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RESEARCH ARTICLE

Rationale, design and methodology of TESEO study: a registry of thrombosis and neoplasia of SEOM (Spanish Society of Medical Oncology)

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Abstract

Background and rationale Thromboembolic complications are a serious, preventable and common event in cancer patients that contributes to increasing morbidity and mortality. Despite increasing knowledge on cancer-associated thrombosis (CAT), there are still several aspects of diagnosis, clinical management, treatment and prognosis with uncertainties that are under-represented in randomized clinical trials. For this reason, the Spanish Society of Medical Oncology (SEOM) launched in June 2018 a registry of CAT.

Methods/design TESEO is an ongoing prospective, non-interventional, multicentric study in consecutive cancer patients with newly diagnosed of thromboembolic event (TEE). Eligibility criteria include being > 18 years with a histologically confirmed diagnosis of cancer and a symptomatic or incidental TEE confirmed with an imaging technique in the previous month or any time after the cancer diagnosis and signing of informed consent. The study consists of two types of integrated but independent prospective registries. Regular CAT sub-registry includes information on patient's cancer´s characteristics, anticoagulant treatment provided and outcome data. Special CAT sub-registry includes variables related to special situations of CAT that comprise patients with severe kidney failure, thrombocytopenia, high risk of bleeding related to the cancer or with coexistence of bleeding and patients who receive new treatments such a targeted therapy, antiangiogenics agents and immunotherapy. The registry considers the status of the cancer and the time to assess how the prognosis is changed based on when the thrombus occurs. Some outcomes such as rethrombosis, major bleeding, tumor progression and survival will be valued in various time intervals including 1, 3, 6 and 12 months after the even in the first year; and then every 6 months until the patient's death.

Results After 18 months and with 35 centers and researchers, the registry has 1128 patients.

Conclusion TESEO registry will provide clinical real-world evidence for prevention, treatment and complications of CAT in different scenarios that are under-represented in randomized clinical trials.

Keywords Registry · Real-world evidence · Cancer-associated thrombosis (CAT) · Venous thromboembolism · Pulmonary embolism · Deep vein thrombosis · Anticoagulation

Introduction and rationale

Venous and arterial thromboembolic complications are a serious, preventable and relatively common event in patients with cancer that significantly contributes to increasing the morbidity and mortality of these patients [1]. Approximately 20% of all venous thromboembolism (VTE) observed in the community occur in patients with cancer, and VTE is present in up to 50% of cancer patient autopsies [2, 3]. Several

TESEO Investigators: En un anexo el listado de todos los investigadores que hayan incluido algún paciente.

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studies with different statistical designs show that presence of a cancer increases the risk of VTE by 4 to 7 time [4]. In contrast, it is estimated that in around 2–12% of cases, VTE is the first manifestation of a hidden cancer which in theory offers an opportunity for its early diagnosis and treatment [5, 6].

VTE is an important cause of in-hospital death in patients with cancer. It is estimated that one in seven cancer patients will die from a potentially avoidable pulmonary embolism (PE) rather than from the cancer [7]. Moreover, VTE is associated with recurrent events, post-thrombotic syndrome, pulmonary hypertension, and bleeding events (as a result of anticoagulant therapy), all of which contribute to the high burden of the disease [8–10]. The risk of both recurrent VTE and major bleeding complications in anticoagulant treatment is higher in cancer patients compared to those without [11, 12]. Otherwise, VTE has a significant impact in healthcare costs nowadays. In United Kingdom the total cost of VTE treatment and management is estimated to be £640 million per year [13].

Despite increasing knowledge about cancer-associated thrombosis (CAT) over the past decades, there are still several aspects of diagnosis, clinical management, treatment and prognosis with uncertainties that need to be addressed. On the one hand, the risk of developing a VTE episode is not the same in all patients with cancer, or even in each patient over time, so that different etiopathogenic factors may interact in the same patient with different prognostic value depending on the time [14]. A wide variety of risk factors have been identified related to the cancer, the patient and the antineoplastic treatment. Although there are several scoring systems that attempt to assess the risk of a first VTE event, none of these is a sufficiently accurate tool to be applied within primary thromboprophylaxis strategies. Furthermore, despite there are factors related to rethrombosis or the risk of bleeding following the onset of VTE treatment, there is also no model that has demonstrated its usefulness in validation studies. Determining the factors related to rethrombosis or the risk of bleeding in patients with CAT provides more knowledge about VTE progression and allows us to construct a predictive model that would facilitate and improve the management of VTE in cancer patients.

