

# Thrombo-Prophylaxis Prevents Thrombotic Events in Home-Managed Covid Patients a Registry Study

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## Abstract

This pilot registry analyzes data from subjects with COVID-19 infection and mild symptoms, followed and treated at home. Antithrombotic prophylaxis was used in all subjects. A comparison was made with comparable cases that had not used prophylaxis. A control group (36 subjects) without prophylaxis was compared to a prophylaxis group (67 subjects using LMWH and 35 using defibrotide). At two weeks, there were no DVTs or thrombotic disease in the prophylaxis groups. Also, the evolution of the main respiratory symptoms was significantly better in the prophylaxis groups ( $p < 0.05$ ). No patients went to ITU: 4 out of 36 patients in the comparative group went briefly to hospitals. In subjects, using LMWH 1 went to hospital as in the defibrotide group. None was put in ventilation. D-dimer values were fluctuating and not usable to define the presence of a thrombotic condition. This aspect is under further evaluation. No significant side effects were observed.

**Conclusions:** Antithrombotic prophylaxis should be started as soon as possible (home patients) and used during all the high-risk conditions. The importance of venous thromboembolism in medical patients with severe respiratory disease (as COVID), even in the early phases, has been stressed and it is well known; it cannot be considered a new observation and requires adequate, immediate prophylaxis.

## Introduction

All acutely ill medical patients should be managed with thromboprophylaxis. In particular, patients >40 years, with acute medical illness, reduced mobility with one or more morbidities (acute heart failure NYHA class III/IV, respiratory disease with respiratory failure with or without ventilation or an exacerbation of respiratory disease, active cancers requiring management, acute infective disease including severe lung infection and sepsis). This list fully covers COVID pneumonia, even in the early phases and with limited symptoms. Also, thrombophilia, rheumatic disease, ischemic stroke, acute myocardial infarction should be considered for prophylaxis.

In acutely ill medical patients, prophylaxis with LMWH for 6-14 days – or until the patient is fully mobile - is strongly recommended [1]. Single daily doses of 2.5 mg of fondaparinux is an alternative to LMWH. LMWH is now preferred to LDUH (low dose unfractionated heparin) because it requires one/two injection per day and is associated with less hemorrhagic complications and less heparin-induced thrombocytopenia (HIT).

Fondaparinux, given as one injection/day and is associated with lower HIT occurrence. Extended thromboprophylaxis may be considered according to the evolution of the problem [1-5].

This pilot registry analyzes data from subjects with COVID-19

infection and mild symptoms, followed and treated at home. Antithrombotic prophylaxis was used in all subjects. A comparison was made with comparable cases that had not used a thrombotic prophylaxis.

## Patients

This registry includes a nonhomogeneous sample collected by observation of COVID-19 patients who were exclusively treated at home. All subjects reported mild, early symptoms that could be managed with symptomatic treatments at home with their full collaboration and in an environment, that was considered suitable for this management.

Their age was <75 and BMI was between 24.5 and 26.6 (including all subjects). These subjects were otherwise healthy, did not use other drugs and had no metabolic conditions or handicaps. They never had lung or respiratory problems or any chest surgery.

**Group A:** LMWH enoxaparin as the first choice (or what was available in the local pharmacies) was used 2 times daily at a dose between 4000 and 6000 Units, broadly according to weight.

**Group B:** Defibrotide BID, IM (10 000 UI BID) was also used in a number of patients that did not want to be treated with LMWH or subjects who preferred to use defibrotide.

**Diagnostic Criteria:** COVID-19 was diagnosed clinically as swabs were and are still basically unavailable for all patients (1-5). Many patients have been symptomatic at home without being able to get a swab. Most physicians still operate in a condition of great scarcity of masks and protective elements.

Criteria to diagnose COVID-19 were:

1. Increased temperature (>37.5 C° for at least 2 days)
2. Cough and upper respiratory symptoms
3. Fatigue
4. Malaise
5. Other (pain, vasospastic symptoms).

The follow up was at least of 3 weeks.

Most patients lost contact with their physicians or with the health authorities during this period.

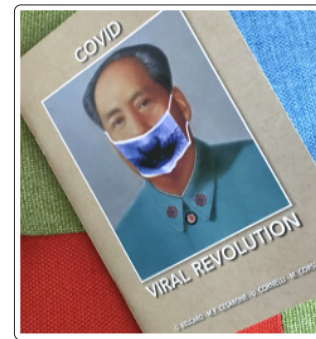
**Management:** the management was based on clinical targets as described in our recent paper (2-4) (Table 1):

1. Symptoms resolution or improvement
2. No DVT or thrombotic disease
3. No need for hospital, oxygen and no intensive care units (ITU).
4. Outcome at 6 weeks (in progress).

