



INTERACT

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PROTOCOL SYNOPSIS

OBSERVATIONAL RETROSPECTIVE STUDY

Title: INTensive dosE tinzapaRin in hospitalized Covid-19 paTients

Short Title: **INTERACT**

Protocol Date: 14 June 2021



PROTOCOL SYNOPSIS

Study Title	<u>INT</u> ensive dos <u>E</u> <u>tin</u> zapa <u>R</u> in in hospit <u>AL</u> ized <u>C</u> ovid-19 pa <u>T</u> ients
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Study Rationale	A prothrombotic state, attributable to a cytokine storm induced by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) and leading to activation of the coagulation cascade, is a recognized feature of Coronavirus disease 2019 (COVID-19) infection. This can manifest in <i>venous thromboembolism (VTE)</i> , <i>arterial thrombosis events (ATE)</i> and <i>disseminated intravenous coagulation (DIC)</i> and coagulopathy is reflective of more severe disease and adverse prognosis [1]. A significant number of patients with COVID-19 require single or multiple organ support on the <i>Intensive Care Unit (ICU)</i> , estimated to be between 12 and 17% of patients [2,3,4,5]. with the reported mortality in these cohorts between 25 and 40% [2, 6].
Introduction	<p>International guidelines recommend that hospitalized patients with COVID-19 should receive pharmacological prophylaxis against VTE, in the absence of contraindications [7,8,9]. With respect to how VTE prophylaxis is achieved, <i>Low Molecular Weight Heparins (LMWH)</i>, in addition to their well-known anticoagulant properties, appear to have additional antiviral and anti-inflammatory effects that may be potentially beneficial in hospitalized COVID-19 patients. [10,11].</p> <p>Though international and national guidelines states that all hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis, the rising incidence of thrombotic complications in COVID-19 patients has led a lot of hospitals to adopt the strategy of increasing the dose of anticoagulation for prophylaxis to 'intermediate' or "therapeutic" doses using a risk-adapted strategy with increased doses administration based on factors associated with increased risk; clinicians weigh the benefits and risks of therapeutic anticoagulation in terms of thrombosis and major bleeding risk for individual patients.</p> <p>Additionally, LMWHs have different physiochemical characteristics as a result of the diverse methods of their manufacturing. The variations in molecular composition and pharmacological properties of LMWHs are reflected in differences in their clinical efficacy and safety. Each LMWH should, therefore, be considered as a unique substance. <i>Tinzaparin</i> is the only LMWH known that is prepared by enzymatic hydrolysis with heparinase [12,13,14,15]. Due to its preparation method, <i>tinzaparin</i> has distinct properties than other LMWHs including and not limited to: higher <i>Anti-IIa activity</i> and <i>Anti-Xa/Anti-IIa activity ratio</i>, higher release of <i>Tissue Factor Pathway Inhibitor (TFPI)</i>, less dependence from renal function for its clearance and more complete neutralization from its antidote, if needed. Due to the key role of increased <i>Thrombin generation (IIa)</i> and <i>Tissue factor (TF)</i> pathway activation in COVID-19-associated thrombosis [16], special properties of <i>tinzaparin</i> in <i>Anti-IIa activity</i> and <i>TFPI</i> production and release from endothelial cells, as well as significant effects of <i>TFPI</i> in various vascular, inflammatory, cardiovascular, hematological and oncological disorders [17,18,19,20,21], <i>tinzaparin</i> could have an expanded role beyond its well-known anticoagulant function.</p> <p>The purpose of this study is to evaluate the overall clinical effectiveness and safety of 'intermediate' or "therapeutic" doses anticoagulation with <i>tinzaparin</i> administered for thromboprophylaxis in COVID-19 patients with moderate disease severity during hospitalization in Greek hospitals.</p>



Study Objectives

Primary Objectives

The **primary objective** of this study is to evaluate the current management approach with “intermediate” or “therapeutic” doses of tinzaparin for thromboprophylaxis in hospitalized patients, non on ICU organ support, with confirmed COVID-19.

- Evaluate incidence of thrombotic events
- Evaluate incidence of bleeding events

Secondary Objectives

The **secondary objective** is to

- ✓ Examine the course of illness of COVID-19 via measure of clinical improvement and/or survival, assessed at pre-specified time points post admission

Patients demographic & somatometric data, medical history (thrombosis & bleedings related history, co-morbidities, chronic use of medications, results of laboratory tests etc.), clinical parameters, anticoagulant prophylaxis dose & duration, efficacy (thrombosis events), safety (bleedings), imaging and laboratory tests results and information about other supportive treatment will be recorded; more than one outcomes could be recorded.

Based on analysis of collected data, **we'll examine correlations between thromboprophylaxis approach, patients' profiles and clinical outcomes.**

Study Endpoints

Primary Endpoints

- **Incidence of thrombotic events** (total & per type e.g. PE, DVT, symptomatic, incidental, proximal, distant etc.)
- **Incidence of bleeding events** (total & per type e.g. Major, CRNMB and minor)

Secondary Endpoint

- **World Health Organization (WHO) progression scale** (range from 0 (healthy) to 10 (death); values below or equal to 5 correspond to the absence of any oxygen supply beside nasal or facial mask)
- **Length of hospital stay (days)**

Study Design

This is a retrospective phase IV, observational, non-interventional cohort study that aims to collect data regarding thromboprophylaxis management in high thrombotic risk hospitalized, non on ICU, patients with COVID-19 pneumonia. Specifically, we will collect retrospectively data for patients received thromboprophylaxis with tinzaparin, according to current clinical practice, during hospitalization, for one year before the study initiation date, to evaluate safety and efficacy of thromboprophylaxis and to examine possible associations of



patients' profiles with thrombotic and bleeding events and the course of illness in this cohort of patients.