On the other hand, in a small but significant percentage of cancer patients, VTE occur in special situations that complicate management and treatment of thrombosis, given that it is usually associated with greater uncertainty and lack of evidence about the optimal approach in such circumstances. These special situations comprise patients with temporary thrombocytopenia due to chemotherapy and/or radiation therapy or sustained chronic thrombocytopenia (splenomegaly, immune thrombocytopenia purpura (ITP), etc.); high risk of bleeding related to the cancer or its treatment or with coexistence of active bleeding; patients who receive new non-cytostatic treatments (targeted therapies, antiangiogenics, immunotherapy) and patients with severe kidney failure. However, only a few randomized clinical trials (RCTs) on CAT have been published in the last two decades CAT, and this trend is unlikely to change despite the knowledge that the course and complications of thrombosis differ in these patients from those without cancer.

Real-world evidence (RWE) and big data are emerging as new tools that can improve patient outcomes and eventually change our clinical practice. Accordingly, medical agencies around the world have focussed on RWE for multiple purposes. For this reason, the Cancer & Thrombosis Section of the Spanish Society of Medical Oncology (SEOM) has launched in June 2018 a specific national study of CAT (TESEO registry) to provide a prospective real-life information including special situations, rare conditions and areas, where randomized trials are extremely difficult if not impossible, to conduct. This information provides data with which to assess the effectiveness of the antithrombotic treatment used, the complications of the thromboembolic event (TEE) and thus enable us to develop useful therapeutic algorithms and generate hypotheses that contribute to planning new studies.

Objectives

The main objective of TESEO study (registry of Thrombosis & NEoplasia of SEOM) is to provide epidemiological and clinical data on CAT. One of the secondary objectives is to determine the factors related to rethrombosis and the risk of bleeding in patients with CAT to construct predictive models of rethrombosis and bleeding that would facilitate and improve the treatment of these patients. Another secondary objective is to provide data to aid in knowledge transfer in cancer patients in special scenarios that complicate the management of thrombosis such as those listed in the introduction. Finally, others secondary objectives will be to provide information in new areas of interest and specific oncological contexts including thrombosis associated with certain molecular or histological varieties of cancer and the new oncological treatments that have appeared in recent and future years (target therapies, antiangiogenics agents, immunotherapy, etc.).

Methods

Study design

TESEO is an ongoing epidemiological, prospective, non-interventional, multicenter study in cancer patients with a newly diagnosed VTE, which aims to collect the

characteristics of the thrombosis through an online web-based data registry for the purposes of biomedical research.

The main characteristics of the study is a multicenter and international online registry through a website operating system with a common and centralised data collection system for all the centers and investigators involved. The aim is to speed up access and use by researchers, under secure conditions while respecting the principles of data protection and confidentiality established by law. The variables are filtered and reviewed online to ensure the accuracy of the information.

Cases are recruited prospectively and consecutively to avoid selection bias. The selected data are collected from that recorded in the patients' clinical records according to the specification in the electronic Case Report Form (eCRF). This is a dynamic and progressive model that will allow the recording of new variables and situations as far as clinical practice justifies. The registry has a non-interventionist character to collect real-life data. Patients are treated according to the best local practice. No additional tests or procedures are required by the registry. Patients are included whether or not they receive anticoagulant therapy, so that the merit of current and future treatment strategies can be properly understood in relation to patients' individual risk profiles. The recruitment period is not established so the study will stay active as long as the wishes and capacity of the research team are maintained. We would like that patients will be followed to a minimum of 5 years, or until death to collect good outcome data. The registry has a scientific committee of six coordinators who agree on decisions and share them with the SEOM Thrombosis working Group.

TEE ranges from arterial thromboembolism (ATE) (myocardial infarction, ischemic brain stroke or ischemic leg amputation), VTE (deep vein thrombosis (DVT), PE), migratory thrombophlebitis (Trousseau syndrome) and non-bacterial thrombotic endocarditis, to systemic syndromes such as microangiopathic haemolytic anaemia and disseminated intravascular coagulation (DIC). Methods of DVT diagnosis include contrast venography, ultrasonography, magnetic resonance, or rarely, plethysmography. PE is diagnosed on the basis of pulmonary angiography, contrast-enhanced computed tomography (CT) of the chest (specifically CT pulmonary angiography), lung scintigraphy, or rarely on the basis of confirmed DVT in patients with signs and symptoms of PE. Most incidental events are diagnosed in an imaging study conducted to evaluate the cancer's response to systemic treatment.