**Type of Study:** This study was a noninterventional, observational registry.

The main management (or standard, SM) included symptomatic management and WHV (warm humid vaporization) with a Prontex Vaporizer for at least 10 min, 3 times daily (with Calyptol, Sanofi), respiratory exercise with a Triflo assistant for improving respiration, careful diet and hours of rest/sleep, soft exercise (at least 20 minutes once daily) according - with what was possible at home i.e. small weights, roll-cycling or treadmill, free-body exercises (i.e. Pilates or yoga or dancing) individualized according to the house environment and patient's characteristics.

Vitamins and energy drinks were also used according to individuals' needs. An information/instruction book was given to all patients [5]. This book, explaining in simple terms and not-obsessively the problems and stimulating full collaboration was considered the pillar of the standard management in this situation.



**Figure 1:** The 100 pg briefing book given to patients to obtain full collaboration.

## Results

Two main groups resulted at the end of the registry:

A Comparative group (36; 11 females), no prophylaxis same SM (age 56.7; 4.4)

B Prophylaxis group (67; 14 females), prophylaxis A (age 56; 3.8); (35; 7 females) prophylaxis B (age 55.2; 5.3).

The two types of prophylaxis were defined on the basis of the informed choice of single patients and not prescribed [6].

In case of more complex thrombogenicity, TED (Thrombo-embolic deterrent stocking. Tyco) were used. In case of suspected DVT, a non-contact thermogram (Flir 440, Flir, Sweden) was made (with clinical evaluation) and the presence/absence of a DVT was excluded.

Table 1 shows the results in the prophylaxis and in the comparative group. At two weeks, there were no DVTs or thrombotic disease in the prophylaxis groups. Also, the evolution of the main respiratory symptoms was significantly better in the prophylaxis groups (p<0.05). No patients went to ITU: 4 out of 36 patients in the comparative group went briefly to hospitals. In subjects, using LMWH, 1 went to hospital as in the defibrotide group. None was put in ventilation. D-dimer values were fluctuating and not usable to define the presence of a thrombotic condition. This aspect is under further evaluation.

**Table 1: Shows the results in the prophylaxis and in the comparative group**

Targets	Comparative group, no prophylaxis, SM		SM+ Prophylaxis groups	%
	CASES %		CASES %	DIFFERENCE
1.Symptoms resolution Improvement	23/36 63.9%	A	56/67 83.6%	19.7%
		B	30/35 86.7	22.8
2.No DVT or thrombotic disease	32/36 88.9	A		11.1
		B		11.1
3.No hospital (no ITU)	32/36 88.9	A	66/67 98.5	9.6
	100	B	34/35 97.14	8.24
			100	
4.Outcome at 6 weeks	not available in progress		not available in progress	

No **significant side effects** were observed. Platelet alterations were limited and within the normal values in all prophylaxis subjects.

## Discussion

COVID pneumonia with massive lung alterations may inevitably alter venous flow and predispose to thrombotic events not only at peripheral level but also at central levels.

**The Risk:** Acute medical conditions (stroke, congestive heart failure, respiratory disease, infections, or myocardial infarction) are associated with a high risk of venous thromboembolism (VTE). Any Infection, erythropoiesis-stimulating agents, blood transfusions are clear risk factors [3]. The patients' overall risk is affected by reduced mobility, cancer with or without chemotherapy, or by patient-related risk factors such as prior VTE, advanced age, obesity, and coagulation disorders [5-9].

The oversimplified thinking about VTE as a venous disease with red thrombus versus coronary artery disease as a separate arterial disease (white thrombus) is outmoded. Four years after acute pulmonary embolism (PE), fewer than half of those who initially survive will remain free of myocardial infarction, stroke, peripheral arterial disease, recurrent VTE, cancer, or chronic thromboembolic pulmonary hypertension [10]. VTE and athero-thrombosis share a common pathophysiology including inflammation, hypercoagulability and endothelial injury as also seen in COVID patients [11, 12]. VTE is part of a panvascular syndrome that includes coronary artery disease, peripheral arterial disease, and cerebrovascular disease. VTE risk factors (smoking, hypertension, diabetes, obesity) overlap with risk factors for atherosclerosis [13, 14].

