotherapy found no difference in the rates of VTE between intermediate and high-risk patients, as estimated by the Khorana score (Table 3) [33,36–38,86]. In the BACAP-VTE study, the KS did not discriminate between patients with intermediate vs. high VTE risk scores [41]. However, all PC patients have a sum score ≥ 2 and being subsequently classified as at least intermediate-risk or high risk of VTE should be considered for prophylaxis. Other RAMs, such as the Vienna modification of the Khorana score (addition of biomarkers D-dimer and soluble P-selectin) [87], the PROTECHT score (addition of GEM and platinum-based chemotherapy), [88] and the CONKO score (addition of WHO performance status) [86] have been developed. However, none of these scores have been externally validated in PC patients.

The ONKOTEV score [89] was developed using a large multicenter prospective cohort of 843 cancers patients. Overall, 73 (8.6%) VTE events occurred during a median follow-up of 8.3 months. In a multivariate analysis, the presence of a metastatic disease, the compression of vascular/lymphatic structures by the tumor, a history of previous VTE, and a KS ≥2 were significantly associated with the risk of VTE. The resulting ONKOTEV score assigns one point to each of these four variables, and according to a sum score of 0, 1, 2, or ≥ 2 points patients are classified as being at “score = 0”, “score = 1”, “score = 2”, or “score > 2”, respectively. In the development cohort, patients with “score = 0” had a cumulative probability of VTE at 12 months of 3.69%, compared to 9.74% for patients with “score = 1” (43.1%), 19.39% for patients with “score = 2” (9.2%), and 33.87% for patients with “score > 2” (6.3%). As expected, the ONKOTEV score demonstrated a significantly higher predictive power than the KS in the same cohort. However, overfitting of the ONKOTEV model is likely and these results should be interpreted with caution. This model was recently externally validated in a retrospective single-center cohort of 165 PC patients [90]. Cumulative incidence of VTE was 3.3%, 12.7%, 50.9%, and 82.4% for patients with ONKOTEV scores of 0 (18.2% of the overall population), 1 (38.2% of the overall population), 2 (33.3% of the overall population), and >2 (10.3% of the overall population), respectively [90]. This study has several limitations including its retrospective and single-center design, and the inclusion of patients with VTE at cancer diagnosis and deserve further confirmation in prospective cohorts of ambulatory PC patients.

**Table 2.** Risk assessment models that have been evaluated in pancreatic cancer patients.

| KINORANA SCORE [85] | |
|----------------------|---|
| Very high-risk tumors (stomach, pancreas) | +2 |
| High risk tumors (lung, gynecologic, genitourinary excluding prostate) | +1 |
| Hemoglobin <10 g/dl or erythropoietin stimulating agents | +1 |
| White blood cell count >11 × 10⁹/L | +1 |
| Platelet count ≥ 350 × 10⁹/L | +1 |
| BMI >35 kg/m² | +1 |

A score of 0 = low-risk category
A score of 1–2 = intermediate-risk category
A score of >2 = very high-risk category

| ONKOTEV SCORE [89] | |
|--------------------|---|
| Khorana score of >2 | +1 |
| Previous venous thromboembolism | +1 |
| Metastatic disease | +1 |
| Vascular/lymphatic macroscopic compression | +1 |
| Total ONKOTEV score | 4 |

**Abbreviations:** BMI = body mass index.
### Table 3. Studies assessing the predictive values of risk assessment models in pancreatic cancer patients.

| Reference          | Type          | RAMs        | Study Population, n | VTE Screening at Study Entry | Median Follow Up (Months) | Number of Patients in Each Group | Patients with VTE During the Total Follow-Up, n (%) | Rates of VTE                                      |
|--------------------|---------------|-------------|---------------------|-----------------------------|--------------------------|----------------------------------|---------------------------------------------------|--------------------------------------------------|
| Pelzer et al. 2013 [86] | Retrospective | Khorana score | 144                | No                          | 12                       | Intermediate risk: 38% High risk: 62% | 21 (14.6%)                                      | At 6 months: Intermediate risk: 7.2% High risk: 19.1% |
| Munoz-Martin et al. 2014 [33] | Retrospective | Khorana score | 73                 | No                          | 9.5                      | Intermediate risk: 51% High risk: 49% | 22 (30.1%)                                      | At 6 months: Intermediate risk: 10.8% High risk: 27.8% |
| Van Es et al. 2017 [37] | Retrospective | Khorana score | 147                | No                          | 7.7                      | Intermediate risk: 31% High risk: 69% | 20 (13.6%)                                      | At 6 months: Intermediate risk: 8.9% High risk: 8.7% |
| Kruger et al. 2017 [36] | Retrospective | Khorana score | 111                | No                          | 9.2                      | Intermediate risk: 62% High risk: 38% | 16 (14.4%)                                      | At 6 months: Intermediate risk: 8.7% High risk: 11.9% |
| Berger et al. 2017 [38] | Retrospective | Khorana score | 150                | No                          | NS                       | Intermediate risk: 58% High risk: 42% | 27 (17.9%)                                      | NS During the total follow-up: no difference between groups (p = 0.44) |
| Godinho et al. 2019 [90] | Retrospective | Onkotev score | 165                | no                          | 6.3                      | Score 0: 18.2% Score 1: 38.2% Score 2: 33.3% Score ≥3: 10.3% | 51 (31%)                                        | During the total follow-up: Score 0: < 10% Score 1: < 10% Score 2: 41.8% Score ≥3: 70.6% |
| Frere et al. 2019 [41] | Prospective   | Khorana score | 731                | Yes                         | 19.3                     | Intermediate risk: 73% High risk: 27% | 152 (20.1%)                                     | NS During the total follow-up: Intermediate risk: 21% High risk: 18% Intermediate vs. high risk: HR 0.63 (95% CI 0.56–1.23), p = 0.363 |

Abbreviations: NS, not specified; RAM, risk assessment model; VTE, venous thromboembolism.
4. Studies Assessing the Benefit of Anticoagulants in Pancreatic Cancer Patients

4.1. Primary Thromboprophylaxis in Ambulatory Pancreatic Cancer Patients

4.1.1. Primary Thromboprophylaxis with LMWH in Cancer Patients

Several RCTs have assessed the efficacy and safety of LMWH for primary thromboprophylaxis in patients with different cancers treated with chemotherapy. The PROTECHT [91] and SAVE-ONCO [92] trials enrolled more than 4000 patients with non-selected solid cancers, but few data were generated from the subgroup analyses of PC patients (Table 4).

In PROTECHT [91], 1150 patients with different cancers were randomized to receive either nadroparin (3800 IU once daily) or placebo for the duration of chemotherapy, up to a maximum of 4 months. A significant reduction in the rate of VTE was observed in the nadroparin arm (2.0% vs. 3.9% in the placebo arm, \( p = 0.02 \)) without difference in major bleeding (0.7% in the nadroparin arm vs. 0 in the placebo arm, \( p = 0.18 \)). Only 53 out of 1150 (4.7%) patients included in PROTECHT had PC, and the rates of VTE did not differ between the placebo and nadroparin treatment arms in this subgroup of PC patients (\( p = 0.755 \)). This lack of difference might be related to the small number of PC patients included in PROTECHT.

In SAVE-ONCO [92], 3212 patients with metastatic or locally advanced cancers beginning a course of chemotherapy were randomized to receive either semuloparin (20 mg once daily) or placebo for the duration of chemotherapy. In the overall population, a significant reduction in the rates of VTE was observed in the semuloparin arm (1.2% vs. 3.4% in the placebo arm; HR 0.36, 95% CI 0.21–0.60; \( p < 0.001 \)), and there was no difference in major bleeding (1.2% vs. 1.1% in the placebo arm; HR 1.05, 95% CI 0.55–1.99; \( p = \) ns). Two hundred fifty four out of 3212 (7.9%) patients had a PC in SAVE-ONCO. In this PC patient subgroup, a significant reduction in the rates of VTE was observed in the semuloparin arm (2.4% vs. 10.9% in the placebo arm; HR 0.22, 95% CI 0.06–0.76; \( p = 0.015 \)). This subgroup effect was not statistically significant different, from the overall effect in the overall population.

4.1.2. Primary Thromboprophylaxis with LMWHs in Pancreatic Cancer Patients

Two dedicated RCTs evaluated the efficacy and safety of primary thromboprophylaxis with LMWH in patients with advanced PC receiving chemotherapy (Table 4) [93,94]. In total, these two studies enrolled more than 400 PC patients.