The study consists of two types of integrated but independent prospective registries (Fig. 1). Type 1 registry o regular CAT sub-registry includes variables related to general CAT. These variables will be used to describe the characteristics of the first TEE in a general population of patients

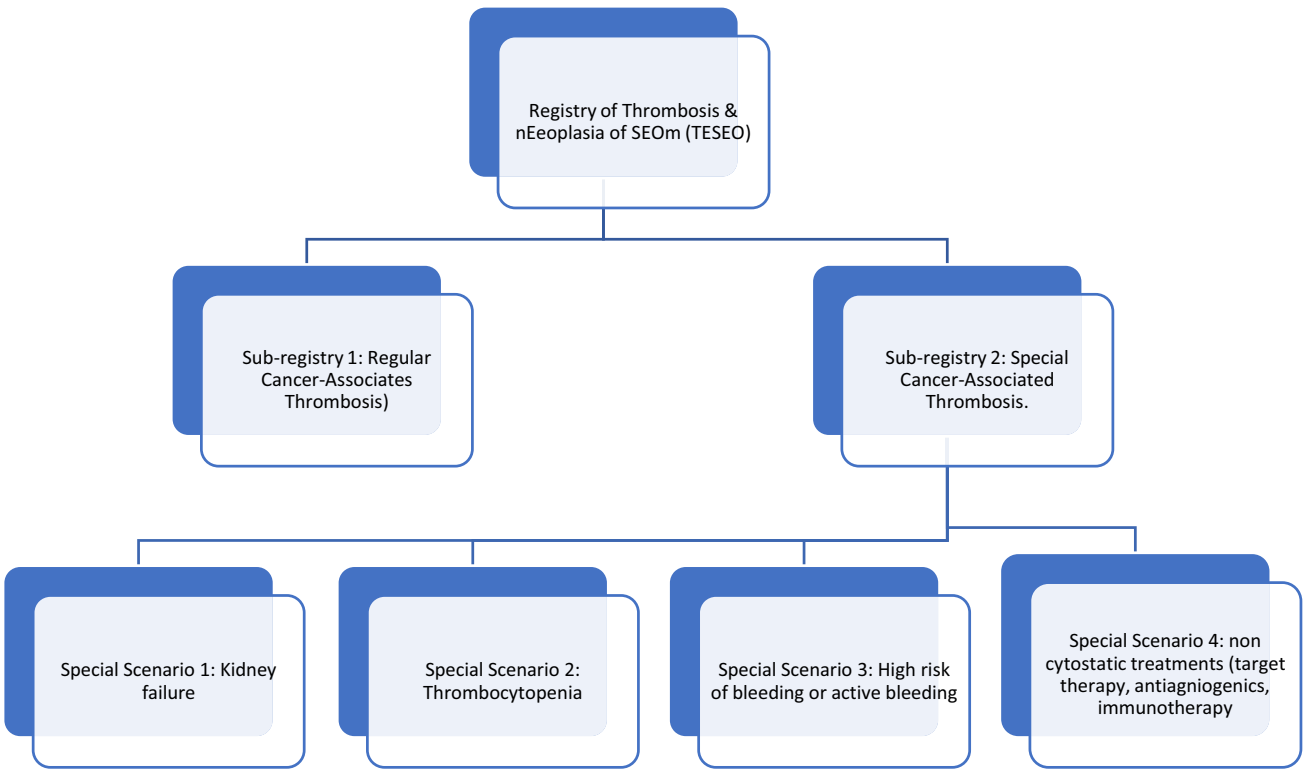

Fig. 1 Structure of TESEO Registry

with cancer and determine predictive factors of rethrombosis and the risk of haemorrhagic complications to construct each predictive model. Type 2 registry or special CAT subregistry includes variables related to special situations of CAT. In each patient who has a TEE within the framework of a special scenarios, the most relevant variables are collected according to the evidence and current clinical practice. These special situations are shown in Fig. 1: (a) patients with temporary thrombocytopenia due to chemotherapy and/or radiation therapy or sustained chronic thrombocytopenia (splenomegaly, immune thrombocytopenia purpura (ITP), etc.); (b) patients at high risk of bleeding related to the cancer (tumors at increased risk of bleeding such as stomach, pancreas, lung, lymphoma, glioma, genitourinary excluding prostate, melanoma and thyroid cancer; local tumor invasion, abnormal tumor vasculature or tumor regression); or related to the antitumor treatments including prior radiation therapy or chemotherapy and others drugs that may exacerbate bleeding such as nonsteroidal anti-inflammatories drugs (NSAIDs) and anticoagulants that are routinely used in cancer patients; or patients with coexistence of active bleeding (hemoptisis, gastrointestinal ulcer with hemorrhage ± perforation; gastrointestinal hemorrhage/bleeding/hematemesis; non traumatic hemorrhagic pleural effusion, hemoperitoneum, hemopericardium; subarachnoid hemorrhage, intracranial hemorrhage; hematuria, etc.); (c) patients who receive new non-cytostatic treatments (targeted therapies, antiangiogenics, immunotherapy); and (d) patients with severe kidney failure (creatinine clearance ≤ 30 ml/min).

