LETTER TO THE EDITOR

Online version at http://www.minervamedica.it
Minerva Medica 2020 mese;111(0):000–000
DOI: 10.23736/S0026-4806.20.06688-4

Thrombo-prophylaxis prevents thrombotic events in home-managed COVID patients

A registry study

All acutely ill medical patients should be managed with thromboprophylaxis. In particular, patients over age 40, 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 acute medical patients, prophylaxis with low-molecular-weight heparin (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 are an alternative to LMWH. LMWH is now preferred to low-dose unfractionated heparin (LDUH) 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 letter reports preliminary results from a pilot registry and analyzes data from subjects with COVID-19 infection and mild-to-moderate symptoms, followed and treated at home. Antithrombotic prophylaxis was used in all subjects. A comparison was made with comparable cases that had not used antithrombotic prophylaxis.

This registry includes a non-homogeneous sample collected by observation of COVID-19 patients who were exclusively treated at home. All subjects reported mild-moderate, 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 kg/m² (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.

Prophylaxis group A was treated with LMWH (Clexane as the first choice or what was available in the local pharmacies) was used 2 times daily at a dose between 4000 and 6000 IU, broadly according to weight.

Prophylaxis group B received defibrotide IM twice a day (10,000 IU) was also used in a number of patients that did not want to be treated with LMWH or subjects who preferred to use defibrotide.

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 or diagnostic tools. Clinical criteria to diagnose COVID-19 were increased temperature (>37.5 °C for at least 2 consecutive days), cough and upper respiratory symptoms, fatigue, malaise, other (pain, vasospastic symptoms).

TABLE I.—*Registry observational data.*

Endpoints	Control group (SM, no prophylaxis)	SM + prophylaxis group	Difference
Symptom resolution/improvement	23/36 (63.9%)	A: 56/67 (83.6%)	19.7%
		B: 30/35(86.7%)	22.8%
No DVT or thrombotic disease	32/36 (88.9%)	A: 67/67 (100%)	11.1%
		B: 35/35 (100%)	11.1%
No hospitalization	32/36 (88.9%)	A: 66/67 (98.5%)	9.6%
		B: 34/35 (97.14%)	8.24%
No ICU	100%		100%
Outcome at 3 weeks (no thrombosis)	31/36 (86.11%)	A: 66/67 (98.5%)	12.39%
		B: 34/35 (97.14%)	11.03%

A: prophylaxis A group (LMWH); B: prophylaxis B group (defibrotide).

Follow-up duration was at least 3 weeks. Most patients lost contact with their physicians of with the health authorities during this period.

The management was based on clinical targets as described in our recent paper (Table I):[2-4] 1) symptom 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).

This study was a non-interventional, observational registry. The standard management (SM) included symptomatic management and warm humid vaporization (WHV) 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) with what was available at home — *i.e.* small weights, roll-cycling or treadmill, free-body exercises (*i.e.* Pilates or yoga or dancing) tailoring the prescription to the house environment and patient's characteristics. Vitamins and energy drinks were also used according to individuals' needs. An information/instruction book on COVID and its possible complications was given to all patients.[5] Two main groups were considered at the end of the registry:

• a control group (N.=36; 11 females), no prophylaxis using SM (age 56.7±4.4 years);

• a prophylaxis group (N.=67; 14 females), further subdivided into a prophylaxis A group (N.=35, 7 females; age 56±3.8 years) and a prophylaxis B group (N.=32, 7 females; age 55.2±5.3 years).

The two types of prophylaxis[6] were defined on the basis of the informed choice of single patients and not prescribed. In case of more complex thrombogenicity risk TED (Thrombo-embolic deterrent stocking (Tyco) were also 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 I shows the results in the prophylaxis and in the control group. At two and 3 weeks there were no DVTs of thrombotic disease in the prophylaxis groups. The evolution of the main respiratory symptoms was significantly better in the prophylaxis groups ($P<0.05$). No patients went to ITU: four of 36 patients in the control group went briefly to hospitals. Among those subjects using LMWH, one 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. No significant side effects were observed.

Platelet alterations were limited and within the normal values in all prophylaxis subjects.

The *impromptu* study extension included subjects previously using oral anticoagulants (AC) for stabilized episodes of fibrillation. The anticoagulant management had been stable for at least two years. The AC management was suspended and the following day, fondaparinux (2.5 mg/day) was initiated. Table II shows the result of this group (N.=30, four females; age 55±3.3 years).

TABLE II.—*Results of the fondaparinux group (N.=30; one dose, 2.5 mg/day).There were no thrombotic events during the 3 weeks of follow-up.*

Endpoints	Results at 3 weeks
Symptom resolution/improvement	25/30 (83.33%)
No DVT or thrombotic disease	30/30 (100% event-free)
No hospitalization	29/30 (96.66%)
No ICU	30/30 (100%)

No side effects were observed. There were no thrombotic events in the 3 weeks of follow-up. Results are broadly comparable to the subjects managed with LMWH.