The phase 2b FRAGEM trial randomized 123 advanced PC patients to receive either GEM with weight-adjusted dalteparin (GEM-WAD, dalteparin 200 IU/kg daily during 4 weeks, then 150 IU/kg daily) for 12 weeks or GEM alone [93]. The primary end point was the occurrence of all-type VTE (symptomatic or incidentally diagnosed). Addition of weight-adjusted dalteparin reduced the rate of VTE from 23% to 3.4% during the treatment period (RR 0.145, 95% CI 0.035–0.612, \( p = 0.002 \)) and from 28% to 12% during the entire follow-up period (RR 0.42, 95% CI 0.19–0.94, \( p = 0.039 \)). VTE-related deaths were observed in 5 (8.3%) patients in the GEM alone arm compared to 0 patients in the GEM with weight-adjusted dalteparin arm (RR 0.092, 95% CI 0.005–1.635, \( p = 0.057 \)). The rates of major bleeding events were low in both arms (3.4% in the GEM-WAD arm vs. 3.2% in the GEM arm), but there was a higher incidence of trivial bleeding (skin bruising, minor epistaxis) in the GEM-WAD arm (9% vs. 3% in the GEM arm) [93].

The prospective, open-label, multicenter phase 2b PROSPECT-CONKO 004 study randomized 312 advanced PC patients to receive enoxaparin during the first 12 weeks of chemotherapy (1 mg/kg daily for the first 3 months, then 40 mg daily, \( n = 160 \)) or chemotherapy alone (i.e., single-agent GEM or an intensified regimen including fluorouracil and folinic acid, depending on performance status and renal function, \( n = 152 \)) [94]. The primary end point was the first event rate of symptomatic VTE within 3 months. Asymptomatic VTE events found on routine imaging during the study were excluded from the analysis. Enoxaparin reduced the cumulative incidence rate of symptomatic VTE from 10.2% to 1.3% within the first 3 months (HR 0.12, 95% CI 0.03–0.52, \( p = 0.001 \)) and from 15.1%
to 6.4% during the entire follow-up period (HR 0.40, 95% CI 0.19–0.83, \( p = 0.01 \)), without an overall difference in major bleeding (8.3% in the enoxaparin arm vs. 6.9% in the control arm, HR 1.23, 95% CI 0.54–2.79, \( p = 0.63 \)). Three fatal bleeding events occurred in the overall population, including one fatal bleed from esophageal varices in the enoxaparin arm and two fatal bleeds from fulminant cancer ulceration in the duodenum in the control arm. There was no significant difference in PFS (HR, 1.06; 95% CI, 0.84 to 1.32; \( p = 0.64 \)) or OS (HR, 1.01; 95% CI, 0.87 to 1.38; \( p = 0.44 \)).

A recent meta-analysis pooling the results from both the FRAGEM [93] and PROSPECT-CONKO 004 [94] trials reported a significant reduction in crude rates of VTE in advanced PC patients receiving LMWH compared to control (2.1% vs. 11.2%, RR 0.18, 95% CI 0.08–0.40), corresponding to a 82% relative risk reduction, without difference in the rate of bleeding events (4.1% vs. 3.3%, RR 1.25, 95% CI 0.48–3.3) [95]. While standard prophylactic doses of LMWH were used in PROTECHT [91] and SAVE-ONCO [92] trials, dalteparin was administered at therapeutic doses in the FRAGEM trial, [93] and enoxaparin was administered at supra-prophylactic doses in the PROSPECT-CONKO 004 trial, [94] suggesting that PC patients might require higher than standard prophylactic doses of anticoagulant for effective VTE prophylaxis.

4.1.3. Direct Oral Anticoagulants (DOAC) As Primary Thromboprophylaxis in Various Cancers, with PC as A Subgroup

Despite limited data on their efficacy and safety in this setting, there is growing interest in the potential role of DOACs for thromboprophylaxis in patients with cancer. Two recent randomized controlled trials evaluated the efficacy and safety of primary thromboprophylaxis with DOACs in various cancers with different inclusion criteria and primary endpoints (Table 4).

The double-blind placebo-controlled CASSINI trial randomized 841 cancer patients initiating chemotherapy at intermediate-to-high risk of VTE (as defined by a Khorana score \( \geq 2 \)) to receive either primary prophylaxis with rivaroxaban (10 mg once daily) or placebo for up to 6 months. [96] Four hundred eighty patients (54.5%) had stage IV disease at enrollment. Screening ultrasound was performed at baseline and every 8 weeks during the follow-up period. The primary efficacy endpoint was a composite of symptomatic DVT, asymptomatic proximal DVT, any PE and VTE-related death within the first 180 days after randomization. During the entire follow-up, there was no statistically significant difference in the primary end point between the two arms: 6.0% in the rivaroxaban arm vs. 8.8% in the placebo arm (HR 0.66, 95% CI 0.40–1.09; \( p = 0.10 \)). However, during the on-treatment period, patients treated with rivaroxaban experienced fewer VTE events compared to those receiving placebo (2.6% vs. 6.4%, HR 0.40, 95% CI 0.20–0.80). There was no difference in major bleeding between the two groups (HR 1.96, 95% CI 0.59–6.49). In a prespecified subgroup analysis of PC patients included in CASSINI \( (n = 273, 32.6\%) \), the primary composite endpoint occurred in five out of 135 (3.7%) PC patients in the rivaroxaban arm compared to 14 out of 138 (10.1%) patients in the placebo arm (HR 0.35, 95% CI 0.13–0.97) during intervention. In PC patients, there was no difference in major bleeding between the two groups (1.5% in the rivaroxaban arm vs. 2.3% in the placebo arm) [97].

The Double-Blind Placebo-Controlled Phase 3 AVERT Trial [98] randomized 574 ambulatory cancer patients initiating chemotherapy at intermediate-to-high risk of VTE (as defined by a Khorana score \( \geq 2 \)) to receive either primary prophylaxis with apixaban (2.5 mg twice daily) or a placebo for up to 6 months. Five hundred and sixty-three patients were included in the modified intention-to-treat analysis. One hundred forty (24.8%) patients had metastatic disease at enrollment and 77 (13.8%) patients had PC. Screening ultrasound was not performed at baseline, nor during the follow-up period. The primary outcome was the occurrence of objectively documented major VTE (proximal DVT or PE) within the first 180 days after randomization. During the on-treatment period, patients receiving apixaban had a significant lower risk of VTE (1% vs. 7.3% in the placebo arm; HR 0.14, 95% CI 0.05–0.42, \( p < 0.001 \)) with no difference in major bleeding (2.1% in the apixaban arm vs. 1.1% in the placebo arm; HR 1.89, 95% CI 0.39–9.24).
Table 4. Studies assessing the clinical benefit of anticoagulants for the prevention of venous thromboembolism in ambulatory pancreatic cancer (PC) patients.

| Reference Study Design | Number of Patients Analyzed | Follow-Up | Population | Intervention | VTE Incidence | Safety | Survival |
|------------------------|----------------------------|-----------|------------|--------------|---------------|--------|----------|
| **PROTECHT**           |                            |           |            |              |               |        |          |
| Agnelli et al. 2009 [91] | Overall population         | 769 patients and 381 patients | 120 days   | Ambulatory patients >18 years on chemotherapy with metastatic or locally advanced lung, gastrointestinal, breast, ovarian, or head and neck cancer | Arm A: nadroparin 3800 IU/day, Arm B: placebo | Overall population Arm A: 11/769 (1.4%), Arm B: 11/381 (2.9%), *p* = 0.02 | Overall population Major bleeding Arm A: 5/769 (0.7%), Arm B: 0/381, *p* = 0.18 | Overall population Minor bleeding Arm A: 57/769 (7.4%), Arm B: 30/381 (7.9%), *p* = ns | Overall population PC subgroup NS | Overall population PC subgroup NS |
| | Arm A: 36 patients         | Arm B: 17 patients          |            |              |               | Overall population Arm A: 3/36 (8.3%), Arm B: 1/17 (5.9%), *p* = 0.755 |                         |                  |                  |
| | Arm A: 1608 patients      | Arm B: 1604 patients        | 3 months   | Patients with metastatic or locally advanced lung, pancreatic, gastric, colorectal, bladder, and ovarian cancer beginning to receive a course of chemotherapy | Arm A: Semuloparin, 20 mg/day, Arm B: placebo | Overall population Arm A: 20/1608 (1.2%), Arm B: 55/1064 (1.2%), HR 0.36 (95% CI 0.21–0.60), *p* < 0.001 | Overall population Major bleeding Arm A: 19/1589 (1.2%), Arm B: 18/1583 (1.1%), OR 1.05 (95% CI 0.55–2.04) | Overall population Minor bleeding Arm A: 26/1589 (2.8%), Arm B: 14/1583 (0.9%), OR 1.86 (95% CI 0.98–3.68) | Overall population PC subgroup NS | Overall population PC subgroup NS |
| | Arm A: 126 patients       | Arm B: 128 patients         |            |              |               | Overall population Arm A: 3/126 (2.4%), Arm B: 14/128 (10.9%), HR 0.22 (95% CI 0.06–0.76), *p* = 0.015 |                         |                  |                  |
| | Arm A: 59 patients        | Arm B: 62 patients          | 3 months   | Patients aged 18 years or older, Histologically/cytologically confirmed advanced or metastatic pancreatic cancer | Arm A: Gemcitabine + Dalteparin 200 IU/kg, sc, od, for 4 weeks, followed by a step-down regimen to 150 IU/kg for a further 8 weeks, Arm B: Gemcitabine alone for up to 12 weeks | At 3 months Arm A: 2/59 (3%), Arm B: 14/62 (23%), RR 0.145 (95% CI 0.035–0.612), *p* = 0.002 | Overall study Arm A: 7/59 (12%), Arm B: 17/62 (28%), RR 0.419 (95% CI 0.187–0.935), *p* = 0.039 | Overall study ISTH non severe Arm A: 5/59 (9%), Arm B: 2/62 (3%) | Overall study ISTH severe Arm A: 2/59 (3%), Arm B: 2/62 (3%) | Overall study PC subgroup NS | Overall study PC subgroup NS |
| | Arm A: 8.7 months         | Arm B: 9.7 months           |            |              |               |                  |                  |                  |

