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Tinzaparin for the prevention of thromboembolic events in ambulatory patients with metastatic colorectal cancer receiving first line treatment: a randomised, clinical trial design

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Abstract

Background Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide. CRC leads to increased activation of the clotting system. Since CRC patients present a higher rate of bleeding, careful evaluation of the risk/benefits of anticoagulant prophylaxis is necessary.

Aims To evaluate low molecular weight heparin (LMWH) for primary thromboprophylaxis in metastatic CRC outpatients receiving first-line systemic cancer therapy.

Methods PROTINCOL (NCT05625932) is a randomized, open-label (PROBE), multicenter study. Patients will receive tinzaparin (75 IU/kg) or no pharmacological prophylaxis for 4 months and will be stratified based on: *BRAF/RAS* mutation, primary resection tumor and antiangiogenic therapy. The study outcomes will be assessed by a blinded central independent adjudication committee.
The primary efficacy endpoints will include the cumulative incidence of any venous thromboembolism (VTE) event (symptomatic or incidental) including symptomatic central venous catheter VTE. Secondary variables will be clinically relevant bleedings, health-related quality of life and the predictive value of validated risk assessment scales of VTE, including the genetic risk score (TIC-ONCO).

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Our hypothesis is that prophylactic LMWH will reduce the 55% relative risk to an estimated VTE incidence of 13.5%. A total of 526 patients will be required.

Discussion Risk prediction of chemotherapy-associated VTE is a compelling challenge in oncology, as VTE may result in treatment delays, impaired quality of life, and increased mortality. Patients with a single type of metastatic cancer with a high risk of VTE will be selected for study inclusion.
For the first time in ambulatory prophylaxis of cancer-associated thrombosis, a precision medicine approach will be used in a clinical trial.
If the individualization of antithrombotic prophylaxis can reduce the complications of outpatient cancer treatment and be cost effective, it would be of great value in the future care of patients with metastatic CRC.

Trial registration NCT05625932. Registered on 15 Nov 2022.

Trial status The trial started recruitment on March 2023.

Keywords Thromboprophylaxis, Venous thromboembolism, Metastatic, Colorectal cancer, Risk factors, Genetics

Background

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second-leading cause of cancer deaths worldwide [1, 2]. Among new CRC diagnoses, approximately 20% of patients present with metastatic CRC (mCRC), and another 40% of previously localized disease will later develop metastases, typically involving the liver or lungs [3].

CRC leads to increased activation of the clotting system, while certain coagulation proteins, such as tissue factor, have upregulated expression in CRC tumors, which may lead to biologically more aggressive cancers, and consequently, to poorer outcomes [4]. This risk is further heightened by all cancer therapies. The incidence of venous thromboembolism (VTE) in patients with CRC has been reported to be of approximately 10%, especially in patients with advanced disease and within the first 6 months after cancer diagnosis [5–7].

Thrombotic events in patients with active cancer may lead to complications in anticancer treatment, which may cause delays in receiving treatment and affect treatment outcomes, thereby contributing to psychological and physical stress. These effects may also exacerbate the socioeconomic burden of cancer and may induce a negative impact on the patient's quality of life [8].

Considerable efforts have been made to identify patients with cancer at high risk of VTE, and to select those who have an appropriate benefit-risk ratio for prophylactic anticoagulant therapy. Khorana's predictive model is usually recommended to identify patients with a high risk of developing thromboembolic complications in an outpatient setting [9]. However, this tool has several limitations. In studies conducted in Spain and Portugal, more than 90% of patients with VTE were classified as having low or intermediate risk [5, 10]. Recently, a new risk assessment model of VTE based on clinical and genetic variables has been developed and externally validated, improving the capacity of predicting VTE compared to the Khorana score [11]. Current guidelines do not recommend routine thromboprophylaxis in ambulatory cancer patients, but it should be considered in high-risk patients [9, 12, 13].