The type record is used to obtain knowledge about the progress of TEE in each situation and to assess the effectiveness and safety of the treatment administered. In addition, the variables dependent on the cancer, its evolution and the response to systemic treatments are collected in detail to know their correlation with the TEE and outcomes. The date of each event is recorded to establish a temporal relation. This will allow us to build models, improve or validated those available.

For further information, please visit: http://www.registroteseo.es or https://clinicaltrials.gov/ (Identifier: NCT03855592).

Study population

At each participating site, consecutive patients with diagnosed of malignancy disease who present a TEE are screened by the investigators and checked for eligibility (Table 1). Eligibility criteria include being >18 years of age with a histologically confirmed diagnosis of malignancy; and a TEE, either symptomatic or incidental, confirmed with an imaging technique in the previous month or any time until 2 years after the cancer diagnosis.

Patients treated for cancer who are under disease-free follow-up for less than 2 years and have a thromboembolic event, such event will be considered cancer-related and could be included in the registry whether or not tumor recurrence is demonstrated. However, cancer patients in follow-up after being treated for more than 2 years and presenting a thromboembolic event, this event will be considered related to the cancer and could be included in the registry if tumor recurrence is demonstrated in the 12 months after the event. Before data collection, all participants provide written, signed, informed consent.

Patients with clinical diagnosis of TEE without radiological confirmation or with a single episode of superficial thrombophlebitis without association with another TEE are excluded. Each patient is recorded only once, and therefore, a second TEE is considered a rethrombosis and recorded as such. Patients with a rethrombosis and a previous TEE before the start of the study at each center and patients enrolled in blinded treatment trials are ineligible. Lack or withdrawal of patient consent is a criterion for exclusion.

Table 1 Inclusion and exclusion Criteria for TESEO Registry

Inclusion criteria
Over 18 years of age
Histologically confirmed malignant tumor
Venous or arterial thromboembolism episode, symptomatic or incidental, confirmed with an imaging technique, in the month prior or any time until 2 years after the cancer diagnosis.
Signing of informed consent
Exclusion criteria
Clinical diagnosis of TEE without radiological confirmation
A single episode of superficial thrombophlebitis without association with another TEE
Patients with a previous TEE before the start of the study
Previous enrollment in the registry: a second TEE is considered a rethrombosis and recorded as such
Patients enrolled in blinded treatment trials
Lack or withdrawal of patient consent

Study variables

Two types of variables are collected in the TESEO registry. For all patients, *general variables* are collected. These are related to demographic and clinical patients characteristics (date of birth, sex, ethnicity, general health status, weight, height, smoking history, thrombosis history, coagulopathy history, Charlson comorbidity index, etc.); characteristics of the tumor at the time of the TEE (origin, histological type, stage, molecular biomarkers, etc.); characteristics of cancer treatment (type of antineoplastic therapy [surgery, chemotherapy, radiation therapy, hormonal therapy, target therapy, immunotherapy]; type of supportive treatment [erythropoietin, blood red or platelet transfusions]; purpose [adjuvant, neoadjuvant, palliative]; line of systemic treatment; venous catheter, etc.); characteristics of TEE (date, type [venous/arterial], finding [incidental/symptomatic], symptoms, vital signs, treatment [outpatient/hospitalised], imaging findings); characteristics of laboratory parameters at the time of the TEE; and description of the anticoagulant treatment administered (drug, dose, other therapies, etc.) and outcomes, causes and dates (rethrombosis, bleeding, tumor progression, death, etc.).

In the case of patients in special situations discussed above, variables and laboratory and radiological parameters are collected according to the specific clinical situation. A description of the therapeutic adjustment in each special situation is also recorded.

Outcome

The main outcomes of interest from the TESEO study include VTE recurrent; major bleeding and clinically relevant non-major bleeding (CRNMB); ATE; prevalence of TEE by type of cancer or treatment administered, molecular biomarkers; side-effects of the prescribed anticoagulant therapies; all-cause of death, tumor progression and survival; and therapeutic algorithm used in each special situation.

The Subcommittee on Control of Anticoagulation of the International Society on Thrombosis and Haemostasis (ISTH) recommends the following criteria for major bleeding in non-surgical patients: [1] Fatal bleeding, and/or [2] Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or [3] bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells [15].

