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# FONDENOXAVID: A Retrospective Analysis on Utility of Thromboprophylaxis with Fondaparinux and Enoxaparin in Patients with COVID19 Infection in Italy

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**ABSTRACT**

**Background:** After the outbreak of a novel coronavirus (i.e. SARS COV2) in China and its diffusion around the world, great attentions was reserved to the increased incidence of venous thromboembolism in these patients. A specific antiviral action of heparins toward SARS COV2 has been reported in vitro such as a well know action of heparins to prevent VTE in inpatients with infective disease has already been reported since several years. Yet, because fondaparinux represent the pharmacological antithrombotic active sequence of all heparins and because its clinical indication o prevent VTE in inpatients is similar to heprains, we realized a retrospective analysis in inpatients with SARS COV2 on the incidence of VTE during pharmacological prophylaxis with enoxaparin or fondaparinux. This retrospective analysis was named FONDENOXAVID.

**Methods:** We conducted a retrospective cohort study that used patients with SARS COV2 during the Italian outbreak from February 18, 2020 to april30, 2020.
Our aim was to compare the clinical characteristics, prophylactic treatment and outcomes in inpatients positive to SARS COV2 at risk to develop venous thromboembolism, in particular venous thrombosis with or without pulmonary embolism, during in-hospital primary thromboprophylaxis with enoxaparin (40 mg or 60 mg once daily) or fondaparinux (2.5 mg once daily).
Statistical analysis was conducted with using MatLab R2016B and eventually ad hoc functions.

**Results:** There were not significative differences in clinical characteristics between patients that used enoxaparin or fondaparinux as thromboprpophylaxis for SARS COV2. The cumulative incidence of thrombotic events was not different in patients that used enoxaparin or fondaparinux as thromboprpophylaxis. No differences were found also in d-dimer and fibrinogen levels test at the admission and after 3 weeks as markers of prolonged inflammation due to SARS COV2.

**Discussion:** The increased incidence of VTE in vivo has been reported in several studies although prophylaxis with low molecular weight heparin was conducted in some of them. The clinical indication to prevent VTE was similar for heparins and fondaparinux. In our results a non-inferiority to prevent VTE was recorded when inpatients with SARS COV2 were treated with prophylactic doses of enoxaparin or fondaparinux according to

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international guidelines. The incidence of VTE in this retrospective analysis showed that Fondaparinux at fixed doses of 2.5 mg daily was not inferior to enoxaparin (4000 UI daily).

Our results testify that fondaparinux and enoxaparin showed the same efficacy to reduce the incidence of VTE in inpatients with SARS COV2.

**Keywords:** venous thromboembolism, fibrinogen, d-dimer, COVID19, SARS-CoV2, fondaparinux, enoxaparin

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## Background

After the outbreak of a novel coronavirus (i.e. SARS COV2) in China and its diffusion around the world (1), several therapeutic strategies have been reported in the Literature (2). The main attention of therapeutic support has been given to oxygen support and then to antiviral treatment but also to other several drugs tested to counteract the infection although not univocal data are available (3). Yet, in this way, inpatients affected by SARS COV2 showed also an increased trend to hypercoagulable state (4) and then to thrombotic diseases as venous thromboembolism (VTE) (5). For this reason, several Authors supported the protective action of heparin, in particular low molecular weight heparin as enoxaparin, because its specific antinflammatory and antiviral showed in vitro also versus SARS COV2 (6-7). Furthermore, the protective actions of heparins are exerted also for the prevention of VTE events (8). Pulmonary embolism, in fact, has been reported to be associated to COVID19 in different autoptical studies (9) and of course also in vivo in several cohort of inpatients in ICU (10).

All described actions (i.e. antiviral action and prevention of VTE for inpatients with SARS COV2) are well documented in vitro and in vivo for heparins while data regarding the same action for fondaparinux are lacking in the Literature,althoughfondaparinux is the syntheticpenthasaccharidic sequence with antithrombotic actions present in all heparins. Furthermore, in daily clinical practice, fondaparinux and enoxaparin has the same clinical indication for prevention of VTE (11).

