MeTHOS PROTOCOL SYNOPSIS: OBSERVATIONAL STUDY

Title: **Metaxa's Thromboprophylaxis program in Oncological & Surgical patients**

Short Title **MeTHOS**

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Study Principal Investigators

Spyridon Xynogalos, MD, sxyn@otenet.gr
Panagiotis Manikis, MD , paniman14@gmsil.com

Co- Investigator

Nikolaos Ziras , MD, zirasngr@otenet.gr

Konstantinos Ntatsis

George Vorias

Sub – Investigators

Evangelos Fergadis

Iovatso Hristos

David Simeonidis

Orestis Sidiripoulos

Georgia Migga

Chrysa Kapsokoli

Maria Leonti

Evridiki Maslimoglou

Emmanouil Mpakalinis

PROTOCOL SYNOPSIS

Study Title	**Metaxa's Thromboprophylaxis program in Oncological & Surgical patients**
Study Rationale Introduction	Venous thromboembolism (VTE) is common in cancer patients, with the risk being 4- to 7-fold higher compared with noncancer patients. [1]. VTE is associated with increased mortality, morbidity, [2,3] and burden on health care resources. [4]. The risk of recurrence and bleeding complications are major concerns during anticoagulant therapy, as up to 9% of cancer patients with VTE develop recurrent thrombotic events, despite treatment with low-molecular-weight heparin (LMWH), [5–8]. Consequently, more effective prevention measures, especially during high-risk circumstances such as the postoperative period, may improve outcomes in these patients.
Cancer patients undergoing surgery treatment	It has been well established that major surgery itself increases the risk of VTE even in the absence of cancer. [9]. Historical data from 1970s and 1980s using routine screening procedures reported a 37% incidence of deep vein thrombosis (DVT) following general surgery in patients with cancer, in contrast to an estimated risk of 20% in patients without cancer. [10]. However, changes in surgical techniques, use of perioperative chemotherapy, and the practice of early postoperative mobilization with increased awareness of perioperative VTE likely have altered VTE incidence over time. The absolute VTE risk varies with the type of surgery, including site, technique (e.g., open vs. laparoscopic approach), duration of surgery, type of anesthesia, the presence of postoperative infection and immobilization, and patients' comorbidities (e.g., body mass index [BMI] and previous history of VTE). Surgeries for resection of malignant tumors are associated with a particularly high risk of VTE likely because of the extensive vascular injury from tumor invasion and dissection as well as lengthy operation time, and in some cases, residual tumor or nodal mass continues to cause venous compression and stasis. Prolonged postoperative immobility is also quite common in these patients. The risk of thrombosis is not only increased during the immediate postoperative period but also extends at least up to 30 days or even longer after surgery. In the @RISTOS study that prospectively followed 2,373 patients who underwent surgery for cancer, 40% of symptomatic VTE occurred more than 3 weeks after surgery and 46% of deaths were due to fatal pulmonary embolism (PE). [11] The investigators of the @RISTOS study found that a previous history of VTE, anesthesia lasting 2 hours or longer, bed rest for 4 days or longer, advanced tumor stage, and age 60 years or older were significant risk factors for VTE. Similarly, in the Million Women Study, the incidence of symptomatic VTE was observed to peak at 3 weeks postoperatively for all surgeries, but the risk remained

high up to 4 to 12 months for cancer patients.[12]. Relative to patients without cancer, the risk of VTE after surgery for cancer was 91-fold higher at 6 weeks, 53-fold at 7 to 12 weeks, and 34- fold at 4 to 12 months after surgery.

Estimated risk of venous thromboembolism associated with various types of surgery 13

Surgical setting	Incidence of DVT, %	Incidence of PE, %
Major abdominal and pelvic surgery (colorectal/gynecological)	15–40[a]	1.3–2[d]
Major open urological surgery	15–40[a]	0.2[e]
Neurosurgery	15–40[a]	Insufficient data
Thoracic surgery	4–14[a]	5–12[f]
Breast surgery	0.8–2.1[b]	Insufficient data
Laparoscopic surgery	1–11[c]	Insufficient data

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.
Source: Adapted and modified from Geerts et al.[16]
[a]Routine screening of asymptomatic patients without prophylaxis.
[b]Symptomatic patients without prophylaxis or mechanical prophylaxis alone (from retrospective studies).
[c]Routine screening of asymptomatic patients with or without prophylaxis.
[d]Symptomatic patients without prophylaxis.
[e]Symptomatic patients without prophylaxis or mechanical prophylaxis alone.
[f]Routine screening of asymptomatic patients with CT chest.