ISTH: International Society on Thrombosis and Haemostasis; CRNMB: Cytoreductive Neoadjuvant Multimodal Treatment; VTE: Venous Thromboembolism; PC: Pancreatic Cancer; HR: Hazard Ratio.
Table 4. Cont.

| Reference                          | Study Design                                      | Number of Patients Analyzed | Follow-Up | Population | Intervention | VTE Incidence | Safety | Survival |
|-----------------------------------|---------------------------------------------------|----------------------------|-----------|------------|--------------|---------------|--------|----------|
|                                   |                                                   |                            |           |            | At 3 months  |               |        |          |
|                                   |                                                   |                            |           |            | Arm A: 2/160 (1.25%) | Arm B: 15/152 (9.8%) | HR 0.12 (95% CI 0.03–0.52) | p = 0.001 |          |
|                                   |                                                   |                            |           |            | Cumulative incidence rates | Of major bleeding |
|                                   |                                                   |                            |           |            | Arm A: HR 0.40 (95% CI 0.19–0.83) | Arm B: HR 1.23 (95% CI 0.54–2.79) | p = 0.63 |          |
|                                   |                                                   |                            |           |            | HR 0.12 (95% CI 0.03–0.52) | p = 0.001 |        |          |
|                                   |                                                   |                            |           |            | arm A: 6.4% | Arm B: 15.1% | Cumulative incidence rates |
|                                   |                                                   |                            |           |            | HR 0.12 (95% CI 0.03–0.52) | p = 0.001 |        |          |
|                                   |                                                   |                            |           |            | arm A: 8.2 months | Arm B: 8.51 months | HR 1.01 (95% CI 0.87–1.38) | p = 0.44 |          |
|                                   |                                                   |                            |           |            | Overall population VTE at 6 months |
|                                   |                                                   |                            |           |            | Arm A: 25/420 (5.95%) | Arm B: 37/421 (8.79%) | HR 0.66 (95% CI 0.40–1.09) | p = 0.101 | NNT = 35 |
|                                   |                                                   |                            |           |            | Arm A: HR 0.40 (95% CI 0.20–0.80) | Arm B: HR 0.40 (95% CI 0.20–0.80) | p = 0.007 | NNT = 26 |
|                                   |                                                   |                            |           |            | Overall population Major bleeding |
|                                   |                                                   |                            |           |            | Arm A: 8/405 (1.98%) | Arm B: 4/404 (0.99%) | HR 1.96 (95% CI 0.59–6.49) | p = 0.265 | NNH = 101 |
|                                   |                                                   |                            |           |            | Overall population Clinically relevant non-major bleeding |
|                                   |                                                   |                            |           |            | Arm A: 2/72 (2.72%) | Arm B: 1/40 (0.25%) | HR 1.96 (95% CI 0.59–6.49) | p = 0.265 | NNH = 101 |
|                                   |                                                   |                            |           |            | Overall population All-cause mortality |
|                                   |                                                   |                            |           |            | Arm A: 20.0% | Arm B: 23.8% | HR, 0.83, 95% CI 0.62–1.11 | p = 0.213 | PC subgroup |
|                                   |                                                   |                            |           |            | PC subgroup Composite of VTE and death from VTE |
|                                   |                                                   |                            |           |            | Arm A: 5/135 (3.7%) | Arm B: 14/138 (10.1%) | HR 0.35 (95% CI 0.130–0.97) | p = 0.03 |          |
|                                   |                                                   |                            |           |            | Arm A: HR 0.35 (95% CI 0.130–0.97) | Arm B: HR 0.35 (95% CI 0.130–0.97) | p = 0.007 | NNT = 26 |
|                                   |                                                   |                            |           |            | Overall population All-cause mortality |
|                                   |                                                   |                            |           |            | Arm A: 2/135 (1.5%) | Arm B: 3/138 (2.3%) | HR 0.35 (95% CI 0.130–0.97) | p = 0.03 |          |
|                                   |                                                   |                            |           |            | Arm A: HR 0.35 (95% CI 0.130–0.97) | Arm B: HR 0.35 (95% CI 0.130–0.97) | p = 0.007 | NNT = 26 |

**Table 4.** Table of clinical trial data.

**CONKO-0004** Pelzer et al. 2015 [94]
Prospective, open label, randomized, multicenter and group-sequential 2b trial

Arm A: 160 patients
Arm B: 152 patients

Patients with histologically proven advanced pancreatic cancer were randomly assigned to ambulant first-line chemotherapy

Arm A: Enoxaparin 1 mg/kg/day
Arm B: no enoxaparin

At 3 months
Arm A: 2/160 (1.25%)
Arm B: 15/152 (9.8%)
HR 0.12 (95% CI 0.03–0.52)
p = 0.001

Cumulative incidence rates
Arm A: 6.4%
Arm B: 15.1%
HR 0.40 (95% CI 0.19–0.83)
p = 0.01

Overall population
Arm A: 420 patients
Arm B: 404 patients

VTE at 6 months
Arm A: 25/420 (5.95%) | Arm B: 37/421 (8.79%) | HR 0.66 (95% CI 0.40–1.09) | p = 0.101 | NNT = 35 |

VTE during the on-treatment period
Arm A: 11/420 (2.62%) | Arm B: 27/421 (6.41%) | HR 0.40 (95% CI 0.20–0.80) | p = 0.007 | NNT = 26 |

PC subgroup
Composite of VTE and death from VTE
Arm A: 5/135 (3.7%) | Arm B: 14/138 (10.1%) | HR 0.35 (95% CI 0.130–0.97) | p = 0.03 |          |
Table 4. Cont.

| Reference Study Design | Number of Patients Analyzed | Follow-Up | Population | Intervention | VTE Incidence | Safety | Survival |
|------------------------|----------------------------|-----------|------------|--------------|---------------|--------|----------|
| **AVERT** Carrier et al. 2019 [98] | Overall population Arm A: 288 patients Arm B: 275 patients PC patients: 77 | 6 months Arm A: 2.5 mg twice daily up to day 180 Arm B: placebo up to day 180 | Ambulatory cancer patients receiving chemotherapy who are at high-risk for VTE (as defined by a Khorana score of ≥2) | Arm A: apixaban 12/288 (4.2%) HR 0.41 (95% CI 0.26–0.65) p < 0.001 Arm B: placebo up to day 180 | VTE at 6 months Overall population Arm A: 12/288 (4.2%) Arm B: 28/275 (10.2%) HR 0.41 (95% CI 0.26–0.65) p < 0.001 PC subgroup NS | Major bleeding Arm A: 10/288 (3.5%) Arm B: 5/275 (1.8%) HR 2.00 (95% CI 1.01–3.95) p = 0.046 Clinically relevant non-major bleeding Arm A: 21/288 (7.3%) Arm B: 15/275 (5.5%) HR 1.28; 95% CI, 0.89–1.84 | All-cause mortality Arm A: 35/288 (12.2%) Arm B: 27/275 (9.8%) HR 1.29 (95% CI 0.98–1.71) p = ns PC subgroup NS |
| Ramathan et al. 2018 [99] | Arm A: 18 patients Arm B: 16 patients | Median of 8 weeks | Locally advanced ductal adenocarcinoma of the pancreas diagnosed ≤6 months prior to enrollment | Arm A: Gemcitabine + PCI-27433 1.2 mg/kg/day Arm B: Gemcitabine alone | VTE (any grade) Arm A: 10/18 (56%) Arm B: 3/16 (19%) | Bleeding (any grade) Arm A: 1/18 (6%) Arm B: 2/16 (13%) | Arm A: 5.7 months Arm B: 5.6 months |

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non major bleeding; HR, hazard ratio; OR, odds ratio; NNH, number needed to harm; NNT, number needed to treat; NS, not specified; PC, pancreatic cancer; RR, relative risk; VTE, venous thromboembolism.
During the entire follow-up, patients receiving apixaban experienced fewer VTE events compared to those receiving placebo (4.2% vs. 10.2%; HR 0.41, 95% CI 0.26–0.65, p < 0.001). In the modified intention-to-treat analysis, patients receiving apixaban had a significant higher risk of major bleeding (3.5% vs. 1.8% in the placebo arm; HR 2.00, 95% CI 1.01–3.95; p = 0.046). Results were not reported separately for the subgroup of PC patients.