The FONDENOXAVID study gave information alsoon the antinflammatory actions of fondaparinux and enoxaparin (tailored prophylactic doses) during SARS COV2 besides information onVTE prevention.

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## Patients and methods

*Inclusion criteria*

Selected patients with symptomatic, confirmed SARS COV2 were selected for a retrospective analysis in order to understand the incidence and mortality for VTE during thromboprophylaxis with fondaparinux or enoxaparin at doses suggested by international guidelines on VTE prevention or to update the role of the progressive lung inflammation with its related morbidity and mortality.

Oral or written informed consent was given for participation to this retrospective analysis that is named FONDENOXAVID.Ethics committee approval was obtained.

Physicians participating to FONDENOXAVID retrospective analysis made all efforts to select consecutive patients although in a retrospective way.

Data were recorded onto a computer-based report from at each participating hospital and sent to a centralized coordinating centre through a secure system.

FONDENOXAVID also used electronic data monitoring to detect inconsistencies or errors and
attempted to resolve discrepancies by contacting the local coordinators.

*Exclusion criteria*

Patients aged less than 18 yy were excluded from the retrospective analysis. Patients that were taken anticoagulants at therapeutic doses before SARS COV2 diagnosis for any medical reason were excluded from the selection; patients positive for SARS COV2 but with recent bleeding (i.e. within 30 days of hospital admission), were excluded from the selection too.

Patients were also excluded if they were currently participating in any clinical trials regarding for COVID19 or VTE.

*Design*

We conducted a retrospective cohort study that used patients with SARS COV2 during the Italian outbreak from February 18, 2020 to April 30, 2020.
Our aim was to compare the clinical characteristics, prophylactic treatment and outcomes in inpatients positive to SARS COV2 at risk to develop venous thromboembolism, in particular venous thrombosis with or without pulmonary embolism, during in-hospital primary thromboprophylaxis with enoxaparin (40 mg or 60 mg once daily) or fondaparinux (2.5 mg

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once daily) or the inflammatory progression associated to prothrombotic state testified by increased levels of fibrinogen and d-dimer.

Main outcomes were the rate of VTE (i.e. deep vein thrombosis or superficial vein thrombosis or pulmonary embolism), mortality for VTE, clotting abnormalities associated to progressive inflammation testified by increased levels of fibrinogen and d-dimer, incidence of morbidity and mortality for progressive inflammation.

*Clinical definitions and variables*

Antropometric, clinical, laboratory, instrumental and therapeutic data were retrospectively collected in patients with COVID19.

Patients were divided into 2 different group for analysis: patients that performed enoxaparin 40 mg (standard dose) or 60 mg daily (intermediate dose for high risk patients) (11) for primary thromboprophylaxis of VTE (i.e. group 1) and patients that performed fondaparinux 2.5 mg daily for primary thromboprophylaxis of VTE according to international agreement for prevention of VTE (12).

Selected variables to be analysed were sex, age, weight, BMI, clinical presentations (i.e. isolated pneumonia or SARS). Inflammatory state associated to specific acquired hypercoagulables state was evaluated testing d-dimer, fibrinogen and C reactive protein valueswere at the hospital admission and after 14 days from hospital admission.

Venous thrombotic events of lower limbs were evaluated with Compressive ultrasonography (CUS), performed for all patients between day 5 and day 8 after the hospital admission; PE events were looked for all patients during clinical observation when the suspect was high and according to internal guidelines protocol: GENEVA SCORE and 2-3-fold increase of d-dimer after first d-dimer sampling.

For all patients we considered also overall mortality after discharge from hospital at day 28$^{th}$ after SARS COV2 identification and beginning of thromboprophylaxis.

Data about pharmacological thromboprophylaxis was recorded since the hospital admission both for enoxaparin and fondaparinux.

*Statistical analysis*

Statistical analysis was performed using MatLab R2016B and eventually ad hoc functions.