Need for a trial

CRC is a heterogeneous disease from a molecular point of view. Approximately 55% of patients with metastatic CRC have mutations in the *KRAS* or *NRAS* genes. In addition, *BRAF* mutations occur in another 10% of cases [5, 14]. It has been suggested that *KRAS* mutation in patients with mCRC could increase the risk of VTE [5]. However, data are conflicting and other biomarkers, such as *BRAF* mutation in metastatic patients, have recently been identified as possible risk factors of thrombosis in cancer patients [5, 7]. In addition, CRC has the potential to develop bleeding, leading to greater doubt regarding risk-benefit relationship. The burden of bleeding varies in sub-groups of patients, such as higher bleeding rates in patients without primary tumor resection or in those treated with antiangiogenic therapy.

Two main randomized control trials have evaluated the impact of thromboprophylaxis with low molecular weight heparins (LMWHs) in various types of cancer. The SAVE ONCO [15] trial studied the use of semuloparin, and the PROTECHT trial [16] examined the use of nadroparin. In both studies, the median duration of prophylaxis was approximately 4 months.

The PROTINCOL study has been designed to evaluate the efficacy and safety of tinzaparin versus placebo for primary thromboprophylaxis in metastatic colorectal cancer outpatients receiving systemic cancer therapy and are at risk of VTE.

Patients and methods

Study design and setting

PROTINCOL (NCT05625932) is an investigator-initiated, phase III, randomised, open-label (PROBE), non-placebo controlled, low intervention, multicentre study designed to compare the efficacy and safety of tinzaparin

versus placebo as primary prophylaxis of VTE in ambulatory patients with metastatic CRC scheduled to initiate first line systemic cancer therapy. The SPIRIT Checklist are attached as Additional file 1.

The study consists of 3 periods: a 4-week screening period, a 4-month post-randomisation period, and a post-prophylaxis follow-up period until the last visit, scheduled 2 months after withdrawal or 6 months after randomisation (whichever is more recent). The duration of participation in the study for each subject is approximately 6 months. A further 18 months of follow-up by telephone could be carried out at the end of the study to monitor for progression and survival. Tumour follow-up assessments will adhere to the standard clinical practice of each participating site (Fig. 1).

The study will be carried out in 40 centres in Spain and Portugal (a list of participating centres and study sites can be obtained from ClinicalTrials.gov identifier: NCT05625932). The inclusion of patients started in March 2023.

Patients will provide written informed consent before initiation of any study-related procedures, and the study will be conducted following the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory and country-specific requirements. This study has been approved by the independent ethics committee of the participating centres and the pertinent health authorities.

Rationale for the prospective randomised open-label blinded evaluation design

An open-label, non-placebo-controlled trial design was chosen to avoid the use of a 4-month daily placebo injection in the control group, which may reduce the willingness of patients with advanced cancer to participate in the study. The majority of studies with LMWH are not blinded, even the more recent one [17]. Furthermore, since quality of life is a secondary objective, the injection of a placebo could alter the perception of quality of life.

The study already includes a blinded endpoint (PROBE) design for VTE and bleeding events. The assessment of the study outcomes made by a central independent adjudication committee unaware of study treatment allocation is a reasonable guarantee of the appropriateness as well as the consistency of the assessment of study outcome events in the two groups.