Pharmacological Prophylaxis

Pharmacological Prophylaxis for cancer patients undergoing surgery

Studies in the late 1980s and early 1990s showed that pharmacological prophylaxis reduces the risk of postoperative VTE by 60% compared with no prophylaxis.[14-17]

LMWH is generally the preferred choice of anticoagulant over UFH based on its ease of administration (once daily vs. twice to three times per day for UFH) and lower risk of heparin-induced thrombocytopenia (HIT).

Cancer patients may also tolerate higher doses of LMWH without increasing the bleeding risk further.[18]

The optimal duration of thromboprophylaxis after cancer surgery has not been established and the available data are limited to major abdominal and pelvic surgery. Although studies have shown that a longer duration of prophylaxis up to 1 month after major abdominal and pelvic surgery can further reduce the risk of VTE compared with standard duration (typically while in hospital or up to 7–10 days) [19-21]

In the ENOXACAN II trial, patients who received extended thromboprophylaxis (ETP) with LMWH up to 30 days after open surgery for abdominal and pelvic cancer had a 60% VTE risk reduction (95% CI: 10–82%), compared with those who received standard duration of 6 to 10 days (4.8 vs. 12%; p = 0.02).[19]

These findings are supported by a recent meta-analysis of seven RCTs and prospective studies which concluded that ETP is associated with a significant risk reduction of all VTE (2.6 vs. 5.6%; (RR: 0.44, 95% CI:

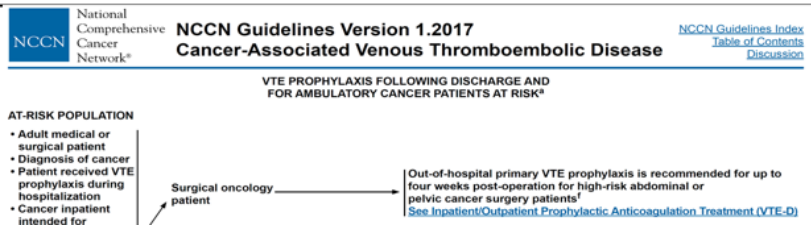
0.28–0.70) and proximal DVT (1.4 vs. 2.8%; RR: 0.46, 95% CI: 0.23–0.91). [22]

Guidelines for thromboprophylaxis for cancer patients undergoing surgery

Consensus guidelines on primary thromboprophylaxis in cancer patients undergoing surgery

Methods	Guideline	Recommendations
Pharmacological thromboprophylaxis	ACCP 2012	• For general and abdominal-pelvic surgery and thoracic patients at high risk for VTE who are not at high risk for major bleeding complications, pharmacological prophylaxis with LMWH or LDUH is recommended over no prophylaxis. • For craniotomy and spinal surgery patients at high risk for VTE, pharmacological prophylaxis should be added to mechanical prophylaxis once adequate hemostasis is established and risk of bleeding decreases
	ASCO 2015	• All patients with malignant disease undergoing major surgical intervention should be considered for pharmacological thromboprophylaxis with either UFH or LMWH unless contraindicated • Prophylaxis should be commenced preoperatively
	ESMO 2011	• In cancer patients undergoing major cancer surgery (laparotomy, laparoscopy, thoracotomy, or thoracoscopy lasting more than 30 min), prophylaxis with LMWHs or UFH is recommended
Mechanical thromboprophylaxis	ACCP 2012	• Mechanical prophylaxis with elastic stockings or IPC should be added to pharmacological prophylaxis in patient with high risk of VTE • For high VTE risk general and abdominal pelvic surgery patients, who are also at high risk for major bleeding complications, mechanical prophylaxis, preferably with IPC, is suggested over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated • For high VTE risk patients in whom the consequence of bleeding might be severe, mechanical prophylaxis is suggested over no prophylaxis
	ASCO 2015	• A combined regimen of pharmacological and mechanical prophylaxis may improve efficacy, especially in the highest risk patients • Mechanical prophylaxis should not be used as monotherapy unless pharmacological methods are contraindicated
	ESMO 2011	• Mechanical methods such as pneumatic calf compression may be added to pharmacological prophylaxis but should not be used as monotherapy unless pharmacological prophylaxis is contraindicated because of active bleeding
IVC filter	ACCP 2012	• IVC filter should not be used for primary VTE prevention for all risk groups
	ASCO 2015	• Not specified in primary prophylaxis setting
	ESMO 2011	• Not specified in primary prophylaxis setting
Duration of thromboprophylaxis	ACCP 2012	• Not specified
	ASCO 2015	• 7–10 d
	ESMO 2011	• At least 10 d
Extended thromboprophylaxis	ACCP 2011	• For high-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, extended duration pharmacologic prophylaxis (4 wk) with LMWH is recommended over limited-duration prophylaxis
	ASCO 2015	• Extended prophylaxis with LMWH for up to 4 wk postoperatively should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or with additional risk factors
	ESMO 2011	• Cancer patients undergoing elective major abdominal or pelvic surgery should receive in-hospital and postdischarge prophylaxis with LMWH for up to 1 mo after surgery

Abbreviations: IVC filter, inferior vena cava filter; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.