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The Anderson–Darling test was used to analyze data normality. Continuous variables were reported using the median and interquartile intervals. Categorical variables were indicated as frequency counts and percentages. Differences inter 2 groups were evaluated using the 2-tailed Fligner–Policello and Fligner–Killeen tests for continuous data and the Barnard's or Fisher's test for categorical variables. Differences inter 3 groups were evaluated using the 2-tailed Dunn's multiple comparison test with Bonferroni correction. Differences intra 2 groups were evaluated using the 1-tailed Wilcoxon's test.

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## Results

The clinical and laboratory characteristics of study population were shown in Table 1; data were reported as percentage**.** There were not significative differences in clinical characteristics between patients that used enoxaparin or fondaparinux as thromboprpophylaxis for SARS COV2.

Venous thrombosis was detected in 5 patients in the enoxaparin group vs 2 patients in the fondaparinux group; 3 deep vein thrombosis, 1 isolated distal vein thrombosis and 1 superficial vein thrombosis for the enoxaparin group while 2 deep vein thrombosis for the fondaparinux group.Pulmonary embolism was detected in 4 patients in the enoxaparin group while no pulmonary embolism was found in the fondaparinux group. Data about distribution of thrombotic events were summarized in table 1. Barnard's test was used to analyze data.

No differences were found for overall mortality or mortality for VTE as reported in table 1. Data were analyzed using Barnard test.

We did not find differences in d-dimer distribution on admission as reported also in table 2 and in figure 1. Data were obtained usingFligner-Policello and Fligner-Killeen teststhat did not show differences about medians or variances into unmatched D-dimer distributions.

None differences were found also analyzing d-dimer distribution after 3 weeks.

1-tailed Wilcoxon's test was also used onto matched data analyzing Enoxaparin or Fondaparinux groups and no differences were found.

We did not find differences in fibrinogen and CRP distributions on admission and after 3 weeks as reported also in table 2 and in figure 2. Data were obtained using Fligner-Policello and Fligner-Killeen tests that did not show differences about medians or variances into unmatched fibrinogen distributions;

None differences were found also analyzing fibrinogen distribution after 3 weeks.

1-tailed Wilcoxon's test was also used onto matched data analyzing Enoxaparin or Fondaparinux groups and no differences were found.

Table 3 show all categories of drug used to treat SARS COV2 in our cohort in which heparinoids (i.e. enoxaparin and fondaparinux) were the only drugs to reach 100% of patients.

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## Discussion

D-dimer testing is one of laboratory procedures used to suspect or to esclude venous thromboembolism (13). Furthermore, d-dimer levels may have also prognostic value after the confirm of a VTE event (14).

Furthermore, if VTE event is not present d-dimer levels may be increased for several other reasons and infections are one of this (15-16). SARS COV2 infection, in fact, is associated to abnormal levels of d-dimer and fibrinogen (17-18).

In our study the incidence of VTE in patients that used pharmacological prophylaxis was low (no higher than 10%) but abnormal and increased values of d-dimer were present in more than 75% of patients both at the admission and after 3 weeks although reduced; for this reason, we associated the clinical surveillance of admitted patients with increased d-dimer both for VTE events and also for inflammatory markers as fibrinogen and C reactive protein. The SARS COV2 pathophysiology, in fact, usually showed a prolonged clinical course because the association with it is associated to prolonged inflammation of respiratory system that may exceed 20 days (19).

On the other hand, the treatment of SARS COV2 infection is based on the administration of several kind of drugs with multiple actions in order to reduce the inflammatory damages (i.e. antivirals, immunomodulants, antibiotics, steroids, antithrombotics). For their pharmacological properties heparinoids showed to be drugs that may fight SARS COV2 infection in multiple ways: a specific antiviral action of heparin toward n-COV19 has been found in vitro (20-21) as well a specific antinflammatory action of heparinoids and fondaparinux has known (22-23) and these action should be added to their antithrombotic actions. Yet the specific active action of heparin, that is a saccharidic polymer is exerted by a penthaccaridic sequence and fondaparinux is the synthetic pentasaccharidic sequence of heparin (24). For this reason, we postulated that all therapeutic actions exerted by enoxaparin, the most studied of all heparins, could be effective also for fondaparinux.