A high prevalence of DVT (28%-33%) has been detected in medical intensive care patients [15-17]. The prevalence of symptomatic VTE ranges from 3.4% to 6.6% [18-20]. In hospitalized medical patients, asymptomatic proximal DVT is associated with a higher mortality rate [21]. Fatal PE is the leading cause of sudden death in hospitalized medical patients. Approximately 25% of the patients dying from PE in general hospitals had recent surgery and the rest were immobilized with medical illnesses [22].

Overall mortality in medical patients admitted to hospitals is about 10%; 1 in 10 hospital deaths is due to PE [22, 23]. In the absence of VTE prophylaxis, 1 of 20 hospitalized medical patients may have a fatal PE [24, 25]. A model predicts patients with a very high risk of VTE; it helps to identify medical patients at high risk of VTE and may optimize the prevention (Padua Score) COVID patients are not different [26].

**Prophylactic Methods:** Recommendations [5]: For acutely ill medical patients low-density unfractionated heparin (LDUH) has been used to prevent DVT decreasing its rate from 21% to 5.5% [27-32]. LMWH prevents asymptomatic DVT reducing the incidence of DVT from 13% to 4.7%. There is no increased bleeding [33]. Several studies confirm the efficacy and safety of LMWH [34-40].

Prophylaxis is generally underutilized in medical patients compared to surgical patients [1, 6, 41-43]. VTE prophylaxis is frequently withheld in high-risk medical patients; causes are not known. This is possibly due to a stronger legal pressure in surgical patients. Failure to implement VTE prophylaxis is a global problem [44, 45]. In one study, patient refusal was the most common reason for lack of VTE anticoagulant medication adherence [46]. All hospitalized medical patients should be assessed for risk of VTE and those at moderate

(immobilized patients with active disease) or high risk (stroke, age > 70, cardiac failure, shock, history of previous VTE, malignancy, or thrombophilia) should receive prophylaxis [47-49].

**Duration of prophylaxis:** During hospitalization, nurses and therapists "push" patients to ambulate and minimize immobilization. Patients often receive less physical therapy after discharge leading to a paradoxical worsening of immobility and a higher risk of VTE. Patients treated at home for any reason, do not use prophylaxis according to their risks.

According to the international Consensus Recommendations, all acutely ill medical patients (including home patients) should be considered for thromboprophylaxis [50]. Patients >40 years with acute medical illness and/or reduced mobility with one of the following morbidities - acute heart failure NYHA class III/IV, respiratory disease (respiratory failure with or without ventilation or exacerbation of respiratory disease), active cancer requiring therapy, acute infective disease including severe infection and sepsis (this fully covers COVID), thrombophilia, rheumatic disease, ischemic stroke, or acute myocardial infarction should be always considered for prophylaxis. For acutely ill medical patients, prophylaxis with LMWH for 6 to 14 days is recommended. Single daily doses of 2.5 mg of fondaparinux is an important alternative. Extended duration of thromboprophylaxis may be considered on an individual basis.

## Conclusions

Our study (in progress) indicates and confirm that home patients using prophylaxis do not produce thrombosis that may worsen the clinical condition. From the International Consensus (will all its updates) medical patients should be always considered for prophylaxis [50].

COVID; comments. Cases of severe pulmonary infections are well covered in the consensus and in international guidelines [50, 51]. Any infection linked to vasculitis is an important thromboembolic risk and patients must be immediately protected with prophylaxis considering that, LMWH is safe, well known and poses very limited risks. Prophylaxis should be started as soon as possible and used during all the high-risk conditions [52, 53]. The importance of venous thromboembolism in medical patients with heart failure or severe respiratory disease (as COVID), even in the early phases, has been stressed and it is well known; it cannot be considered a new observation and requires adequate prophylaxis [36-39].

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**COMMENT:** G BELCARO, M DUGALL:

In this 'war' situation, with lack of communications, the *best interest* of the patient is the most important guide.

Guidelines, are just guidelines in normal times, in average situations and the careful Physician should apply managements and treatments according to '*timely, contextual judgement*' that may be very different from instructions/rules in 'peace time'.

That's why, we have physicians able to think and decide. Not robots. However, the '*thinking-deciding*' physician is often seen not as a value but as a glitch.

Rex Stout would say: '*a fly in the soup*'.

*Out of label* use of drugs is not legally sanctionable, and may be a good solution that any Physician may consider in case there is nothing else and in war conditions.

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