The percentage of patients who prematurely discontinued the trial regimen was relatively high in both trials (47% in CASSINI and 38% in AVERT) and there was no significant difference in overall survival between patients receiving DOAC or placebo.

In an updated meta-analysis pooling the results from FRAGEM, [93] PROSPECT-CONKO 004 [94] and from subgroups of PC patients included in PROTECHT [91], SAVE-ONCO [92] and CASSINI, [96] PC patients receiving primary thromboprophylaxis with either LMWH or a DOAC had significantly lower rates of VTE compared to controls (5.43% vs. 12.07%, RR 0.44, 95% CI 0.29–0.70), with a risk difference of −0.06 (95% CI −0.11–−0.01, p = 0.01) with no difference in the rate of major bleeding between the two groups (4.11% vs. 3.27%) [100]. However, pooling subgroup analyses of RCTs is prone to biased results and these results should be interpreted with caution.

Compared to LMWH, DOACs have the advantage of being orally administered at fixed doses. However, there are some limitations for their use in cancer patients that should be taken in consideration. Certain patient characteristics (e.g.: weight and age) and comorbidities (e.g.: renal or hepatic impairment), as well as potential drug-drug interactions may affect anticoagulant pharmacokinetics and result in over or under-coagulating [101–103]. Vomiting and diarrhea, common side effects of cancer treatment, can also limit drug absorption in these patients. Finally, DOACs have been associated with an increased risk of GI bleeding, particularly in cancers of the upper GI tract. In each case, full consideration of the appropriate balance of benefits and harms is warranted.

4.2. Anticoagulants as Adjuvant Treatment to Improve Survival in Pancreatic Cancer Patients

Several studies evaluated the hypothesis that targeted inhibition of the coagulation cascade might improve survival in cancer patients. However, few data were obtained from PC patients due to their short life expectancy.

The FAMOUS trial [104] randomized 385 cancer patients to receive either dalteparin (5000 IU daily) or placebo for 1 year. One year after randomization, OS was 46% in patients receiving dalteparin compared to 41% in patients receiving placebo (p = 0.19). Thirty eight (10%) PC patients were included in the study, but results were not reported for this subgroup [104].

The MALT trial [105] assessed the effect of nadroparin compared to placebo for 6 weeks on survival in 302 patients with advanced cancer without VTE. In the intention-to-treat population, the median survival was significantly longer in the nadroparin group (8.0 months vs. 6.6 months in the placebo group; HR 0.75, 95% CI 0.59–0.96, p = 0.021), even after adjustment for WHO performance status, concomitant treatment, and type and histology of cancer (HR 0.76, 95% CI 0.58–0.99). In a pre-specified subgroup of patients with a life expectancy longer than 6 months at enrollment, the median survival was 15.4 months in the nadroparin group compared to 9.4 to months in the placebo group (HR 0.64, 95% CI 0.45–0.90; p = 0.01). These results are difficult to extrapolate to PC patients since only 18 out of 302 (6%) patients included in the MALT trial had PC [105].

In a multicenter, open-label, randomized controlled trial, 503 patients with non-small-cell lung cancer, hormone-refractory prostate cancer, or locally advanced PC received either nadroparin for 6 weeks (2 weeks at therapeutic dose, and 4 weeks at half therapeutic dose) in addition to their cancer treatment, or no nadroparin. One hundred thirty four out of 503 (27%) patients had PC. In PC patients, the mortality rate did not differ between the two study arms (79% in the nadroparin arm vs. 73.6% in the control arm; HR 1.14, 95% CI 0.77–1.68; p = 0.53). The median survival was 8.0 months in the nadroparin arm compared to 10.4 months in the control arm (p = ns) [106].

Finally, a non-randomized trial reported that the use of nadroparin improved survival in 69 consecutive patients with advanced pancreatic ductal adenocarcinoma treated with GEM plus cisplatin
every 21 days with or without nadroparin until disease progression. The overall response rate on PFS was 58.8% with nadroparin compared to 12.1% without nadroparin \((p = 0.0001)\). Patients receiving nadroparin had longer median time to progression and survival compared to those without \((7.3 \text{ vs. } 4.0 \text{ months}, \ p = 0.0001 \text{ and } 13.0 \text{ vs. } 5.5 \text{ months}, \ p = 0.0001, \text{ respectively})\) [107].

Survival was a secondary efficacy end point in FRAGEM [93] and PROSPECT-CONKO 004 [94], but despite established association between VTE and mortality in PC patients, both studies failed to demonstrate a benefit of LMWH on overall survival (Table 4). This lack of difference between the LMWH and placebo arms might be related to the short life expectancy of PC patients included in these studies [108], or might suggest that the activities driving VTE and progression are not equally susceptible to LMWH. It may well be that clinical VTE per se is not the sole determinant of survival and neither could be FXa and FIIa since TF activities unrelated to those e.g., PAR2 would not be altered by LMWH.

A recent phase 2 study evaluated the safety and efficacy of PCI-27483, a reversible small-molecule inhibitor of activated factor VII. This study randomized 34 patients with metastatic or locally advanced PC to receive PCI-27483-GEM \((n = 18)\) or GEM alone \((n = 16)\). OS did not significantly differ between patients treated with PCI-27483- GEM and those with GEM alone but there was a nonsignificant trend toward longer PFS in patients receiving PCI-27483- GEM compared to those receiving GEM alone (PFS: 3.7 months vs. 1.9 months; HR 0.62; \(p = 0.307\)) [99]. There was no difference in the rates of grade \(\geq 3\) bleeding between the two arms and there was a trend toward lower rates of VTE in the PCI-27483- GEM arm \(6\% \text{ vs. } 13\% \text{ in the GEM arm}\). Overall, there is yet no evidence that points towards any survival benefit of anticoagulants as adjuvant treatment in PC patients.

5. Current Guidelines for VTE Thromboprophylaxis in PC Patients

Since 2013, the ITAC CPGs have recommended the use of thromboprophylaxis with LMWH in surgical PC patients undergoing major surgery, hospitalized patients with acute medical illness and reduced mobility [12–14], and in locally advanced or metastatic ambulatory PC patients receiving chemotherapy [12–14]. New data have now emerged on the benefit of DOACs for primary thromboprophylaxis, which provide another option in selected patients [96,98]. The ITAC working group [14], the American Society of Clinical Oncology (ASCO) [15], and the National Comprehensive Cancer Network (NCCN) [109] updated their recommendations for VTE prophylaxis in cancer patients in 2019.

5.1. Thromboprophylaxis in Surgical PC Patients

Thromboprophylaxis is recommend in PC patients undergoing major surgery by all current guidelines [12–15,109]. The 2019 ITAC CPGs [14] recommend thromboprophylaxis with the highest prophylactic dose of LMWH in PC patients undergoing major surgery, in the absence of contraindications (creatinine clearance <30 mL·min\(^{-1}\), high bleeding risk, active bleeding) [Grade 1A]. Low dose of unfractionated heparin (UFH) three times daily can also be used [Grade 1A]. There are insufficient data to support the use of fondaparinux as an alternative to LMWH in surgical PC patients [2C] and no data to support the use of DOACs [Best clinical practice]. Extended prophylaxis for 4 weeks should be used in patients undergoing laparotomy or laparoscopic surgery with a low bleeding risk [Grade 1A]. External compression devices are not recommended as monotherapy, except when pharmacological methods are contraindicated [Grade 2B], and the use of inferior vena cava filter is not recommended for routine thromboprophylaxis [Grade 1A] [14].

5.2. Thromboprophylaxis in Hospitalized PC Patients with Acute Medical Illness or with A Reduced Mobility

All current CPGs recommend thromboprophylaxis in hospitalized PC patients with acute medical illness or reduced mobility in the absence of bleeding or other contraindications [12–15,109]. The 2019 ITAC CPGs [14] recommend to use of prophylactic dose of LMWH in hospitalized PC patients with acute medical illness or with a reduced mobility in the absence of contraindications (creatinine
clearance <30 mL·min⁻¹, high bleeding risk, active bleeding) [Grade 1B]. Prophylaxis with UFH or fondaparinux can also be used [Grade 1B], but DOACs are not recommended routinely in this setting due to the lack of data [Best clinical practice] [14].