Because of the antithrombotic indication is similar for both drugs (i.e. enoxaparin and fondaparinux) (12), beside to compare the incidence of VTE events in our population of patients affected by SARS COV2, we compared also their action toward the levels of d-dimer, fibrinogen and C reactive protein as markers of associated prolonged inflammation present in SARS COV2.

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As already underlined in our results, the incidence of thrombotic events was similar in both groups as well as the rate of death for VTE and overall death.

Yet, regarding the increased levels of fibrinogen, C reactive protein and d-dimer due to the prolonged inflammation a progressive reduction of all values has been recorded in both groups in particular for C reactive protein but without statistical differences for patients that performed prophylaxis with enoxaparin or fondaparinux.

So, we can assume that the association of heparinoids as enoxaparin or fondaparinux to standard therapies for SARS COV2 infection has multiple clinical advantages as the reduction of VTE rate, the reduction of death for VTE and the progressive adjuvant and ancillary action to counteract the prolonged inflammatory state present in the disease (21). As we reported in table 3, in fact, heparinoids were the only class of drug used in all selected patients, so their antinflammatory effect gave a contribution in the improvement of levels of inflammatory markers as C reactive protein and fibrinogen beside d-dimer. In this specific field we added and enlarged this knowledge to the use of fondaparinux; Literature, in fact, in this fields, reports more data on the use of low molecular weight heparin as enoxaparin, Interestingly, patients that performed thromboprophylaxis with fondaparinux showed at the admission values of CRP higher than patients treated with enoxaparin and this difference raised statistical significance; after 21 days of treatment there were not differences in values of CRP in patients that performed treatment with fondaparinux or enoxaparin,so we may speculate that antinflammatory actions of fondaparinux are stronger than those of enoxaparin but these data should be confirmed by further studies.

In conclusion, fondaparinux showed its non-inferiority to enoxaparin in VTE prevention, VTE mortality and antiviral and antinflammatory actions during SARS COV2 infection.

Of course our study shows several limitations, first of all the selection of patients that was conducted by a retrospective analysis. Furthermore, the fondaparinux has a unique dosage for thromboprophylaxis while different dosages are available for enoxaparin and we selected only patients that performed standard dosage with 4000 u daily; last but not least the outcome of events has been limited to 4 weeks that has been the duration of hospitalization for the major of Italian inpatients but it could be different if we analyse same outcomes in different times.

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## REFERENCES


1. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, Iosifidis C, Agha R. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg. 2020;76:71-76
2. Juul S, Nielsen N, Bentzer P, Veroniki AA, Thabane L, Linder A, KlingenbergS,Gluud C, Jakobsen JC. Interventions for treatment of COVID-19: a protocol for a living systematic review with network meta-analysis including individual patient data (The LIVING Project). Syst Rev. 2020;9(1):108
3. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, LiX, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;382(19):1787-1799
4. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associatedwith poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847
5. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, BoumanCCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI, van Es N. Incidenceof venous thromboembolism in hospitalized patients with COVID-19. J ThrombHaemost. 2020 May 5.
6. Cattaneo M, Bertinato EM, Birocchi S, Brizio C, Malavolta D, Manzoni M, Muscarella G, Orlandi M. Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified? ThrombHaemost. 2020 Apr 29
7. Belen-Apak FB, Sarialioglu F. The old but new: Can unfractioned heparin and low molecular weight heparins inhibit proteolytic activation and cellular internalization of

 doi:10.20944/preprints202005.0309.v1

SARS-CoV2 by inhibition of host cell proteases? MedHypotheses. 2020 Apr 20;142:109743

8. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, DrigginE, Nigoghossian C, Ageno W, Madjid M, Guo Y, Tang LV, Hu Y, Giri J, Cushman M, Quéré I, Dimakakos EP, Gibson CM, Lippi G, Favaloro EJ, Fareed J, Caprini JA, Tafur AJ, Burton JR, Francese DP, Wang EY, Falanga A, McLintock C, Hunt BJ, Spyropoulos AC, Barnes GD, Eikelboom JW, Weinberg I, Schulman S, Carrier M, Piazza G, Beckman JA, Steg PG, Stone GW, Rosenkranz S, Goldhaber SZ, Parikh SA, Monreal M, Krumholz HM, Konstantinides SV, Weitz JI, Lip GYH. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. J AmCollCardiol. 2020 Apr 15. pii: S0735-1097(20)35008
9. Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A,Heinrich F, Mushumba H, Kniep I, Schröder AS, Burdelski C, de Heer G, NierhausA,Frings D, Pfefferle S, Becker H, Bredereke-Wiedling H, de Weerth A, PaschenHR,Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, AepfelbacherM,Püschel K, Kluge S. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med. 2020 May 6
10. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM,Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence ofthrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020 pii: S0049-3848(20)30120-1
11. Eck RJ, Bult W, Wetterslev J, Gans ROB, Meijer K, Keus F, van der Horst ICC. Intermediate Dose Low-Molecular-Weight Heparin for Thrombosis Prophylaxis: Systematic Review with Meta-Analysis and Trial Sequential Analysis. Semin Thromb Hemost. 2019;45(8):810-824
12. Harrington DW. Choosing the right heparin prophylaxis strategy in medicalpatients at risk for developing VTE: an evidence-based approach. Hosp Pract(1995). 2010;38(4):18-28.
13. Streiff MB, Agnelli G, Connors JM, Crowther M, Eichinger S, Lopes R, McBane, RD, Moll S, Ansell J. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. J Thromb Thrombolysis. 2016;41(1):32-67.

14. Lobo JL, Zorrilla V, Aizpuru F, Grau E, Jiménez D, Palareti G, Monreal M; RIETE Investigators. D-dimer levels and 15-day outcome in acute pulmonary embolism. Findings from the RIETE Registry. J Thromb Haemost. 2009;7(11):1795-801
15. Schutte T, Thijs A, Smulders YM. Never ignore extremely elevated D-dimer levels: they are specific for serious illness. Neth J Med. 2016;74(10):443-448
16. Di Micco P, D'Uva M, Strina I, Mollo A, Amato V, Niglio A, De Placido G. The role of d-dimer as first marker of thrombophilia in women affected by sterility: implications in pathophysiology and diagnosis of thrombophilia induced sterility. J Transl Med. 2004 Nov 9;2(1):38
17. Di Micco P, Russo V, Carannante N, Imparato M, Rodolfi S, Cardillo G,Lodigiani C. Clotting Factors in COVID-19: Epidemiological Association and Prognostic Values in Different Clinical Presentations in an Italian Cohort. J Clin Med. 2020;9(5). pii: E1371
18. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395:1340
19. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020 May 6
20. Madu IG, Chu VC, Lee H, Regan AD, Bauman BE, Whittaker GR. Heparan sulfate is a selective attachment factor for the avian coronavirus infectious bronchitis virus Beaudette. Avian Dis. 2007;51(1):45-51
21. Ghiselli G. Heparin Binding Proteins as Therapeutic Target: An Historical Account and Current Trends. Medicines (Basel). 2019;6(3). pii: E80.
22. Lean QY, Eri RD, Randall-Demllo S, Sohal SS, Stewart N, Peterso GM, Gueven N,Patel RP. Orally Administered Enoxaparin Ameliorates Acute Colitis by Reducing Macrophage-Associated Inflammatory Responses. PLoS One. 2015;10(7):e0134259
23. Frank RD, Schabbauer G, Holscher T, Sato Y, Tencati M, Pawlinski R, Mackman N. The synthetic pentasaccharide fondaparinux reduces coagulation, inflammation and neutrophil accumulation in kidney ischemia-reperfusion injury. J Thromb Haemost. 2005; 3(3):531-40
24. Zhang Y, Zhang M, Tan L, Pan N, Zhang L. The clinical use of Fondaparinux: A synthetic heparin pentasaccharide. Prog Mol Biol Transl Sci. 2019;163:41-53.