The same subcommittee recommend the following criteria for the definition of clinical relevant non-major bleeding in non-surgical VTE studies: any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: [1] requiring medical intervention by a healthcare professional; [2] leading to hospitalization or increased level of care; [3] prompting a face to face (i.e., not just a telephone or electronic communication) evaluation [16].

Of all these variables, the date on which they occur is collected to establish temporal associations between cancer events and those related to the TEE or its treatment.

Some outcomes such as rethrombosis, major bleeding, CRNMB, complications, tumor progression and survival are assessed at various time intervals, including 30 days, 3, 6 and 12 months after the even in the first year; and then every 6 months for a minimum of 5 years or until death.

Description of registry

The registry is support by the SEOM and its standardization and scientific committees (SSC) is made up of six coordinators from the Cancer & Thrombosis Section of the SEOM.

This registry collects data via an eCRF using a validated electronic data capture (EDC) system. This database is housed on a secure server at MFAR Clinical Research CRO. The high quality of data is enhanced by the supervision of an independent audit committee, which oversees site-dependent verification, remote site monitoring and electronic database monitoring.

The organisation of the case registry is based on a network of investigators and co-investigators distributed throughout Spain and is currently being initiated at centers of Portugal and is expected to be expanded to other countries. All participating researchers are physicians who care for cancer patients and have authorisation to access the TESEO eCRF to register new cases or update previous cases. Professionals acting as "notifiers" may belong to different medical specialities (oncologists, internal medicine physicians, haematologists, pneumologists, vascular surgeons), belong to public and private hospitals, who generously support data collection.

The study receives funding by the sponsor (SEOM) and from funds provided by a research grant from Sanofi laboratory for structural and administrative support.

Ethical issues and authorization

The researchers adhere strictly to the provisions put forth in the protocol, the rules of good clinical practice and confidential treatment of personal data. The study is carried out in compliance with current safety legislation and established in Spanish Organic Law 3/1018 and EU Regulation 2016/679 of the European Parliament and of the Council on the Protection of Personal Data.

Prior to inclusion in the study, patients receive all the information about the registry, a patient information sheet and after clarifying all their doubts and agreeing to participate, they sign an informed consent form. Participants can refuse to consent and revoke such consent once given. Only the notifiers are aware of the full identification of their patients. The personal data recorded in the eCRF is gender and date of birth. Thus, no sensitive or identifying information is recorded.

The study was approved by the Research Ethics Committee of all the Autonomous Communities and participating hospitals and was classified as a prospective, post-marketing surveillance study by the Spanish Medicines and Health Products by the Spanish Agency of Drugs and Medical Devices (*Agencia Española de Medicamentos y Productos Sanitarios*, AEMPS).

Discussion

Although RCTs are the gold standard for evaluating the safety and efficacy of new therapies, they are subject to rigorous inclusion and exclusion criteria, and, therefore, may not be geographically or clinically applicable to real-world settings. In contemporary clinical research, there is a move towards collecting evidence from observational studies. Large prospective disease registries have a number of advantages over RCTs. These include: (a) avoiding bias and allowing the full range of clinical evidence to be explored in terms of patient types, clinical settings and outcomes; (b) informing clinicians and policy makers about under-represented groups, such as the elderly, women during pregnancy and those with existing comorbidities (e.g., kidney failure or high risk of bleeding), for whom disease management may be a challenge; and (c) documenting routine clinical management at a national and global level.

Most international thrombosis registries are not specific or exclusive for cancer patients but collect data on VTE in the general population. Some of them include only a specific type of VTE [PE [17–19], splanchnic thrombosis [20]], while others include several types of VTE [the MASTER registry [21], the SWIss VTE registry [22], the PREFER registry [23], the VTEval project [24] and the RIETE registry [25]. It is important to recognise that these registries differ in their design, recruitment strategies, care setting, geographic spread and duration of follow-up (see Table 2).