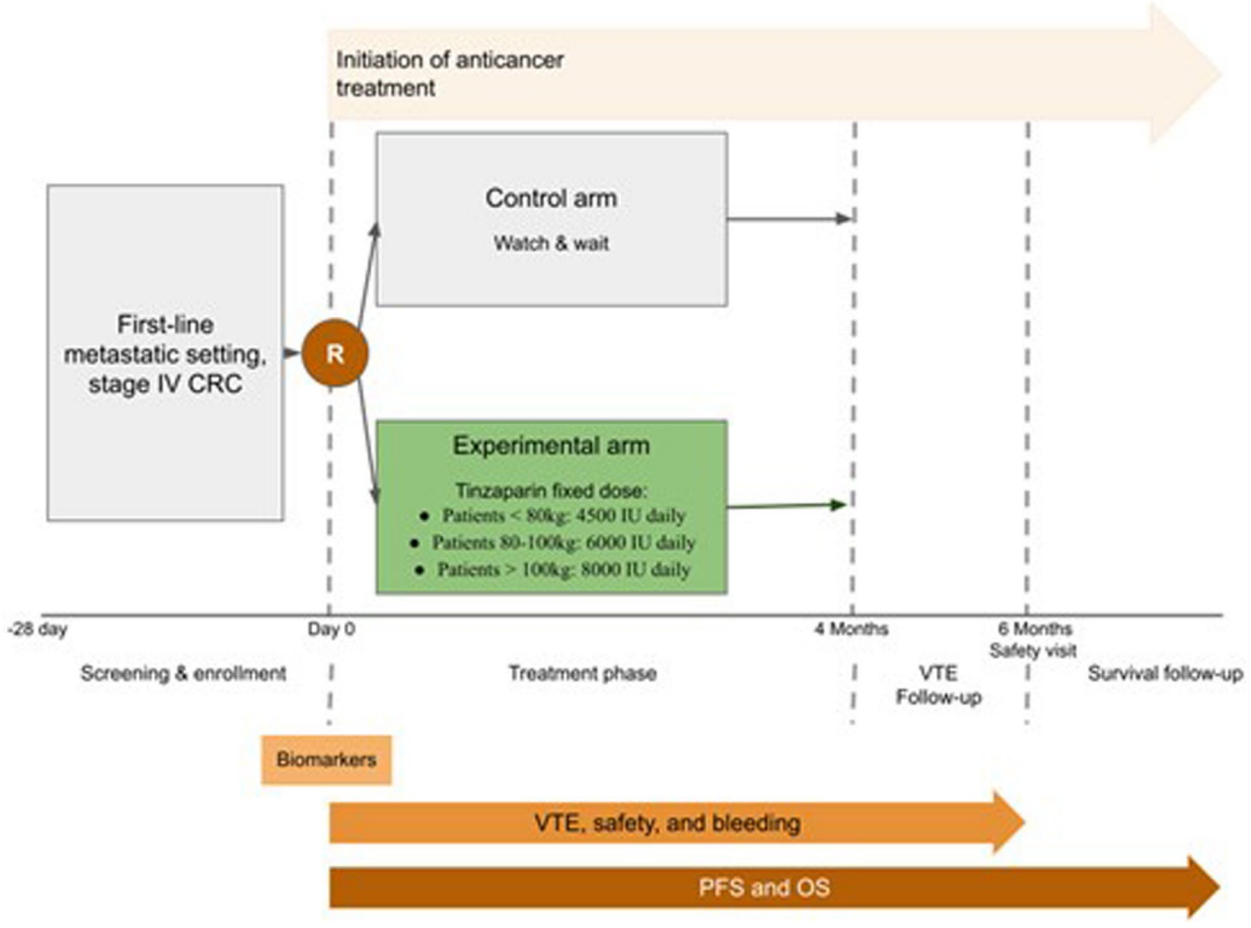

Fig. 1 Study schema

Study population and eligibility

Consecutive ambulatory patients with a histologically confirmed diagnosis of stage IV colon or rectal adenocarcinoma (mCRC) scheduled to initiate systemic cancer therapy, in whom *BRAF* and *RAS* genomic alterations are available during screening, have a life expectancy greater than 6 months and are considered by the investigator to be candidates for thromboprophylaxis based on their clinical status will be eligible to participate in the study.

Patients will be excluded if they have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 3 or more or have active bleeding or are at risk for bleeding (i.e. with severe renal insufficiency -creatinine clearance < 30 ml/min- or platelet count lower than 80,000/mL). Patients with any contraindication to the use of LMWH will also be excluded. In order to avoid overdose, patients weighing less than 50 kg will also be excluded. Full selection criteria are attached as additional file 2.