Introduction for cancer patients undergoing chemotherapy

Venous Thromboembolism (VTE) is a frequent malignancy complication which often results in serious health deterioration and death. The risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) is considerably higher in cancer patients, compared to general population four to seven times [23, 24]. Venous thromboembolism is the second leading cause of death in patients with cancer and overall mortality is increased among patients who have both conditions. [25, 26, 27]

Evidences suggest that Thromboembolism risk could be cancer related, patient related or treatment related. This risk is highest for patients with certain types of solid tumors (stomach, pancreas, lung, gynecologic, bladder, testicular) and hematologic cancers and is increased for patients who are receiving chemotherapy 6.5 times [28] or radiotherapy, who have undergone operative procedures, who have metastatic disease, or who have inherited thrombophilias. Studies have indicated that the mechanisms of this effect may include mucin production by tumors, exposure of tissue factor rich surfaces and tissue factor bearing microparticles, cysteine proteinase production leading to thrombin generation, and local hypoxia. [28,29,30]

The development of VTE in cancer patients is associated with several adverse consequences including worsened short- and long-term prognosis and survival, mortality, morbidity, chemotherapy postponement, potential hospitalization, need for long-term anticoagulation with attendant bleeding complications and high rates of recurrent VTE [31,32]. In addition, VTE leads to significant consumption of health care resources; [33]. Therefore the optimal prevention and treatment of VTE are crucial components of patient care in this population. Currently, Low!Molecular! Weight Heparin (LMWH), is the gold standard for the CAT management for the last 15 years [34-36]

Moreover, in a variety of high-risk thrombosis clinical settings, LMWHs agents are safe and effective in preventing VTE [37-38]. Multiple randomized trials of thromboprophylaxis have been conducted focusing on ambulatory cancer patients receiving chemotherapy [39-40] . ESMO and ASCO current guidelines suggest considering thromboprophylaxis in high-risk ambulatory cancer patients with LMWHs.

Several contemporary studies have investigated independent predictors for VTEs in patients actively receiving chemotherapy leading to the development of risk models for identifying patients at highest risk. [41] The Khorana model is a validated scoring system that utilizes specific patient characteristics and laboratory values to stratify patients into low, intermediate, or high risk for venous thromboembolism;

Moreover , chemotherapy and thrombosis for over three decades, it remains an underappreciated risk that has not been routinely incorporated into thrombosis risk assessment models.[42] . Cytotoxic chemotherapy has a multifactorial contribution to the risk of thrombosis. It induces vascular injury through apoptosis. In the case of cisplatin, this leads to release of prothrombotic particles that trigger thrombin generation via tissue factor independent mechanisms along with drastically increased vWF activity. Other agents, like 5-FU, also drive thrombin formation in combination with depleted protein C activity. L-asparaginase administration is tied to drastically decreased protein C, protein S, and antithrombin levels, creating a prothrombotic milieu through loss of anticoagulant factors. VEGF inhibition does not directly lead to thrombosis, but instead 'primes' the endothelium through a VEGF starved state to be more susceptible to injury. Additionally, platelet activation through PAR-1 and increased Gp llb/llla activity in the case of immunomodulatory agents or increased vWF among others in the case of small molecule inhibitors contributes to this 'primed' state.[43-81]

Cancer patients undergoing systemic treatment for their malignancy are among the highest risk populations for thromboembolic complications; often, the treatment itself contributes to this risk. Recognition of the antineoplastic agents most likely to cause thrombosis can help raise provider awareness and lead to earlier diagnosis and treatment.

In our approach, we will protect our patient taking under consideration their treatment (surgery either chemotherapy)

Study Objective

In this study we will collect Real World Data of our clinical practice regarding Thromboprophylaxis in high thrombotic risk solid tumors patients undergoing surgical and /or chemotherapeutical treatment, for one year following the protocol initiation date.

- **Specifically we will focus on the following :**
  - Number of thrombotic events
  - Anti-thrombotic management dosage & duration
  - Any bleedings related to anticoagulation
  - Patients' adherence and compliance

Study Design

This is a prospective, phase IV, observational, non-interventional cohort study that aims to record the daily clinical practice regarding thromboprophylaxis in high thrombotic risk cancer patients (under surgry or chemotherapy) initiated December 2018 for a year time.
Patients demographic data, cancer type and stage, anticoagulant treatment dose & duration, efficacy (VTE events), safety (bleedings) and information about adherence will be collected; more than one outcomes could be recorded.

Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or due to termination of study observation period. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported in accordance with current regulations. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative format.
Authorized staff will perform periodic site visits to review CRFs for completeness, but will have no direct access to patient records; although they could request further information from the hospital staff. The anonymized data will be collated centrally and entered into an electronic database using double data entry where appropriate. Any discrepancies identified by electronic logic checks and will be resolved using data clarification forms sent to sites.
Ethics committee approval will be obtained where approval of a prospective non-interventional study is required. This study will be conducted in full accordance all applicable Research Policies and Procedures and all applicable laws and regulations. The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unanticipated problems involving risks to subjects or others in accordance with Policies and Procedures and all regulatory

	requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Patients who were diagnosed with histological confirmed high thrombotic risk cancers (GI, thoracic, gynecologic and genitourinary) undergoing surgery 2. Age ≥ 18 years 3. ECOG 0-2 4. Life expectancy >6 months 5. Signed informed consent **Exclusion Criteria** 1. Patients who were not diagnosed with histological confirmed high thrombotic risk cancers (GI, thoracic, gynecologic and genitourinary) undergoing surgery 2. Age < 18 years 3. ECOG >2 4. Life expectancy <6 months 5. Not signed informed consent
Study Duration	Each subject's participation will last from inclusion (enrolment visit) to follow up visit (if applicable; four weeks post hospital discharge) The entire study is expected to last by the end of 2019
Study Phases **Screening** **Study Treatment** **Follow-Up**	(1) Screening: screening for eligibility, obtaining consent and administer thromboprophylaxis (2) Observation Period: monitoring subjects over treatment time (3) Follow-up Phase (only if applicable e.g. by the end of treatment period)
Efficacy Evaluations	• Symptomatic/Suspected vein thromboembolism, including pulmonary embolism and deep vein thrombosis Confirmation of symptomatic PE requires symptoms of PE and one of the following findings 1. A (new) intraluminal filling defect in (sub) segmental or more proximal branches on spiral CT scan; 2. A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels on the pulmonary angiogram;

3. A (new) considerable perfusion defect (~ 75% of a segment) with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy (V/Q scan);
4. An inconclusive lung scan accompanied by documentation of (new) DVT in the lower extremities e.g., by compression ultrasound or venography.

- Confirmation of symptomatic DVT requires symptoms of DVT and:

1. A (new) noncompressible venous segment on ultrasonography

- Incidental PE with one of the following:

1. A (new) intra-luminal filling defect on CT scan, MRI scan, or pulmonary angiogram;

- An inconclusive lung scan accompanied by documentation of (new) DVT in the lower extremities e.g., by compression ultrasound or venography.

- Fatal PE is:

1. PE based on objective diagnostic testing or autopsy or
2. death not attributed to a documented cause and for which DVT/PE cannot be ruled out

- Incidental DVT with the following finding:

Confirmation of recurrent incidental DVT requires inconclusive or no-symptoms of DVT and:

1. A (new) noncompressible venous segment on ultrasonography

Safety Evaluations Major, clinically relevant non-major bleeding, and minor bleeding

Major bleeding will be defined as overt bleeding associated with: a fall in hemoglobin of 2 g/dL or more, or leading to a transfusion, or bleeding that occurs in a critical site or contributing to death.

- **Bleeding in a critical area or organ such as:**

Retroperitoneal

Intracranial

Intraocular

	Intraspinal Intra-articular Pericardial Intramuscular with compartment syndrome • **A clinically overt bleeding event** that is associated with a fall in hemoglobin of 2.0 g/dL (>1.24 mMol/L) or more, or leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood. • **Bleeding contributing to death** Other clinically relevant non-major bleeding will be defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with discomfort for the patient such as pain, or impairment of activities of daily life. All other bleeding events will be classified as minor
Statistical And Analytic Plan	Descriptional statistical analysis will be performed for all study data along with epidemiology methods. Continuing parameters will be presented with standards descriptional statistical measures (mean values, median values, percentages etc.) and the results will be presented accordingly into tables. For more complex correlations we will use, among other methods, chi-square tests, ANOVA and t-tests, in order to evaluate the relationships between different patient and disease characteristics, such as: • Number of patients enrolled • Tumor characteristics • Co-morbidities • Type of Surgical operation • Type of antineoplastic treatment • Type of thromboprophylaxis therapy • Therapy outcomes • Number of therapy disruptions for any reason • Complications (AE- SAE) and to present them, accordingly. Due to the fact that this is an observational study the results of all correlations will be carefully discussed and will be used only to assess hypotheses.
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APPENDIX

1. **Informed Consent Form (in Greek: ΕΝΤΥΠΟ ΣΥΓΚΑΤΑΘΕΣΗΣ ΜΕΤΑ ΑΠΟ ΕΝΗΜΕΡΩΣΗ)**
2. **Case Report Form (In Greek: ΕΝΤΥΠΟ ΑΝΑΦΟΡΑΣ ΠΕΡΙΣΤΑΤΙΚΟΥ)**