Of all these, the RIETE registry is the largest and most important VTE registry in general population by the number of patients included, 75,000 patients and the number of countries and centers involved. The RIETE, a multinational, prospective registry started in Spain in 2001, has offered an extraordinary amount of evidence with more than 120 articles published in the main journals. It is an excellent example of a clinical registry that has helped clinicians to improve their knowledge in VTE and patient care. Nevertheless, RIETE is not a registry of CAT so important specific variables related to VTE risk in cancer patients are not collected. In the last decade we have learnt that these variables have a significant impact in VTE. For example, ALK-rearranged non-small-cell lung cancer (NSCLC) is associated with a higher rate of VTE than other NSCLC ranging from 30–47%, and with a deep impact in overall survival [26, 27]. Furthermore, chemotherapy has classically been considered as an independent risk factor for VTE [4]; however, the risk of VTE is not homogenous among different cytostatic agents, even inside the same drug category. Cisplatin, an alkylating agent, has been associated with the highest risk of thrombosis [28]. Nevertheless, a fewer incidence of VTE has been described with other platinum analogues, oxaliplatin and carboplatin [29]. With all this amount of evidence we can no longer consider chemotherapy or type of cancer as single and homogenous risk factors for CAT, and specific approach and more detailed and concise analysis of the VTE risk in cancer patients should be carried out. In addition, most of the cancer patients included in the RIETE registry were diagnosed more than 15 years ago, when targeted therapies and immunotherapy were not available. Also, over the last decade, the risks of TEE and diagnostic imaging methods have changed, there is a better awareness of TEE among oncology specialists, and a greater availability and adherence to clinical guidelines. These facts may make that patients included in RIETE and TESEO are not comparable and may not provide the same information. Therefore, TESEO can be a good complement to the RIETE registry, more adapted to the current reality of CAT.

There are few specialized or cancer-focused thrombosis registries. Most of them only include patients with some type of VTE, and some have closed recruitment with a short follow-up. Below we briefly describe the most relevant of these CAT registries.

GARFIELD-VTE is an international, multicenter, observational, and prospective study of patients with newly diagnosed VTE [30]. The aim of this global registry is to follow patients for at least 3 years and observe management according to local practices, recording clinical, patient-reported and economic outcomes. One of the initial objectives was to perform a specific analysis of the subgroup of patients with cancer. The registry enrolled more than 10,000 patients with DVTand/or PEfrom 415 sites in 28 countries worldwide, including the Americas, Europe, Africa and Asia–Pacific and completed the follow-up in 2020. The GARFIELD-VTE registry is supported by an unrestricted educational grant from Bayer AG, Berlin, Germany. See https://vte.garfieldregistry.org/ for more information.

PERCEIVE (Prospective Registry of Cancer and Events Involving Venous Thromboembolism) is a large prospective,

Table 2 Features about some of the large prospective VTE registries both in global population and only dedicated cancer patients

Registry	Patients enrolment	Setting	End points	Follow-up
General Population (included cancer patients)				
EMPEROR [18]	Adults with objectively confirmed PE. January 2005 to December 2008	Emergency departments from 22 academic and community hospitals in the United States. Sample size: 1880	To define the presenting symptoms, signs, risk factor profile, treatments (including use of anticoagulants), and short-term outcomes of patients with PE presenting to emergency departments	Main follow-up was up to 30 days.
IPER [19]	Adults with objectively confimed PE. September 2006 to 2010	47 hospitals from Italy. Sample size: 1717	To describe the demographics, risk factors, clinical features, and outcomes of patients with VTE during short-term and long-term follow-up	NA, follow-up ended in August 2014
MASTER [21]	Adults with objectively confimed VTE January 2002 to October 2004	25 centers from Italy Sample size: 2111 Patient management was at the discretion of the attending physicians	Similar to IPER (see above)	All patients were followed up to 24 months
SWIVTER [22]	Adults with objectively confirmed VTE. January 2009 to May 2010	18 hospitals in Switzerland. Sample size: 1247	A study to determine characteristics of patients with VTE, and key subgroups, including the elderly, and those with cancer	No systematic follow-up beyond hospital discharge
PREFER-VTE [23]	Adults with diagnosis of acute VTE (primary or recurrent); recruitment aim ratio of PE:DVT of 2:3 Target: 3600	European registry of 381 sites in 7 countries (Austria, France, Germany, Italy, Spain, Switzerland, and the UK). Patients managed according to local standard practice	12-month direct healthcare resource utilisation; assessment of the real-life acute and mid-term management of patients with VTE (prevention of VTE recurrence, treatment of bleed- ing), incidence of recurrent DVT/PE, myocardial infarction, stroke, systemic embolic events, PTS and death	≥1 year
VTEval Project [24]	Adults with a clinical suspicion of either: acute PE (with or without DVT) (cohort 1), acute DVT (without symptomatic PE) (cohort 2) or with an incidental diagnosis of VTE (PE or DVT) (cohort 3). Target: 2000 (unclear details). Estimated last follow-up: 2023	Started as single center study at University Medical Center of the Johannes Gutenberg University Mainz, Germany, with plan to involve more centers	To determine the symptoms, risk factors, as well as psychosocial, environmental and lifestyle factors associated with VTE. The study is also collecting blood samples for future "omics" studies, on genome, transcriptome, proteome, metabolome and phenome	Active follow-up is planned for 36 months and passive follow-up of patients up to 5 years