Study treatments and treatment allocation

All the patients included will receive the first-line anticancer treatment deemed most appropriate according to physician criteria and current guideline recommendations. Patients will receive care for their cancer following the standard clinical practices of the participating sites. Enrolled patients will be randomised in a 1:1 ratio to the control or the experimental arm:

- Patients allocated in the control arm will receive no interventions related to VTE risk. No placebo will be administered to avoid producing discomfort in these patients who are already receiving cancer treatment.
- The participants randomized to the experimental group will be separated into 3 groups according to weight. One group will include patients weighing > 100 kg and these patients will receive 8000 units subcutaneously (sc) daily of tinzaparin. Another group will include patients weighing 80 to 100 kg who will receive 6000 units sc daily of tinzaparin. Finally, patients < 80 kg in weight will be included in a third study group and will receive 4500 units sc of tinzaparin daily. Accordingly, the effective dose of tinzaparin is estimated to be in the range of 56–90 IU/kg. The first administration of the drug will be supervised by the study personnel (i.e. nurse) at the study site. Tinzaparin will be started on the same day chemotherapy is started. Subsequent tinzaparin doses will be self-administered by patients at-home. Thromboprophylaxis could be stopped in case of unacceptable toxicity, patient consent withdrawal or physician criteria. Tinzaparin dose reduction for toxicity management will not be permitted.

Although bleeding is a secondary criteria, careful evaluation of the risk/benefits of anticoagulant prophylaxis is necessary. With the intention that the risk factors for thrombosis and bleeding are well balanced, patient's randomisation (1:1 ratio) will be stratified based on:

- *BRAF/RAS* mutation.
- Primary tumour resection.
- Antiangiogenic therapy.

A. Rationale of LMWH tinzaparin administration in cancer patients.

The clinical value of tinzaparin for the treatment of cancer-associated thrombosis has been demonstrated in four randomised controlled trials in which the effectiveness and safety of tinzaparin have been described [18–22].

Real-life data are available on the use of tinzaparin in thromboprophylaxis in 407 patients with different types of cancer treated on an outpatient basis (8% CRC). Tinzaparin was administered at an intermediate dose (8,000-12,000 Anti-Xa IU; once daily) to 52.4% of patients, while the remaining patients received a prophylactic dose (4,500 Anti-Xa IU; once daily). The average duration of prophylaxis with tinzaparin was 5.0 ± 3.1 months. Furthermore, a favorable benefit/risk ratio was observed with a total of 14 (3.4%) thrombotic events and an acceptable safety profile (1.5% minor bleeding events) [23].

B. Rationale for dose of tinzaparin adjusted to body weight.

The 75 IU/kg dose of tinzaparin has previously been used for VTE prophylaxis in pregnant women and in patients undergoing orthopaedic surgery [24–26]. In hip replacement surgery, patients received doses of tinzaparin ranging from 50 IU/kg to 90 IU/kg [26]. In all these studies tinzaparin showed a good safety profile [27–29].

Higher doses were used in the Tinzaparin in Lung Tumors (TILT) study. Patients with completely resected stage I, II, or IIIA non-small cell lung cancer were randomly assigned to receive subcutaneous tinzaparin 100 IU/kg once daily for 12 weeks or no treatment in addition to standard care. Only two patients in the tinzaparin group (0.74%) (versus none in the control group) experienced a major non-fatal bleeding event during the treatment period [24].

More recently, a retrospective observational study conducted in 110 patients with advanced or metastatic pancreatic cancer was conducted with the aim of evaluating the anticancer effect of tinzaparin [25]. In terms of safety, patients who received high prophylactic doses of tinzaparin (10000 anti-Xa IU/day) during chemotherapy

with nab-paclitaxel and gemcitabine presented only two non-major bleeding events (1.9%; 95% confidence interval, 0.5–7.6%).

Study objectives and outcomes

The primary hypothesis of the study is that patients with mCRC scheduled to receive systemic cancer therapy have an increased risk of VTE. Therefore, the main objective is to evaluate the efficacy of 4 months of prophylaxis with tinzaparin for the prevention of symptomatic or incidental VTE events.