Krykhtina MA, Bielosludtseva KO, Botvinikova LA, Matikina NM. Lung vessels thrombosis in hospitalized patients with community-acquired pneumonia: role of endothelial function, hemostasis, fibrinolysis and inflammation on different phases of treatment. WiadLek. 2019 Aug 31;72(8):1463-146

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**Table 1. Demographic, clinical, and laboratory characteristics of the study population.**

| Patients' Characteristics | Enoxaparin N: 62 | Fondaparinux N: 38 | p-value |
|---|---|---|---|
| Males, n (%) | 40 (65%) | 23 (61%) | 0.76 |
| Age <40 yy, n (%) | 3 (5%) | 6 (16%) | 0.09 |
| Age 40–60 yy, n (%) | 34 (34%) | 17 (45%) | |
| Age >60 yy, n (%) | 38 (61%) | 15 (39%) | |
| VT | 5 (8%) | 2 (5%) | 0.76 |
| PE | 4 (6%) | 0 (0%) | 0.12 |
| Death for VTE | 1 (2%) | 0 (0%) | 0.50 |
| Overalldeath | 6 (9%) | 4 (10%) | 0.82 |

**Legend to table 1. Age was analyzed by Fisher's test; other variables were analyzed by Barnard's test.**

VT: Vein Thrombosis;
PE: pulmonary embolism

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**Table 2. Comparisons of D-dimer, fibrinogen and CRP distributions between Enoxaparin and Fondaparinux groups at baseline and after 3 weeks.**

| D-dimer mcg/dL | Enoxaparin N: 62 | Fondaparinux N: 38 | FP-test p-value | FK-test p-value |
|---|---|---|---|---|
| Admission | 710.5 (520 – 1208) | 643.5 (502 – 919) | 0.10 | 0.14 |
| 3 week later | 602 (428 – 1230) | 606 (450 – 810) | 0.38 | 0.21 |
| Wilcoxon test p-value | 0.09 | 0.33 | | |
| Fibrinogen mg/dL | Enoxaparin N: 62 | Fondaparinux N: 38 | FP-test p-value | FK-test p-value |
| Admission | 600 (478 – 734) | 570 (503 – 632) | 0.15 | 0.07 |
| 3 weeks later | 631 (497 – 722) | 535 (450 – 630) | **0.01** | 0.07 |
| Wilcoxon test p-value | 0.29 | 0.28 | | |
| CRP mg/dL | Enoxaparin N: 62 | Fondaparinux N: 38 | FP-test p-value | FK-test p-value |
| Admission | 11.53 (3.60 – 21.97) | 44.00 (15.00 – 52.00) | **0.000004** | **0.0011** |
| 3 weeks later | 13.00 (5.00 – 40.50) | 15.00 (9.00 – 21.00) | 0.3051 | 0.17 |
| Wilcoxon test p-value | **0.006** | **0.0005** | | |

**Legend to table 2:**

FP: Fligner–Policello; FK: Fligner–Killeen

CRP: C Reactive Protein

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**Table 4. class of drugs used in the described cohort of patients treated for SARS COV2.**

| **Patients (n 100)** | **N** | **%** |
|---|---|---|
| Antibiotics | 64 | 64 |
| Biologics (tocilizumab or others) | 12 | 12 |
| Antivirals | 21 | 21 |
| Steroids | 55 | 55 |
| Immunomodulants (hydroxicloroquine or others) | 65 | 65 |
| Heparinoids (enoxaparin or fondaparinux) | 100 | 100 |

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**Figure 1. distributions of d-dimer in both group at the admission and after 3 weeks.**