5.3. Thromboprophylaxis in Ambulatory PC Patients Receiving Chemotherapy

The KS assigns +2 points for PC patients. Therefore, according to the most recent guidelines, all ambulatory PC patients should be considered for thromboprophylaxis with either LMWH or DOACs. [14,15] In locally advanced or metastatic PC patients, the 2019 ITAC CPGs [14] recommend primary prophylaxis with LMWH for those patients having a low risk of bleeding and receiving systemic anticancer therapy [Grade 1B] [14], based on available evidence. [93–95] The 2019 ITAC CPGs [14] also recommend thromboprophylaxis with apixaban or rivaroxaban in cancer outpatients at intermediate-to-high risk (KS ≥2 prior to starting chemotherapy) with a low bleeding risk and in the absence of drug-drug interactions [Grade 1B] [14].

Similarly, the ASCO guidelines recommend that thromboprophylaxis with apixaban, rivaroxaban or LMWH may be offered in high-risk cancer outpatients (KS ≥2 or higher prior to starting a new systemic chemotherapy regimen) in the absence of significant risk factors for bleeding and drug interactions [15].

6. Conclusions

Evidence (Grade 1B) that appropriate use of primary thromboprophylaxis significantly and safely reduces the burden of VTE in PC patients has been available since 2013. Despite this fact, thromboprophylaxis remains largely underused. Increased awareness among healthcare professionals and adherence to evidence-based guidelines can decrease the burden of VTE in PC patients. Clinical tools based on the 2019 ITAC-CME international guidelines, such as a free accessible web-based mobile application with a decision-tree algorithm (downloadable at www.itaccme.com), can be used to assist clinicians in optimizing treatment in daily clinical practice. In the absence of head-to-head comparison between LMWH and DOACs, a discussion with the patient about the relative benefits and risks, drug cost, duration and tolerance of prophylaxis is warranted before prescribing thromboprophylaxis in PC ambulatory patients.

Author Contributions: D.F. and C.F. wrote the first draft of the manuscript and contributed to the concept and design, critical of intellectual content, and final approval; all other authors contributed to critical of intellectual content of the manuscript, and final approval. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: D.F. reports non-financial support from Leo Pharma, Aspen Pharmacare, and Pfizer, outside of the submitted work. C.F. reports personal fees and non-financial support from Leo Pharma, personal fees and non-financial support from Bayer, Aspen Pharma Care, and Pfizer, outside of the submitted work. Other authors declare no conflicts of interest.

References
1. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2018. CA Cancer J. Clin. 2018, 68, 7–30. [CrossRef] [PubMed]
2. Ryan, D.P.; Hong, T.S.; Bardeesy, N. Pancreatic Adenocarcinoma. N. Engl. J. Med. 2014, 371, 1039–1049. [CrossRef] [PubMed]
3. GBD 2017 Pancreatic Cancer Collaborators The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol. Hepatol. 2019, 4, 934–947. [CrossRef]
4. Rahib, L.; Smith, B.D.; Aizenberg, R.; Rosenzweig, A.B.; Fleshman, J.M.; Matrisian, L.M. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014, 74, 2913–2921. [CrossRef]
5. American Cancer Society. Cancer Facts & Figures 2019. Available online: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf (accessed on 10 October 2019).

6. Azar, I.; Virg, G.; Esfandiarifar, S.; Wazir, A.; Mehdi, S. Treatment and survival rates of stage IV pancreatic cancer at VA hospitals: A nation-wide study. *J. Gastroint. Oncol*. 2019, 10, 703–711. [CrossRef]

7. Lambert, A.; Schwarz, L.; Borbach, I.; Henry, A.; Van Laethem, J.-L.; Malka, D.; Ducrœux, M.; Conroy, T. An update on treatment options for pancreatic adenocarcinoma. *Ther. Adv. Med. Oncol*. 2019, 11, 175883919875568. [CrossRef]

8. Burris, H.A.; Moore, M.J.; Andersen, J.; Green, M.R.; Rothenberg, M.L.; Modiano, M.R.; Cripps, M.C.; Portenoy, R.K.; Storniolo, A.M.; Tarasoff, P.; et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J. Clin. Oncol*. 1997, 15, 2403–2413. [CrossRef]

9. Conroy, T.; Desseigne, F.; Ychou, M.; Bouché, O.; Guimbaud, R.; Bécouarn, Y.; Adenis, A.; Raoul, J.-L.; Gourgou-Bourgade, S.; de la Fouquardière, C.; et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N. Engl. J. Med*. 2011, 364, 1817–1825. [CrossRef]

10. Von Hoff, D.D.; Ervin, T.; Arena, F.P.; Chioarean, E.G.; Infante, J.; Moore, M.; Seay, T.; Tjulandin, S.A.; Ma, W.W.; Saleh, M.N.; et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N. Engl. J. Med*. 2013, 369, 1691–1703. [CrossRef]

11. Conroy, T.; Hammel, P.; Hebbar, M.; Ben Abdelghani, M.; Wei, A.C.; Raoul, J.-L.; Choné, L.; Francois, E.; Artru, P.; Biagi, J.J.; et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *N. Engl. J. Med*. 2018, 379, 2395–2406. [CrossRef]

12. Farge, D.; Debourdeau, P.; Beckers, M.; Baglin, C.; Bauersachs, R.M.; Brenner, B.; Brilhante, D.; Falanga, A.; Gerotzafias, G.T.; Haim, N.; et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *J. Thromb. Haemost*. 2013, 11, 56–70. [CrossRef] [PubMed]

13. Farge, D.; Bounameaux, H.; Brenner, B.; Cajfinger, F.; Debourdeau, P.; Khorana, A.A.; Pabinger, I.; Solymoss, S.; Douketis, J.; Kakkar, A. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2016, 17, e452–e466. [CrossRef]

14. Farge, D.; Frere, C.; Connors, J.M.; Ay, C.; Khorana, A.A.; Munoz, A.; Brenner, B.; Kakkar, A.; Rafii, H.; Solymoss, S.; et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2020, 20, e566–e581. [CrossRef]

15. Key, N.S.; Khorana, A.A.; Kuderer, N.M.; Bohlke, K.; Lee, A.Y.Y.; Arcelus, J.I.; Wong, S.L.; Balaban, E.P.; Flowers, C.R.; Francis, C.W.; et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J. Clin. Oncol*. 2020, 38, 496–520. [CrossRef] [PubMed]

16. Moffat, G.T.; Epstein, A.S.; O’Reilly, E.M. Pancreatic cancer-A disease in need: Optimizing and integrating supportive care. *Cancer* 2019, 125, 3927–3935. [CrossRef]

17. Levitan, N.; Dowlati, A.; Remick, S.C.; Tahsildar, H.I.; Sivinski, L.D.; Beyth, R.; Rimm, A.A. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. *Medicine* 1999, 78, 285–291. [CrossRef]

18. Heit, J.A.; Silverstein, M.D.; Mohr, D.N.; Peterson, T.M.; O’Fallon, W.M.; Melton, L.J. Risk factors for deep vein thrombosis and pulmonary embolism: A population-based case-control study. *Arch. Intern. Med*. 2000, 160, 809–815. [CrossRef]

19. Timp, J.F.; Braekkan, S.K.; Versteeg, H.H.; Cannegieter, S.C. Epidemiology of cancer-associated venous thrombosis. *Blood* 2013, 122, 1712–1723. [CrossRef]

20. Blom, J.W.; Vanderschoot, J.P.M.; Oostindier, M.J.; Osanto, S.; van der Meer, F.J.M.; Rosendaal, F.R. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: Results of a record linkage study. *J. Thromb. Haemost*. 2006, 4, 529–535. [CrossRef]

21. Chew, H.K.; Wun, T.; Harvey, D.; Zhou, H.; White, R.H. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch. Intern. Med*. 2006, 166, 458–464. [CrossRef]

22. Horsted, P.; West, J.; Grainge, M.J. Risk of venous thromboembolism in patients with cancer: A systematic review and meta-analysis. *PLoS Med*. 2012, 9, e1001275. [CrossRef] [PubMed]
23. Sproul, E.E. Carcinoma and Venous Thrombosis: The Frequency of Association of Carcinoma in the Body or Tail of the Pancreas with Multiple Venous Thrombosis. *Am. J. Cancer* 1938, 34, 566–585.