Acute medical conditions (stroke, congestive heart failure, pneumonia, infections, myocardial infarctions) are associated with high risk of venous thromboembolism (VTE).[5] Infections, erythropoiesis-stimulating agents, blood transfusions are clear risk factors. The patients' overall risk is affected by reduced mobility, cancer with or without chemotherapy, or by patient-related risk factors (prior VTE, advanced age, obesity, coagulation disorders). VTE is not only a venous disease with red thrombus different from, *i.e.*, coronary artery disease as a separate disease (white thrombus). After acute pulmonary embolism (PE), only half of those who initially survive will remain free of myocardial infarction, stroke, peripheral arterial disease, recurrent VTE, cancer, or chronic thromboembolic pulmonary hypertension. VTE and atherothrombosis share a common pathophysiology including inflammation, hypercoagulability and endothelial injury as also seen with prevalence in COVID patients. VTE is part of a panvascular syndrome and risk factors (smoking, hypertension, diabetes, obesity) overlap with risk factors for atherosclerosis). A high prevalence of DVT (28-33%) is found in medical intensive care patients. The prevalence of symptomatic VTE ranges from 3.4% to 6.6%. In hospitalized medical patients proximal DVT is associated with a high mortality rate. 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. Overall mortality in medical patients admitted to hospitals is about 10% and one in 10 hospital deaths is due to PE. In absence of VTE prophylaxis, one of 20 hospitalized medical patients may have a fatal PE. Patients with a very high risk of VTE may be identified and COVID patients are not different.

For acute medical patients low-density unfractionated heparin (LDUH) has been used to prevent DVT decreasing its rate from 21% to 5.5%. LMWH prevents asymptomatic DVT reducing its incidence from 13% to 4.7%. There is no increased bleeding. Prophylaxis is generally underutilized in medical patients compared to surgical patients. VTE prophylaxis is frequently withheld in high-risk medical patients. This is possibly due to a stronger legal pressure in surgical patients. Failure

to use VTE prophylaxis is a global problem. Patient refusal may be a common reason. Hospitalized medical patients must 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.

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,[5] all acute medical patients (including home patients) should use thromboprophylaxis. Patients >40 years with acute medical illness and/or reduced mobility with comorbidities (acute heart failure, NYHA class III/IV, respiratory disease, respiratory failure with or without ventilation, pneumonia), active cancer requiring therapy, acute infections including sepsis (this fully covers COVID), thrombophilia, rheumatic disease, ischemic stroke, acute myocardial infarction should be always considered for prophylaxis. For acute 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 — and adapted, individualized dosages for thromboprophylaxis — may be considered according to conditions.

In conclusion, our study indicates and confirm that home patients using prophylaxis do not produce thrombosis that may worsen the clinical condition. From the International Consensus (with all its updates)[5] medical patients should be always considered for prophylaxis.

COVID comments. Cases of severe pulmonary infections are well covered in the consensus and in international guidelines.[5, 7, 8] 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. 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. We suggest that for these patients a weight-adapted dose, twice daily, may be the best option for COVID subjects but research is needs. For more severe cases (hospitalized, in ICU), using also a complex of several drugs and in more severe conditions a specific prophylaxis (individualized on patients and conditions) should be evaluated.

Gianni BELCARO [1, 2] *, Marcello CORSI [1, 2], Giovanni B. AGUS [1, 2], Maria R. CESARONE [1, 2], Umberto CORNELLI [1, 2], Roberto COTELLESE [1, 2], Beatrice FERAGALLI [1, 2], Shu HU [1, 2]

[1]Oolex Center for COVID, IRVINE3 Labs, Chieti-Pescara University, Chieti, Italy; [2]Department of Medical and Oral Sciences and Biotechnologies, Chieti-Pescara University, Pescara, Italy

*Corresponding author: Gianni Belcaro, Oolex Center for COVID, IRVINE3 Labs, Chieti-Pescara University, Chieti, Italy. E-mail: cardres@abol.it

References

1. Goldhaber SZ, Turpie AG. Prevention of venous thromboembolism among hospitalized medical patients. Circulation 2005;111:e1–3.

2. Belcaro G, Cornelli U, Cesarone MR, Feragalli B, Bombardelli E, Dugall M. Spread of Respiratory Viruses: Temperature and Physical Environment. Temperature Control May Exploit Virus Hypo-Thermolabity; A Possibile, Immediate Solution for COVID-19. Med Clin Res 2020;5:30–3.

3. Belcaro G, Cornelli U, Cesarone MR, Feragalli B, Bombardelli E, Dugall M. Possible, Immediate Solution for COVID-19: temperature control may exploit virus hypo-thermolability. Asia Pac Biotech News 2020;24:22–6.

4. Belcaro G, Cornelli U, Cesarone MR, Feragalli B, Bombardelli E, Dugall M, *et al.* 7 immediate strategies to control the coronavirus. Exploiting viral thermolabity. Possibile, immediate solutions for COVID-19. A position paper; 2020 [Internet]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3575496 [cited 2020, May 26].

5. Bergqvist D, Bonnar J, Caprini J, Carter C, Comerota A, Conard J, *et al.*; Cardiovascular Disease Educational and Research Trust; European Venous Forum; North American Thrombosis Forum; International Union of Angiology; Union Internationale du Phlebologie. Prevention and treatment of venous thromboembolism: international consensus statement (guidelines according to scientific evidence). Clin Appl Thromb Hemost 2013;19:116–8.

6. Belcaro G, Cesarone MR, Cornelli U, Corsi M. Viral Revolution, Oolex, Pescara, April 2020.

7. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, *et al.* COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. J Am Coll Cardiol 2020;S0735-1097(20)35008-7. [Epub ahead of print]

8. Feragalli B, Mantini C, Sperandeo M, Galluzzo M, Belcaro G, Tartaro A, *et al.* The lung in systemic vasculitis: radiological patterns and differential diagnosis. Br J Radiol 2016;89:20150992.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

History.—Article first published online: _____. - Manuscript accepted: May 25, 2020. - Manuscript received: May 21, 2020.

(*Cite this article as:* Belcaro G, Corsi M, Agus GB, Cesarone MR, Cornelli U, Cotellese R, *et al*. Thrombo-prophylaxis prevents thrombotic events in home-managed COVID patients. A registry study. Minerva Med 2020;111:000–000. DOI: 10.23736/S0026-4806.20.06688-4)