Table 2 (continued)

Registry	Patients enrolment	Setting	End points	Follow-up
RIETE [25]	Adults with objectively- confirmed VTE. In recent years, also enrolling patients with thrombosis at unusual sites. 72,107 patients as of June 2017. Still recruiting	179 centers from 24 countries	To describe the epidemiology, treatment patterns and outcomes of a large group of patients with VTE, including many of the understudied subgroups. Also, to provide a platform for several additional investigations, including pragmatic trials	Minimum follow-up for 3 months, but many have longer follow-up
GARFIELD-VTE [30]	Patients with newly diagnosed VTE: DVT and/or PE (either primary or recurrent). Target: 10,000 planned To date: 10,874 Recruitment is completed	415 sites from 28 countries from nationally representative clinical settings (hospital and community). Patients are managed according to local standard practice	Exploring acute and long-term management and outcomes in patients with symptomatic DVT and PEs treated in a real-world setting with standard therapy and new oral anticoagulants (OACs). The treatment for VTE: VTE recurrence (early & late): Bleeding complications; All-cause mortality; VTE complications	Minimum follow-up for 36 months. Estimated last follow-up: 2019
Only dedicated Cancer Patients				
PERCEIVE (https://www.perceiveregistry.org.)	Adults with newly diagnosed malignancy of the breast, colon and rectum, pancreas, lung, prostate or ovary. To date: 6822 (initiated in February 2005)	Nine hospital cancer centers in 6 countries (Austria, India, Italy, Singapore, UK, USA). Patients are treated according to local best practice	Incidence of VTE, stroke, myocardial infarction, bleeding and mortality over 10 years from diagnosis of cancer	10 years or until death
ISTH Registry [31]	Patients with active cancer who developed an objectively verified new VTE within the previous 12 months while receiving anticoagulant treatment. Target: 200 patients	Seventeen sites in 10 countries contributed a total of 212 cases. From 30 June 2004 to 4 June 2014	To explore different antithrombotic regimens used to manage patients with cancer and new VTE despite anticoagulation, and to assess the 3-month incidence of rethrombosis and bleeding	Until death or for a maximum of 3 months
Cancer-VTE registry [32]	patients with colorectal, lung, stomach, breast, gynaecological or pancreatic cancer between, that planned initiation of cancer therapy and VTE screening with venous ultrasonography in the 2 months prior to registration	This registry intended to enrol 10,000 patients between March 2017 and March 2019, In more than 20 Japanese centers	Incidences of symptomatic and incident TEE, bleeding events, stroke, overall and symptomatic VTE-free survival	1 year

Table 2 (continued)

Registry	Patients enrolment	Setting	End points	Follow-up
TESEO (http://www.registroteseo.es)	Cancer patients who developed a TEE, either symptomatic or incidental, confirmed with an imaging technique in the previous month or any time until 2 years after the cancer diagnosis. No sample size is planed (unlimited). Start in June 2018	At this moment, 37 centers from Spain and Portugal have recruited 939 patients. Patients managed according to local standard practice	To provide epidemiological and clinical data on CAT; incidence and risk factors related to rethrombosis and bleeding. To provide information in new areas of interest (thrombosis associated with certain molecular or histological varieties of cancer, new oncological treatments, etc.)	minimum for 5 years or until death

EMPEROR: Multicenter Emergency Medicine Pulmonary Embolism in the Real-World Registry

IPER: The Italian Pulmonary Embolism Registry

MASTER: Multicenter Advanced Study for a ThromboEmbolism Registry

SWIVTER: The SWIss Venous ThromboEmbolism Registry (SWIVTER)

PREFER-VTE: Prevention of thromboembolic events–European registry in venous thromboembolism. At UK research Network Portfolio Database http://public.ukcrn.org.uk/search/StudyDetail.aspx?Stu-dyID=15273

VTEval Project: Prospective Cohort Studies to Evaluate and Improve Diagnostics, Management Strategies and Risk Stratification in VTE. https://clinicaltrials.gov/ct2/show/NCT02156401

RIETE registry website https://www.riete.org/info/general/index.php

GARFIELD-VTE: Global Anticoagulant Registry in the FIELD. Thrombosis Research Institute at https://vte.garfieldregistry.org

PERCEIVE: Prospective Registry of Cancer and Events Involving Venous Thromboembolism at https://www.perceiveregistry.org

ISTH Registry: The international registry on recurrent VTE in anticoagulated patients with cancer within the subcommittees of anticoagulation control and hemostasis and malignancy of the International Society on Thrombosis and Haemostasis (ISTH)