24. Blom, J.W.; Osanto, S.; Rosendaal, F.R. High risk of venous thrombosis in patients with pancreatic cancer: A cohort study of 202 patients. *Eur. J. Cancer* 2006, 42, 410–414. [CrossRef] [PubMed]

25. Mandalá, M.; Reni, M.; Cascini, S.; Barni, S.; Florianì, I.; Cereda, S.; Berardi, R.; Mosconi, S.; Torri, V.; Labianca, R. Venous thromboembolism predicts poor prognosis in irresectable pancreatic cancer patients. *Ann. Oncol.* 2007, 18, 1660–1665. [CrossRef] [PubMed]

26. Mitry, E.; Taleb-Fayad, R.; Deschamps, A.; Mansencal, N.; Lepère, C.; Decleyt, G.; Lièvre, A.; Vaillant, J.-N.; Lesur, G.; Cramer, E.; et al. Risk of venous thrombosis in patients with pancreatic adenocarcinoma. *Gastroenterol. Clin. Biol.* 2007, 31, 1139–1142. [CrossRef]

27. Oh, S.Y.; Kim, J.H.; Lee, K.-W.; Bang, S.-M.; Hwang, J.-H.; Oh, D.; Lee, J.S. Venous thromboembolism in patients with pancreatic adenocarcinoma: Lower incidence in Asian ethnicity. *Thromb. Res.* 2008, 122, 485–490. [CrossRef]

28. Poruk, K.E.; Firpo, M.A.; Huerter, L.M.; Scaife, C.L.; Emerson, L.L.; Boucher, K.M.; Jones, K.A.; Mulvihill, S.J. Serum platelet factor 4 is an independent predictor of survival and venous thromboembolism in patients with pancreatic adenocarcinoma. *Cancer Epidemiol. Biomark. Prev.* 2010, 19, 2605–2610. [CrossRef]

29. Shaib, W.; Deng, Y.; Zilberman, D.; Lundberg, B.; Saif, M.W. Assessing risk and mortality of venous thromboembolism in pancreatic cancer patients. *Anticancer Res.* 2010, 30, 4261–4264.

30. Epstein, A.S.; Soff, G.A.; Capanu, M.; Crosbie, C.; Shah, M.A.; Kelsen, D.P.; Denton, B.; Gardos, S.; O’Reilly, E.M. Analysis of incidence and clinical outcomes in patients with thromboembolic events and invasive exocrine pancreatic cancer. *Cancer* 2012, 118, 3053–3061. [CrossRef]

31. Menapace, L.A.; Peterson, D.R.; Berry, A.; Sousou, T.; Khorana, A.A. Symptomatic and incidental thromboembolism are both associated with mortality in pancreatic cancer. *Thromb. Haemost.* 2011, 106, 371–378. [CrossRef]

32. Afsar, C.U.; Gunaldi, M.; Kum, P.; Sahin, B.; Erkisi, M.; Kara, I.O.; Paydas, S.; Duman, B.B.; Ercolak, V.; Karaca, F.; et al. Pancreatic carcinoma, thrombosis and mean platelet volume: Single center experience from the southeast region of Turkey. *Asian Pac. J. Cancer Prev.* 2014, 15, 9143–9146. [CrossRef] [PubMed]

33. Muñoz Martínez, A.J.; García Alfonso, P.; Rupérez Blanco, A.B.; Pérez Ramírez, S.; Blanco Codesido, M.; Martín Jiménez, M. Incidence of venous thromboembolism (VTE) in ambulatory pancreatic cancer patients receiving chemotherapy and analysis of Khorana’s predictive model. *Clin. Transl. Oncol.* 2014, 16, 927–930. [CrossRef] [PubMed]

34. Krepline, A.N.; Christians, K.K.; George, B.; Ritch, P.S.; Erickson, B.A.; Tolat, P.; Evans, D.B.; Tsai, S. Venous thromboembolism prophylaxis during neoadjuvant therapy for resectable and borderline resectable pancreatic cancer-Is it indicated? *J. Surg. Oncol.* 2016, 114, 581–586. [CrossRef] [PubMed]

35. Lee, J.-C.; Ro, Y.S.; Cho, J.; Park, Y.; Lee, J.H.; Hwang, J.-H.; Choi, H.J.; Lee, S. Characteristics of Venous Thromboembolism in Pancreatic Adenocarcinoma in East Asian Ethnicities: A Large Population-Based Observational Study. *Medicine (Baltimore)* 2016, 95, e3472. [CrossRef]

36. Kruger, S.; Haas, M.; Burkl, C.; Goehring, P.; Kleespies, A.; Roeder, F.; Gallmeier, E.; Ormanns, S.; Westphalen, C.B.; Heinemann, V.; et al. Incidence, outcome and risk stratification tools for venous thromboembolism in advanced pancreatic cancer—A retrospective cohort study. *Thromb. Res.* 2017, 157, 9–15. [CrossRef] [PubMed]

37. van Es, N.; Franke, V.F.; Middeldorp, S.; Wilming, J.W.; Büller, H.R. The Khorana score for the prediction of venous thromboembolism in patients with pancreatic cancer. *Thromb. Res.* 2017, 150, 30–32. [CrossRef]

38. Berger, A.K.; Singh, H.M.; Werft, W.; Muckenhuber, A.; Sprick, M.R.; Trumpf, A.; Weichert, W.; Jäger, D.; Springfeld, C. High prevalence of incidental and symptomatic venous thromboembolic events in patients with advanced pancreatic cancer under palliative chemotherapy: A retrospective cohort study. *Pancreatology* 2017, 17, 629–634. [CrossRef]

39. Chen, J.-S.; Hung, C.-Y.; Chang, H.; Liu, C.-T.; Chen, Y.-Y.; Lu, C.-H.; Chang, P.-H.; Hung, Y.-S.; Chou, W.-C. Venous Thromboembolism in Asian Patients with Pancreatic Cancer Following Palliative Chemotherapy: Low Incidence but a Negative Prognosticator for Those with Early Onset. *Cancers* 2018, 10, 501. [CrossRef]

40. Kim, J.S.; Kang, E.J.; Kim, D.S.; Choi, Y.J.; Lee, S.Y.; Kim, H.J.; Seo, H.Y.; Kim, J.S. Early venous thromboembolism at the beginning of palliative chemotherapy is a poor prognostic factor in patients with metastatic pancreatic cancer: A retrospective study. *BMC Cancer* 2018, 18, 1260. [CrossRef]
41. Frere, C.; Bournet, B.; Gourgou, S.; Fraisse, J.; Canivet, C.; Connors, J.M.; Buscail, L.; Farge, D. Incidence of Venous Thromboembolism in Patients with Newly Diagnosed Pancreatic Cancer and Factors Associated With Outcomes. Gastroenterology 2019. [CrossRef]

42. Ouaisi, M.; Frasconi, C.; Mege, D.; Panicot-Dubois, L.; Boiron, L.; Dahan, L.; Debourdeau, P.; Dubois, C.; Farge, D.; Sielezneff, I. Impact of venous thromboembolism on the natural history of pancreatic adenocarcinoma. HBPD INT 2015, 14, 436–442. [CrossRef]

43. Khorana, A.A.; Fine, R.L. Pancreatic cancer and thromboembolic disease. Lancet Oncol. 2004, 5, 655–663. [CrossRef]

44. Mier-Hicks, A.; Raj, M.; Do, R.K.; Yu, K.H.; Lowery, M.A.; Varghese, A.; O’Reilly, E.M. Incidence, Management, and Implications of Visceral Thrombosis in Pancreatic Ductal Adenocarcinoma. Clin. Colorectal Cancer 2018, 17, 121–128. [CrossRef][PubMed]

45. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Cancer Therapy Evaluation Program: Bethesda, MD, USA, 2009.

46. Khorana, A.A.; Francis, C.W.; Culakova, E.; Kuderer, N.M.; Lyman, G.H. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 2007, 110, 2339–2346. [CrossRef] [PubMed]

47. Khorana, A.A.; Francis, C.W.; Culakova, E.; Kuderer, N.M.; Lyman, G.H. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J. Thromb. Haemost. 2007, 5, 632–634. [CrossRef] [PubMed]

48. Afzal, A.; Suhong, L.; Gage, B.F.; Schoen, M.W.; Carson, K.; Thomas, T.; Sanfilippo, K. Splanchnic vein thrombosis predicts worse survival in patients with advanced pancreatic cancer. Thromb. Res. 2019, 185, 125–131. [CrossRef] [PubMed]

49. Larsen, A.C.; Brøndum Frøkjaer, J.; Wishwanath Iyer, V.; Vincents Fisker, R.; Sall, M.; Yilmaz, M.K.; Kuno Møller, B.; Kristensen, S.R.; Thorlacius-Ussing, O. Venous thrombosis in pancreaticobiliary tract cancer: outcome and prognostic factors. J. Thromb. Haemost. 2015, 13, 555–562. [CrossRef]

50. Kaur, S.; Kumar, S.; Momii, N.; Sasson, A.R.; Batra, S.K. Mucins in pancreatic cancer and its microenvironment. Nat. Rev. Gastroenterol. Hepatol. 2013, 10, 607–620. [CrossRef]