The primary efficacy endpoints will be the cumulative incidence of any VTE event (symptomatic pulmonary thromboembolism, symptomatic lower-limb deep vein thromboembolism [DVT], symptomatic upper extremity DVT, incidentally diagnosed pulmonary embolism [PE] including subsegmental PE or proximal DVT, symptomatic central venous catheter [CVC] thromboembolism, incidentally or symptomatic visceral vein thrombosis and VTE-related deaths), during a period of 4 months. In addition to objectively confirmed VTE events, the incidence of arterial thromboembolic events, thrombosis-free survival, progression-free survival, and overall survival will be assessed. The mortality rate throughout the study period and up to the second month post-treatment visit will be recorded.

The safety objective is aimed at evaluating the occurrence of major bleedings and clinically relevant non-major bleedings (CRNMB) at 4 months, according to International Society of Thrombosis and Hemostasis (ISTH) criteria. Health-related quality of life (HRQoL) will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) version 3.

The secondary efficacy endpoints will include the occurrence of VTE and the following features: the laterality of the primary tumor (right-sided or transversal vs. left-sided); antiangiogenic or anti- epidermal growth factor receptor (EGFR) treatment; resection of the primary tumor; *RAS/BRAF* mutational status; evaluation of cancer-specific survival outcomes in both study arms; and the association between the genetic risk scores and the Khorana score versus the presence of a VTE event. All these secondary efficacy endpoints will be to assess in the two months following discontinuation of tinzaparin, completing a period of 6 months.

The exploratory objectives aim to assess the predictive value of different risk assessment models and genetic/clinic risk scores and their evolution along the study period, 4 months of prophylaxis with tinzaparin plus two months following discontinuation of tinzaparin, completing a period of 6 months. Microsatellite instability (MSI) and other biomarkers in CRC will also be evaluated in local laboratories.

Patients will be genotyped for the genetic variants mainly identified in genome-wide analysis as associated with VTE using DNA from blood extracted at the time of inclusion until the first month after randomization in the study [11]. Genotyping will be done centrally using TaqMan genotyping assays and the EP1 Fluidigm (an efficient end point polymerase chain reaction system for high-throughput single nucleotide polymorphisms genotyping) [11].

Study procedures and evaluations

After confirming that the patients fulfill all the eligibility criteria of the study, the baseline assessments and procedures should be performed within 28 days before inclusion. The screening phase will be performed as shown in Table 1. Study visits will take place at month 1 (day 1 ± 7 d), month 2 (day 1 ± 7 d), month 3 (day 1 ± 7 d) and month 4 (day 1 ± 7 d) end of treatment. At the first visit, the patient will also be given a patient diary and instructed to complete it daily, including concomitant medication, injection of study medication, and any other information the patient deems relevant. The patient will return the patient's diary at each visit for verification by the investigator. Study drug compliance will be assessed by the Investigator at each corresponding patient's visit, and it will be captured in the patient's records as part of source documentation. Computerized tomography (CT) or magnetic resonance imaging scans will be performed with the frequency and modality according to standard clinical practice. The exact date of the objectively confirmed incidental or symptomatic venous or arterial events will be recorded in the next scheduled visit. All patients, including those who discontinued the study drug before month 4, will be contacted for follow-up 2 months after end of study treatment (total of 6 months) for VTE and until 18 months after the end of study for survival status. Safety parameters (i.e., major bleedings and clinically relevant non-major bleeding, and patient reported outcomes) will be recorded. Thrombotic and haemorrhagic events, as well as any death will be reviewed by the blinded Independent Data Monitoring Committee (IDMC). The deaths will be classified by the IDMC in fatal PE, myocardial infarction, stroke, other cardiovascular event, cancer progression, bleeding, other (to be specified) or unknown. Adverse events and concomitant medications will be recorded at each visit.