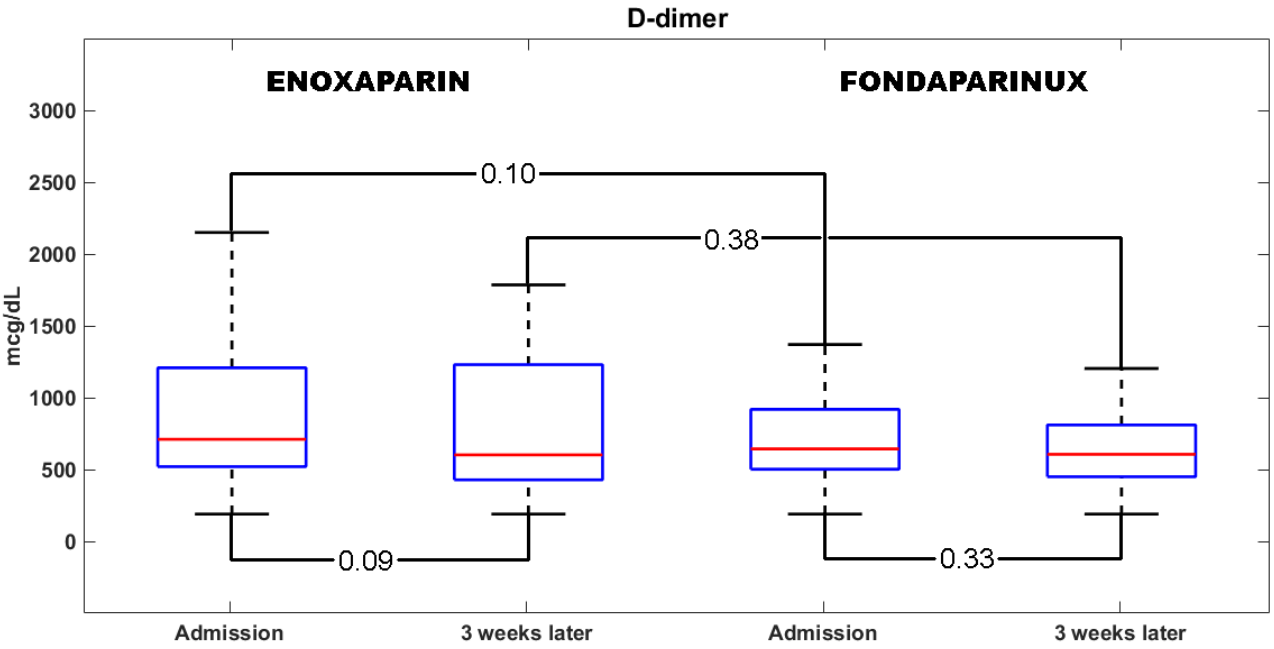

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**Figure 2. distributions of fibrinogen in both group at the admission and after 3 weeks.**