TESEO: registry of **T**hrombosis & N**E**oplasia of **SEOM** (Spanish Society of Medical Oncology). At http://www.registroteseo.es or https://clinicaltrials.gov/ (Identifier: NCT03855592)

PE pulmonary embolism, *VTE* venous thromboembolism, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *OACs* new oral anticoagulants, *NA* not available, *PTS* post-thrombotic syndrome, *TEE*: thromboembolic event, *CAT*cancer associated thrombosis

non-interventional cancer registry designed to record TEE and cardiovascular events in patients with a newly diagnosed cancer of the breast, colon and rectum, pancreas, lung, prostate or ovary. This multi-center, international registry recruited patients from North America, Europe and Asia, allowing comparison of different strategies and includes up to 11 years follow-up to assess the long-term risk of VTE. Recruitment began in 2004 and has been closed. See https://www.perceiveregistry.org/ for more information.

The international registry on recurrent VTE in anticoagulated patients with cancer was launched in 2006 within the subcommittees of anticoagulation control and hemostasis and malignancy of the International Society on Thrombosis and Haemostasis (ISTH) [31]. The aims were to explore what different antithrombotic regimens were used to manage patients with cancer and new VTE despite anticoagulation, and to assess the 3-month incidence of rethrombosis and bleeding. Eligible patients were those with active cancer, who developed an objectively verified, new VTE within the previous 12 months while receiving anticoagulant treatment. Seventeen sites in 10 countries contributed a total of 212 cases, from 30 June 2004 to 4 June 2014. Patients were followed until death or for a maximum of 3 months.

The cancer-VTE registry is a cross-sectional Japanese cohort study based on a multicenter, prospective clinical registry. The study includes two main components with different study designs: a cross-sectional study aiming to clarify the frequency of VTE complications in the sample population, and a cohort study aiming to determine 1-year patient outcomes [32]. This registry intended to enrol 10,000 patients with colorectal, lung, stomach, breast, gynaecological or pancreatic cancer between March 2017 and March 2019, that planned initiation of cancer therapy and VTE screening with venous ultrasonography in the 2 months prior to registration. At baseline, complication rates of VTE and analysis of VTE risk factors will be collected. After 1 year of follow-up, the following data will be collected: incidences of symptomatic and incident TEE, bleeding events and stroke, overall and symptomatic VTE-free survival. One of the limitations of this study is that not all cancer types will be represented.

TESEO registry is an international, multicenter, non-interventional, prospective study designed to record comprehensive data on CAT which has been described in detail throughout this article. The registry provides information on the prevention and treatment of CAT and its complications (rethrombosis, bleeding, etc.), in clinical practice situations that are under-represented in RCTs. Compared to other VTE registries, TESEO has the potential to capture the burden of disease in large-scale populations by employing broad inclusion criteria and also special populations and long-term follow-up data. The TESEO study seeks to provide insights on the impact of anticoagulant therapy on rethrombosis and bleeding complications observed in the general population with CAT and an infrequent but complex specific population of patient at higher potential risk of complications (Fig. 1). It will provide a better understanding of the potential opportunities to improve care and clinical outcomes amongst cancer patients in these special situations o scenarios and patients who receive new treatments such as targeted therapy, antiangiogenics agents and immunotherapy or suffering from cancers with specific molecular and pathological characteristics. This should help physicians and healthcare systems to appropriately adopt innovation to ensure the best outcomes for cancer patients. Another feature of TESEO that differentiates it from other registries is the fact that all patients with CAT are included regardless of the type of TEE and whether they receive anticoagulant therapy or not, so that the merit of current and future treatment strategies can be properly understood in relation to patients' individual risk profiles. Also, contrary to some of the other registries, despite receiving funding from various groups, TESEO is independently investigator-driven and data are entirely managed by the investigators. The funders are not involved in the development of the protocols, nor in the exploitation and dissemination of the information.

Finally, in the era of the "omics", new data are emerging that should be considered in the registries. The next challenging step is to collect biological specimens from both, patient and tumor to perform a translational approach and correlate it with clinical information. RWE and big data can generate not only high-quality evidence, but also improve patients' outcomes through changes in clinical practice. Interestingly, this approach might allow data generation for clinical settings, where RCT do not always answer these issues.

In conclusion, TESEO is an ongoing prospective and dynamic registry of TEE in patient with cancer. It is expected that TESEO will provide clinical RWE for prevention and treatment of CAT and its complications (rethrombosis, bleeding, etc.) in many possible scenarios that are under-represented in RCTs. Nowadays the landscape of oncology is rapidly evolving and this registry will be adapted to include new biomarkers and treatments implemented in the clinical practice.

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Compliance with ethical standards

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