MSI, and *BRAF* and *RAS* status will be determined locally according to standard practice at baseline. Genomic *RAS/BRAF* alterations should be determined before randomizations. All these determinations will be used to evaluate differences in efficacy variables regarding molecular profiling. In addition, blood samples will be collected and will be used for central determination of molecular biomarkers and for DNA extraction to genotype

Table 1 Study determinations

Visit	SCR to randomisation	Treatment period				Visit to evaluate safety	EOS FU
Timeline	≤ 28 d	Month 1	Month 2	Month 3	Month 4	Month 6 or within 60 days after EOT	
Visit. Window		D1 +/- 7d	D1 +/- 7d	D1 +/- 7d	D1 +/- 7d	+/−7d	
Clinical Assessments							
Informed consent	X						
Demographic data	X						
Medical History (Medical and oncology specific)	X						
Physical Exam	X	X	X	X	X	X	
ECOG	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	
ABO Blood type	X						
Thrombotic risk score (Khorana, CATS/MICA Score)	X	X	X	X	X	X	
Laboratory Assessments							
Blood collection for genetic-risk score	X	X					
Coagulation	X	X	X	X	X	X	
D-dimer	X	X	X	X	X	X	
Haematology	X	X	X	X	X	X	
Blood chemistry	X	X	X	X	X	X	
Efficacy Assessments							
Clinical events for VTE		X	X	X	X	X	
Tumor Assessments							
CT or MRI Scans	Frequency and modality according to standard clinical practice						
Anticancer treatment							
First-line/previous systemic cancer treatment	X	X	X	X	X	X	
Study Treatment (Only experimental arm)							
Tinzaparin dispensing & compliance		X	X	X	X	X	
Safety Assessments							
Bleedings	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	
Patient reported outcomes (EORTC QLQ-C30)	X					X	
Translational Assessments							
Local assessment of MSI, *BRAF* and *RAS* mutations	X						
Survival Assessment							
New systemic cancer treatment	If applicable						
Survival assessment						X	X

SCR Screening, *EOS-FU* End of study follow-up, *EOT* End of treatment, *ECOG* Eastern Cooperative Oncology Group performance status, *CATS/MICA* Multinational Cohort Study to Identify Cancer Patients at High Risk of Venous Thromboembolism, *CT* computed tomography; MRI: magnetic resonance imaging, *MSI* Microsatellite Instability

the genetic variants included in the ONCOTRHOMB risk score (rs4524, rs6025, rs2232698, rs2227631, rs268, rs169713, rs11696364, rs5110, rs6003) [11].

Hypothesis, sample size and statistical analysis

In a selection of randomized clinical trials investigating the role of pharmacological thromboprophylaxis in ambulatory cancer patients undergoing anti-cancer therapy, the RRR ranged from 32 to 65% [26]. The primary hypothesis of the trial is that prophylactic tinzaparin treatment will reduce the incidence of VTE at 6 months after the first dose of study treatment from an estimated incidence of 13.5% (null hypothesis) reported in the benchmark study [5, 7] to 6.1% (alternative hypothesis, 55% relative risk reduction). A one-sided two binomial arm sequential asymmetric test will be performed taking into account that the level of significance is 0.025 (equivalent to two-sided, $p = 0.05$), power of 80%, and assuming that the proportion in the reference group is 13.5%, the proportion in the experimental group is 6.1%, and

that the proportion of experimental units in the reference group with respect to the total is 50%. A total of 526 patients will be included in the trial and randomized 1:1 between control and experimental arms, approximately 5% of dropouts were considered. Sample size calculation was performed using Design version: 3.3.0 (R version 4.1.3).

The study will be reviewed for safety and efficacy by the blinded IDMC. Two interim analyses will be performed to identify potential safety concerns: once the first 111 patients are recruited and after the accrual reaches 316 patients (60% of the sample). The study will also be reviewed for efficacy and futility when the accrual reaches 316 patients. According to our sequential statistical methodology, if significance in the interim analysis achieves a p-value < 0.0038 the study could be closed and declared positive, rejecting the null hypothesis. This would mean a difference in VTE event rate from 13.5% in the control arm vs. 3.8% in the experimental arm (72% relative risk reduction). If significance in the interim analysis is > 0.1767, the study will be closed for futility and declared negative. This would mean a difference in VTE events rate of 13.5% in the control arm vs. 9.5% in the experimental arm (29.7% relative risk reduction). The primary analysis will be performed according to "intention to treat". The time to the first outcome event will be estimated by the Kaplan–Meier method. We will perform a time to event analysis of the primary efficacy outcome occurring while the patient is taken tinzaparin or no prophylaxis. Secondary analyses will include a competing-risk analysis to account for deaths from causes other than venous thromboembolism or bleeding. The dataset will be closed, an analysis plan will be made and a multivariate analysis with relevant confounding factors will be performed. Clinical Trial Protocol is attached as additional file 3.