51. Campello, E.; Ilitch, A.; Simioni, P.; Key, N.S. The relationship between pancreatic cancer and hypercoagulability: A comprehensive review on epidemiological and biological issues. Br. J. Cancer 2019, 121, 359–371. [CrossRef]

52. Gasic, G.J.; Koch, P.A.; Hsu, B.; Gasic, T.B.; Niewiarowski, S. Thrombogenic activity of mouse and human tumors: Effects on platelets, coagulation, and fibrinolysis, and possible significance for metastases. Z. Krebsforsch. Klin. Onkol. Cancer Res. Clin. Oncol. 1976, 86, 263–277. [CrossRef]

53. Labelle, M.; Begum, S.; Hynes, R.O. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 2011, 20, 576–590. [CrossRef]

54. Lucotti, S.; Cerutti, C.; Soyer, M.; Gil-Bernabé, A.M.; Gomes, A.L.; Allen, P.D.; Smart, S.; Markelc, B.; Watson, K.; Armstrong, P.C.; et al. Aspirin blocks formation of metastatic intravascular niches by inhibiting platelet-derived COX-1/thromboxane A2. J. Clin. Investig. 2019, 129, 1845–1862. [CrossRef] [PubMed]

55. Buscail, L.; Bournet, B.; Cordelier, P. Role of oncogenic KRAS in the diagnosis, prognosis and treatment of pancreatic cancer. Nat. Rev. Gastroenterol. Hepatol. 2020, 7, 153–168. [CrossRef] [PubMed]

56. Yu, J.L.; May, L.; Lhotak, V.; Shahrzad, S.; Shirasawa, S.; Weitz, J.I.; Coomber, B.L.; Mackman, N.; Rak, J.W. Oncogenic events regulate tissue factor expression in colorectal cancer cells: Implications for tumor progression and angiogenesis. Blood 2005, 105, 1734–1741. [CrossRef] [PubMed]

57. Garrido-Laguna, I.; Hidalgo, M. Pancreatic cancer: From state-of-the-art treatments to promising novel therapies. Nat. Rev. Clin. Oncol. 2015, 12, 319–334. [CrossRef]

58. Kakkar, A.K.; Lemoine, N.R.; Scully, M.F.; Tebbutt, S.; Williamson, R.C. Tissue factor expression correlates with histological grade in human pancreatic cancer. Br. J. Surg. 1995, 82, 1101–1104. [CrossRef]

59. Yu, J.L.; Rak, J.W. Shedding of tissue factor (TF)-containing microparticles rather than alternatively spliced TF is the main source of TF activity released from human cancer cells. J. Thromb. Haemost. 2004, 2, 2065–2067. [CrossRef]

60. Rak, J.; Yu, J.L.; Luyendyk, J.; Mackman, N. Oncogenes, trousseau syndrome, and cancer-related changes in the coagulome of mice and humans. Cancer Res. 2006, 66, 10643–10646. [CrossRef]

61. Rak, J. Cancer: Organ-seeking vesicles. Nature 2015, 527, 312–314. [CrossRef]
62. Sawai, H.; Liu, J.; Reber, H.A.; Hines, O.J.; Eibl, G. Activation of peroxisome proliferator-activated receptor-gamma decreases pancreatic cancer cell invasion through modulation of the plasminogen activator system. *Mol. Cancer Res.* **2006**, *4*, 159–167. [CrossRef]
63. Unruh, D.; Turner, K.; Srinivasan, R.; Kocatürk, B.; Qi, X.; Chu, Z.; Aronow, B.J.; Plas, D.R.; Gallo, C.A.; Kalthoff, H.; et al. Alternatively spliced tissue factor contributes to tumor spread and activation of coagulation in pancreatic ductal adenocarcinoma. *Int. J. Cancer* **2014**, *134*, 9–20. [CrossRef]
64. Unruh, D.; Ünlü, B.; Lewis, C.S.; Qi, X.; Sturm, R.; Keil, R.; Ahmad, S.A.; Soveresaev, T.; Adam, M.; et al. Antibody-based targeting of alternatively spliced tissue factor: A new approach to impede the primary growth and spread of pancreatic ductal adenocarcinoma. *Oncotarget* **2016**, *7*, 25264–25275. [CrossRef] [PubMed]
65. Winter, P.C. The pathogenesis of venous thromboembolism in cancer: Emerging links with tumour biology. *Hematol. Oncol.* **2006**, *24*, 126–133. [CrossRef] [PubMed]
66. Davila, M.; Amirkhosravi, A.; Coll, E.; Desai, H.; Robles, L.; Colon, J.; Baker, C.H.; Francis, J.L. Tissue factor-bearing microparticles derived from tumor cells: Impact on coagulation activation. *J. Thromb. Haemost.* **2008**, *6*, 1517–1524. [CrossRef] [PubMed]
67. Thomas, G.M.; Panicit-Dubois, L.; Lacroix, R.; Dignat-George, F.; Lombardo, D.; Dubois, C. Cancer cell-derived microparticles bearing P-selectin glycoprotein ligand 1 accelerate thrombus formation in vivo. *J. Exp. Med.* **2009**, *206*, 1913–1927. [CrossRef]
68. Zwicker, J.I.; Liebman, H.A.; Neuberg, D.; Lacroix, R.; Bauer, K.A.; Furie, B.C.; Furie, B. Tumor-derived tissue factor-bearing microparticles are associated with venous thromboembolic events in malignancy. *Clin. Cancer Res.* **2009**, *15*, 6830–6840. [CrossRef]
69. Manly, D.A.; Wang, J.; Glover, S.L.; Kashturi, R.; Liebman, H.A.; Key, N.S.; Mackman, N. Increased microparticle tissue factor activity in cancer patients with Venous Thromboembolism. *Thromb. Res.* **2010**, *125*, 511–512. [CrossRef]
70. Bharthuar, A.; Khorana, K.A.; Hutson, A.; Wang, J.; Mackman, N.; Iyer, R. Association of elevated tissue factor (TF) with survival and thromboembolism (TE) in pancreaticobiliary cancers (PBC). *J. Clin. Oncol.* **2010**, *28* (Suppl. 15), 4126. [CrossRef] [PubMed]
71. Khorana, A.A.; Francis, C.W.; Menzies, K.E.; Wang, J.-G.; Hyrien, O.; Hathcock, J.; Mackman, N.; Taubman, M.B. Plasma tissue factor may be predictive of venous thromboembolism in pancreatic cancer. *J. Thromb. Haemost.* **2008**, *6*, 1983–1985. [CrossRef]
72. Thaler, J.; Ay, C.; Mackman, N.; Bertina, R.M.; Kaidar, A.; Marosi, C.; Key, N.S.; Barcel, D.A.; Scheithauer, W.; Kornek, G.; et al. Microparticle-associated tissue factor activity, venous thromboembolism and mortality in pancreatic, gastric, colorectal and brain cancer patients. *J. Thromb. Haemost.* **2012**, *10*, 1363–1370. [CrossRef]
73. Thaler, J.; Ay, C.; Mackman, N.; Metz-Schimmerl, S.; Stift, J.; Kaidar, A.; Müllauer, L.; Gnant, M.; Scheithauer, W.; Pabinger, I. Microparticle-associated tissue factor activity in patients with pancreatic cancer: Correlation with clinicopathological features. *Eur. J. Clin. Investig.* **2013**, *43*, 277–285. [CrossRef]
74. Wei, M.; Tai, G.; Gao, Y.; Li, N.; Hu, W.; Zhou, Y.; Hao, S.; Zeng, X. Modified heparin inhibits P-selectin-mediated cell adhesion of human colon carcinoma cells to immobilized platelets under dynamic flow conditions. *J. Biol. Chem.* **2004**, *279*, 29202–29210. [CrossRef]
75. Mast, A.E.; Stadanlick, J.E.; Lockett, J.M.; Dietzen, D.J.; Hasty, K.A.; Hall, C.L. Tissue factor pathway inhibitor binds to platelet thrombospondin-1. *J. Biol. Chem.* **2000**, *275*, 31715–31721. [CrossRef]
76. Nadir, Y.; Brenner, B. Heparanase procoagulant activity in cancer progression. *Thromb. Res.* **2016**, *140* (Suppl. 1), S44–S48. [CrossRef]
Cancers 2020, 12, 618

81. Mousa, S.A.; Bozarth, J.; Barrett, J.S. Pharmacodynamic properties of the low molecular weight heparin, tinzaparin: Effect of molecular weight distribution on plasma tissue factor pathway inhibitor in healthy human subjects. J. Clin. Pharmacol. 2003, 43, 727–734. [CrossRef]

82. Sandset, P.M.; Abildgaard, U.; Larsen, M.L. Heparin induces release of extrinsic coagulation pathway inhibitor (EPI). Thromb. Res. 1988, 50, 803–813. [CrossRef]

83. Mousa, S.A.; Mohamed, S. Inhibition of endothelial cell tube formation by the low molecular weight heparin, tinzaparin, is mediated by tissue factor pathway inhibitor. Thromb. Haemost. 2004, 92, 627–633.