We will collect data retrospectively in paper CRFs, recorded from the treating physicians.

Additionally, we will assess the association of a panel of laboratory and clinical parameters representing an inflammatory and hemostatic state with VTE and bleeding events and clinical outcomes.

Institutional Review Board will approve the study.

Basic/common markers/parameters

- ✓ *D-Dimers*
- ✓ *C-reactive protein (CRP)*
- ✓ *hemoglobin*
- ✓ *platelets count*
- ✓ *ferritin*
- ✓ *fibrinogen*
- ✓ *SpO₂ in FiO₂ 21%*

In all cases, laboratory and clinical parameters will be collected at 3 time points: at admission/baseline, after one week and at discharge.

Subject Population

Key criteria for Inclusion and Exclusion

Inclusion Criteria

1. Patients admitted to hospital with COVID-19, PCR+ SARS-CoV-2 infection (from any specimen) administered thromboprophylaxis with tinzaparin in intermediate or therapeutic dose
2. Age \geq 18 years
3. Signed informed consent

Exclusion Criteria

1. Patients admitted to ICU with COVID-19, PCR+ SARS-CoV-2 infection (from any specimen)
 2. Age < 18 years
 3. Pregnancy
 4. Current diagnosis or suspicion of pulmonary thromboembolism or deep vein thrombosis
 5. Progression to death was imminent and inevitable within 24 hours from the admission, irrespective of the provision of treatments
 6. Not signed informed consent
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Study Phases**Screening**

(1) Screening: screening patient files for eligibility, obtaining consent, If eligible

All the data will be gathered from medical records by chart review of the individual patients in a retrospective fashion. There will no direct patient interaction in the study.

Data collection

- Demographic data collection (Gender, Date of birth, Weight, Height, etc.)
- Medical history & pathologic features (Thrombosis & bleedings related history, risk factors, recent surgery, co-morbidities, chronic use of medications, results of laboratory tests, clinical parameters etc.)
- Anti-coagulant administration data
- Thrombotic & bleeding events during course of hospitalization
- Other adverse events related to anticoagulation
- Clinical improvement and/or survival during hospitalization

Timepoints of evaluation

Data of Covid-19 pneumonia patients retrospectively enrolled in the study will be evaluated on a regular basis following the Baseline Visit;

Visit 1 – Baseline, at admission;

Visit 2 - will be after 1 week \pm 2 days

Visit 3 - will be by at discharge from hospital

Statistical analysis & report**Statistical analysis****Statistical and Analytic Plan**

Descriptional statistical analysis will be performed for all study data along with epidemiology methods. Categorical data will be analyzed using the *chi-square* and *Fisher exact test*. Continuous variables will be reported as mean and standard deviations (SD) and will be analyzed using the *t-test* analysis. An unadjusted odds ratio (OR) will be calculated using a *Cochran-Mantel-Haenszel test*. To determine the impact of potential effect modifiers a *logistic regression model* will be used to calculate the adjusted odds ratio. For more complex correlations (i.e. inferential statistics) we will use, among other methods, *chi-square* or *Fisher exact tests*, *ANOVA*, *Mann-Whitney U tests* and *t-tests*, according to the data properties and in order to evaluate the relationships between different patient and disease characteristics with the primary and secondary study outcomes, such as:

- ✓ *Number of patients enrolled*
- ✓ *Co-morbidities*
- ✓ *Thrombosis risk factors*
- ✓ *Laboratory parameters*
- ✓ *Clinical parameters*
- ✓ *Type and duration of thromboprophylaxis therapy*
- ✓ *Therapy outcomes*
- ✓ *Thromboprophylaxis related complications*

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.

Finally and depending on the collected data multivariate analysis may be performed in order to reveal confounding factors.

Clinical Study Report (CSR)

Analyzed parameters will be presented with standards statistical measures (mean values, median values, ranges, quartiles, percentages etc.) and the results will be presented accordingly into tables and informative plots.

A p-value of less than 0.05 will be considered statistically significant and all values will be reported with a 95% confidence interval (CI).

Study Registration

Study will be registered in

NIH, U.S. National Library of Medicine, Clinical Trials database of privately and publicly funded clinical studies, <https://clinicaltrials.gov/ct2/home>

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 or on MRI 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. *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) non-compressible venous segment on ultrasonography
Incidental PE with one of the following:*
2. *A (new) intra-luminal filling defect on CT scan, MRI scan, or pulmonary angiogram;*
3. *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*
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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 incidental DVT requires inconclusive or no- symptoms of DVT and:

1. *A (new) non-compressible venous segment on ultrasonography*

**Safety Evaluations
(with regards to
anticoagulation)**

- **Major, Clinically Relevant Non-Major Bleeding (CRNMB), 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 bleedings (CRNMB)** 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**
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- **World Health Organization (WHO) progression scale**

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Figure: WHO clinical progression scale

ECMO=extracorporeal membrane oxygenation. FiO_2 =fraction of inspired oxygen. NIV=non-invasive ventilation. pO_2 =partial pressure of oxygen. SpO_2 =oxygen saturation. *If hospitalised for isolation only, record status as for ambulatory patient.



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