Discussion and implications for clinical practice

As opposed to previous studies including large numbers of patients with different types of cancer [15, 16, 26] and an average low-risk of VTE, we will use a completely different approach by selecting patients with a high risk of VTE with a single type of metastatic cancer, that is, mCRC. PROTINCOL will be the first randomized clinical study to compare the efficacy and safety of tinzaparin versus placebo in the prevention of VTE in patients with mCRC receiving first-line ambulatory systemic cancer therapy. At present, no other anticoagulant is approved for primary thromboprophylaxis in outpatients with CRC.

A LMWH was chosen instead of a direct oral anticoagulant (DOAC) because: (1) in trials comparing DOACs with LMWH for the prophylaxis of VTE in medically ill bedridden patients, the DOACs increased the risk of major bleedings as compared with LMWH [30, 31]; (2) since cancer patients are a high risk group for bleeding, these data favour the use of a LMWH for prolonged prophylaxis, and (3) qualitative studies suggest that most patients who present cancer-associated thrombosis report the symptoms associated with VTE to be profound and distressing and are willing to undergo long-term LMWH injections for the treatment of VTE [8, 32]. We will evaluate the effect of LMWH injection on their quality of life compared to that of the control group [31]. Finally, a substantial number of CRC patients are elderly and frailty in these patients is higher compared with younger patients [33].

The duration of previous primary VTE prophylaxis studies was generally between 4 and 6 months [19, 20, 34]. Given the cumulative VTE risk in patients with CRC receiving chemotherapy in the Cartago study, it was decided to treat patients in the present study with tinzaparin for 4 months. However, the risk of VTE may persist [34], and thus, it is not known whether VTE will actually be prevented or just delayed. Therefore, once thromboprophylaxis is completed, the incidence of VTE will be evaluated for an additional two months.

VTE is a frequent complication of cancer, occurring in about 7% of unselected patients with solid cancer [10, 35]. Although the data available likely reflect an underestimation of VTE events since other studies only report grade 3 and higher toxicities, this omits uncomplicated and incidental cases of VTE [5, 36]. Nowadays, cancer patients are increasingly treated in the ambulatory setting, and thus, most VTE events occur outside the hospital. Therefore, limiting VTE prophylaxis to periods of hospital stay is unable to significantly reduce the burden of VTE in patients with cancer.

Incidental VTE has been included in the main outcome because the diagnosis of this type of VTE is increasingly, currently representing about 50% of all VTE events in cancer patients [37, 38]. In addition, these incidental VTEs are often found to be symptomatic *a posteriori* [36]. Finally, the risk of recurrent VTE and death is about the same in truly symptomatic and clinically unsuspected VTE [37, 39].

Central venous catheter (CVC) thromboembolism has also been included because it was found to be an independent risk factor for VTE in the Prospective COMPASS–Cancer Associated Thrombosis Study [40]. In addition, the concept that the risk presented by CVC is also systemic is supported by the data reported by Ashrani et al. [41]. The present study will allow evaluation of the impact of CVC on the risk of DVT and/or PE.

Classically, the cancers considered to have a higher risk of thrombosis are those of the brain, pancreas and lung. In comparison, CRC is one of the cancers presenting a lower risk of thrombotic events, especially in cases with localized disease [42]. However, the risk of VTE is two to

three-fold higher in patients with metastatic disease as compared to those with localized disease and this is further increased in patients receiving chemotherapy [10, 42].