84. Mousa, S.A.; Mohamed, S. Anti-angiogenic mechanisms and efficacy of the low molecular weight heparin, tinzaparin: Anti-cancer efficacy. Oncol. Rep. 2004, 12, 683–688. [CrossRef]

85. Khorana, A.A.; Kuderer, N.M.; Culakova, E.; Lyman, G.H.; Francis, C.W. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008, 111, 4902–4907. [CrossRef]

86. Pelzer, U.; Sinn, M.; Steiler, J.; Riess, H. Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy? Dtsch. Med. Wochenschr. 2013, 138, 2084–2088.

87. Ay, C.; Dunkler, D.; Marosi, C.; Chriaci, A.-L.; Vormittag, R.; Simanek, R.; Quehenberger, P.; Zielinski, C.; Pabinger, I. Prediction of venous thromboembolism in cancer patients. Blood 2010, 116, 5377–5382. [CrossRef]

88. Verso, M.; Agnelli, G.; Barni, S.; Gasparini, G.; LaBianca, R. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: The Protecht score. Intern. Emerg. Med. 2012, 7, 291–292. [CrossRef]

89. Cella, C.A.; Di Minno, G.; Carломagno, C.; Arcopinto, M.; Cerbone, A.M.; Matano, E.; Tufano, A.; Lordick, F.; De Simone, B.; Muehlberg, K.S.; et al. Preventing Venous Thromboembolism in Ambulatory Cancer Patients: The ONKOTEV Study. Oncologist 2017, 22, 601–608. [CrossRef]

90. Godinho, J.; Casa-Nova, M.; Moreira-Pinto, J.; Simões, P.; Paralta Branco, F.; Leal-Costa, L.; Faria, A.; Lopes, F.; Teixeira, J.A.; Passos-Coelho, J.L. ONKOTEV Score as a Predictive Tool for Thromboembolic Events in Pancreatic Cancer-A Retrospective Analysis. Oncologist 2020, 25, e284–e290. [CrossRef] [PubMed]

91. Agnelli, G.; Gussoni, G.; Bianchini, C.; Verso, M.; Mandalà, M.; Cavanna, L.; Barni, S.; Labianca, R.; Buzzi, F.; Scambia, G.; et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: A randomised, placebo-controlled, double-blind study. Lancet Oncol. 2009, 10, 943–949. [CrossRef]

92. Agnelli, G.; George, D.J.; Kakkar, A.K.; Fisher, W.; Lassen, M.R.; Mismetti, P.; Mouret, P.; Chaudhari, U.; Lawson, F.; Turpie, A.G.G.; et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N. Engl. J. Med. 2012, 366, 601–609. [CrossRef] [PubMed]

93. Maraveyas, A.; Waters, J.; Roy, R.; Fyfe, D.; Propper, D.; Lofs, F.; Sgouros, J.; Gardiner, E.; Wedgwood, K.; Ettelaie, C.; et al. Gemicitabine versus gemicitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur. J. Cancer 2012, 48, 1283–1292. [CrossRef] [PubMed]

94. Pelzer, U.; Opitz, B.; Deutschinoff, G.; Staub, M.; Reitzig, P.C.; Hahnfeld, S.; Müller, L.; Grunewald, M.; Steiler, J.M.; Sinn, M.; et al. Efficacy of Prophylactic Low-Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial. J. Clin. Oncol. 2015, 33, 2028–2034. [CrossRef] [PubMed]

95. Tun, N.M.; Guevara, E.; Oo, T.H. Benefit and risk of primary thromboprophylaxis in ambulatory patients with advanced pancreatic cancer receiving chemotherapy: A systematic review and meta-analysis of randomized controlled trials. Blood Coagul. Fibrinolysis 2016, 27, 270–274. [CrossRef] [PubMed]

96. Khorana, A.A.; Soff, G.A.; Kakkar, A.K.; Vadhan-Raj, S.; Riess, H.; Wun, T.; Streiff, M.B.; Garcia, D.A.; Liebman, H.A.; Belani, C.P.; et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N. Engl. J. Med. 2019, 380, 720–728. [CrossRef] [PubMed]

97. Vadhan-Raj, S.; McNamara, M.G.; Venerito, M.; Riess, H.; O’Reilly, E.M.; Overman, M.J.; Zhou, X.; Vijapurkar, U.; Kaul, S.; Wildgrove, P.; et al. Rivaroxaban thromboprophylaxis in ambulatory patients with pancreatic cancer: Results from a prespecified subgroup analysis of the CASSINI study. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2019, 37, 4016. [CrossRef]

98. Carrier, M.; Abou-Nassar, K.; Mallick, R.; Tagalakis, V.; Shivakumar, S.; Schattner, A.; Kuruvilla, P.; Hill, D.; Spadafora, S.; Marquis, K.; et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N. Engl. J. Med. 2019, 380, 711–719. [CrossRef]
99. Ramanathan, R.K.; Thomas, G.W.; Khorana, A.A.; Shah, S.; Zhou, C.; Wong, S.; Cole, G.; James, D.; Gabrail, N.Y. A Phase 2 Study of PCI-27483, a Factor VIIa Inhibitor in Combination with Gemcitabine for Advanced Pancreatic Cancer. *Oncology* 2019, 96, 217–222. [CrossRef]

100. Thein, K.Z.; Quick, D.P.; Oo, T.H. Updated Meta-Analysis of Randomized Controlled Trials on Primary Ambulatory Thromboprophylaxis (PATP) in Patients with Advanced Pancreatic Cancer (APC) Receiving Chemotherapy. *Blood* 2019, 134 (Suppl. 1), 3469. [CrossRef]

101. Short, N.J.; Connors, J.M. New oral anticoagulants and the cancer patient. *Oncologist* 2014, 19, 82–93. [CrossRef]

102. Bellesoeur, A.; Thomas-Schoemann, A.; Allard, M.; Smadja, D.; Vidal, M.; Alexandre, J.; Goldwasser, F.; Blanchet, B. Pharmacokinetic variability of anticoagulants in patients with cancer-associated thrombosis: Clinical consequences. *Crit. Rev. Oncol. Hematol.* 2018, 129, 102–112. [CrossRef]

103. Mosarla, R.C.; Vaduganathan, M.; Qamar, A.; Moslehi, J.; Piazza, G.; Giugliano, R.P. Anticoagulation Strategies in Patients With Cancer: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* 2019, 73, 1336–1349. [CrossRef]

104. Kakkar, A.K.; Levine, M.N.; Kadziola, Z.; Lemoine, N.R.; Low, V.; Patel, H.K.; Rustin, G.; Thomas, M.; Quigley, M.; Williamson, R.C.N. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: The fragmin advanced malignancy outcome study (FAMOUS). *J. Clin. Oncol.* 2004, 22, 1944–1948. [CrossRef] [PubMed]

105. Klerk, C.P.W.; Smorenburg, S.M.; Otten, H.-M.; Lensing, A.W.A.; Prins, M.H.; Piovella, F.; Prandoni, P.; Bos, M.M.E.M.; Richel, D.J.; van Tienhoven, G.; et al. The effect of low molecular weight heparin on survival in patients with advanced malignancy. *J. Clin. Oncol.* 2005, 23, 2130–2135. [CrossRef] [PubMed]

106. van Doormaal, F.F.; Di Nisio, M.; Otten, H.-M.; Richel, D.J.; Prins, M.; Buller, H.R. Randomized trial of the effect of the low molecular weight heparin nadroparin on survival in patients with cancer. *J. Clin. Oncol.* 2011, 29, 2071–2076. [CrossRef] [PubMed]

107. Icli, F.; Akbulut, H.; Utkan, G.; Yalcin, B.; Dincol, D.; Isikdogan, A.; Demirkazik, A.; Onur, H.; Cay, F.; Büyükelik, A. Low molecular weight heparin (LMWH) increases the efficacy of cisplatinum plus gemcitabine combination in advanced pancreatic cancer. *J. Surg. Oncol.* 2007, 95, 507–512. [CrossRef] [PubMed]

108. Parpia, S.; Julian, J.A.; Thabane, L.; Lee, A.Y.Y.; Rickles, F.R.; Levine, M.N. Competing events in patients with malignant disease who are at risk for recurrent venous thromboembolism. *Contemp. Clin. Trials* 2011, 32, 829–833. [CrossRef] [PubMed]

109. NCCN. *Cancer-Associated Venous Thromboembolic Disease (Version 1.2019)*; NCCN: Plymouth Meeting, PA, USA, 2019; p. 98.

(c) 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).