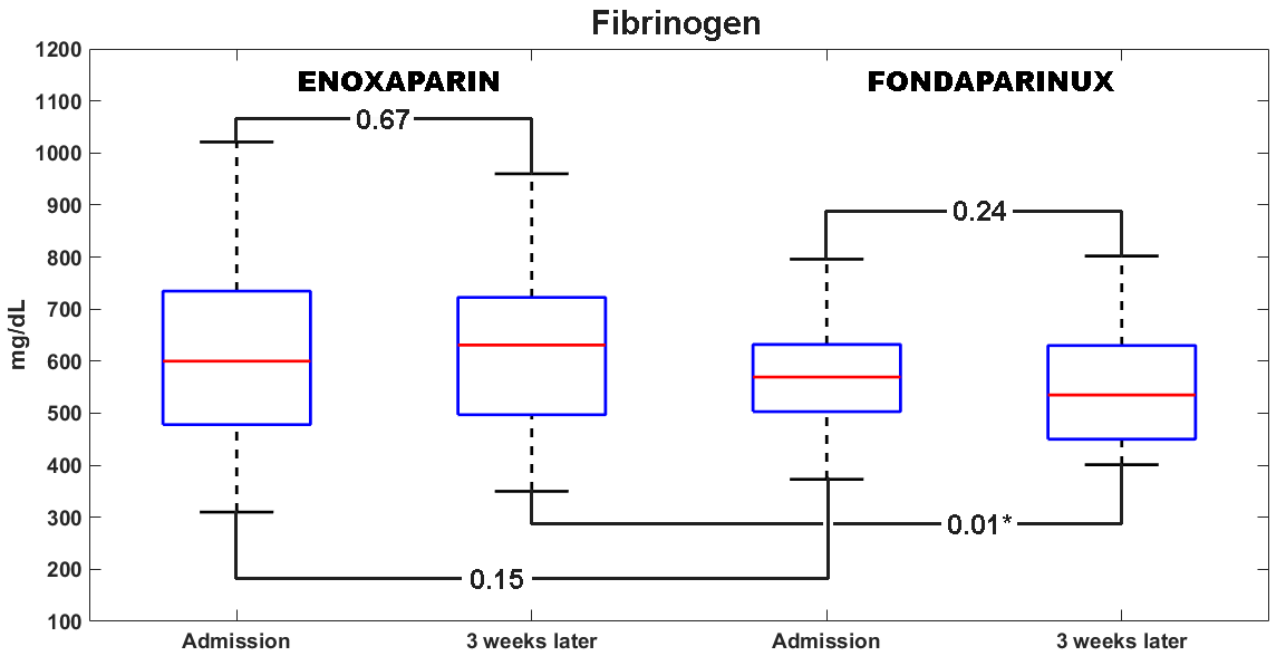

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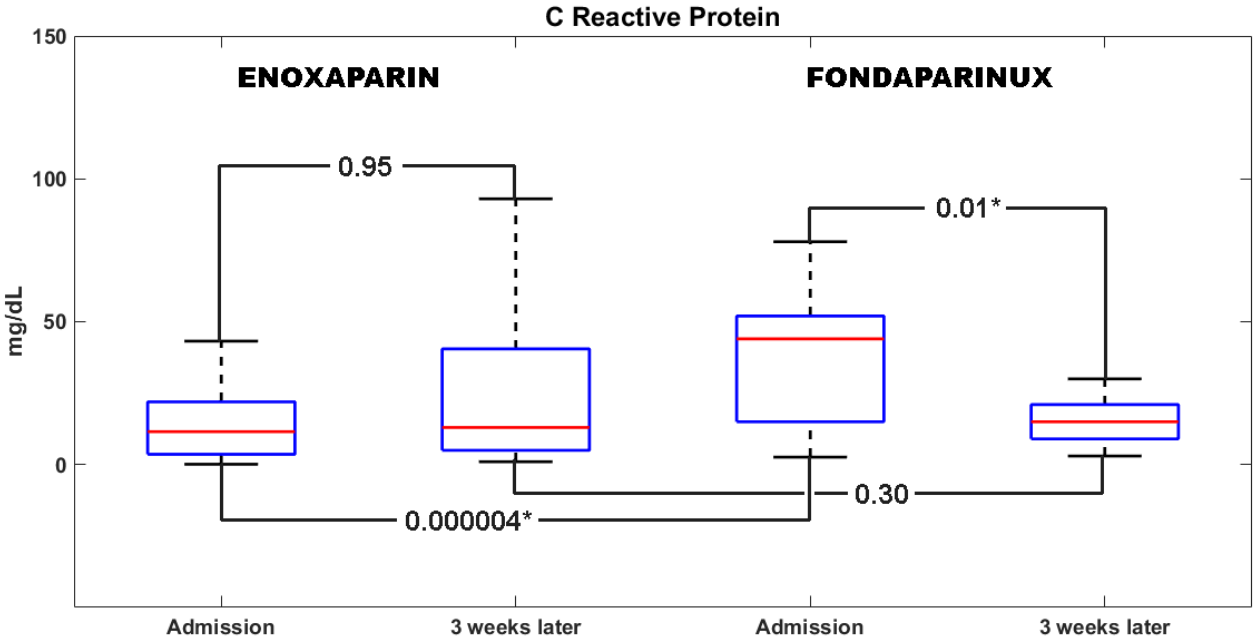
**Figure 3. distributions of CRP in both group at the admission and after 3 weeks.**




**Legend to figure 3**

**CRP: C reactive protein**