The addition of targeted anticancer therapies has improved response rates, progression-free survival and overall survival [43, 44]. However, the benefits of anticancer treatments may be counteracted by an increased risk of VTE, the production of which may interrupt on-going treatments, increase the risk of bleeding in cases receiving anticoagulation, and impair patient quality of life [8].

There are conflicting data about the role of oncogenic status in the prediction of VTE in CRC patients [5]. In addition, it should be noted that the risk of VTE is not consistent among all cytotoxic agents and the relationship between VTE and targeted therapies remains largely unknown [45]. A recent systematic review and meta-analysis investigated the risk of grade 3 and greater VTE events in patients receiving anti-EGFR monoclonal antibodies (cetuximab or panitumumab). This review analyzed 17 studies of which 7 investigated mCRC. From these data, the overall incidence of grade 3/4 VTE in CRC was 8.1%, with anti-EGFR monoclonal antibody containing regimens being associated with an increased risk of VTE [46]. On the other hand, bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody widely used in first line mCRC, has been associated with an increased risk of arterial thrombosis and possibly VTE in the subgroup of patients with CRC, and also increases the risk of bleeding [47], with the latter representing a therapeutic challenge.

When deciding whether to use primary antithrombotic prophylaxis in outpatients with cancer who are candidates for chemotherapy, a clinician needs to determine the risk of VTE and weigh the likely benefits against the risk of bleeding. The present trial could bring important light to this topic. Although the study aims to be pragmatic and answer the question "Should patients with mCRC receiving chemotherapy and or targeted anticancer therapies receive LMWH thromboprophylaxis to reduce the incidence of cancer-associated thrombosis?". To answer this question it is important to note that biomarkers can help identify cancer patients at a higher risk of developing thrombosis. Certain biomarkers, such as D-dimer, P-selectin, and tissue factor, have been associated with an increased risk of thrombosis in cancer patients [48]. However, thrombin generation and soluble P-selectin are not available in routine clinical practice. While clinical factors account for a significant proportion of thromboembolic risk, over 60% of the variation in the risk of VTE can be attributed to genetic factors [49]. In this sense, a score that integrates genetic and clinical data (TiC-ONCO) has been developed and validated [11], being significantly better at predicting VTE than the gold-standard Khorana score (area under the curve 0.73 vs. 0.58; $p < 0.0001$). It is therefore important to highlight that PROTINCOL will include several secondary analyses (i.e. efficacy analysis based on different biomarker risk assessment models including the TiC-ONCO score, *BRAF/RAS* genomic mutations, tumor resection, among others) in order to assess which factors have the greatest impact.

In conclusion, it is well documented that patients presenting VTE have a worse prognosis and generate higher health care costs. If the individualization of antithrombotic prophylaxis, associated with a validated risk model based on biomarkers, can reduce the complications of outpatient cancer treatment and be cost effective, it would be of great value in the future care of patients with mCRC, opening the door to personalized medicine in cancer-associated thrombosis.

Abbreviations

CATS	The Vienna Cancer and Thrombosis Study
CATS-MICA	Multinational Cohort Study to Identify Cancer Patients at High Risk of Venous Thromboembolism
COMPASS-CAT	The Comparison of Methods for Thromboembolic Risk Assessment with Clinical Perceptions and AwareneSS in Real Life Patients-Cancer Associated Thrombosis
CRC	Colorectal cancer
CRNMB	Clinically relevant non-major bleedings
CT	Computerized tomography
CVC	Central venous catheter
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
HRQoL	Health-related quality of life
IDMC	Independent Data Monitoring Committee
ISTH	International Society of Thrombosis and Hemostasis
LMWH	Low-molecular-weight heparin
mCRC	Metastatic colorectal cancer
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
PE	Pulmonary embolism
PS	Performance status
SC	subcutaneously
VTE	Venous thromboembolism

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14620-z.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

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Authors' contributions
Conception and design: MS, AM, JMS Provision of study materials or patients: All authors Manuscript writing, original draft: MS, AM, JMS Manuscript writing, review and editing: All authors Final approval of manuscript: All authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Written Informed consent will be obtained from all subjects involved in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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