

COVID-19 pandemic affects the ability of negative D-dimer to identify venous thromboembolism patients at low risk of recurrence: insights from Apidulcis study

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COVID-19 pandemic affects the ability of negative D-dimer to identify venous thromboembolism patients at low risk of recurrence: insights from Apidulcis study

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Dear Sir,

The Apidulcis study, the report of which was recently published in Blood Advance¹, confirmed the high efficacy and safety of extended anticoagulant treatment with a reduced dose of Apixaban (2.5mg twice a day) in patients (n= 446) who had a positive D-dimer test after a single venous thromboembolic (VTE) event during standard anticoagulant therapy or within two months after its discontinuation. However, the study also showed that negative D-dimer results failed to identify patients in whom an extended anticoagulation might be safely avoided. Indeed, in patients with negative D-dimer at the time of inclusion in the study (n= 286), who remained off anticoagulation, a high incidence of primary outcomes – almost completely represented by recurrent VTE events - was recorded [incidence: 6.2 x100 pt-y; 95% confidence intervals (CI) 3.9-9.5]. This incidence was higher than expected based on what was observed in previous studies^{2,3}, and higher if compared with what observed in a study with similar design (3.0 x100 pt-y; 95% CI 2.0-4.4%)⁴. Furthermore, the incidence was much higher than that recorded in patients who continued anticoagulation with reduced dose Apixaban (0.9 x100 pt-y; 95% CI 0.3-2.2). In line with the per protocol stopping rule, the significant difference between the rates of primary outcomes in the two groups led to a premature interruption of the study in December 2021.

We were surprised by the high incidence of recurrent events in patients with persistently negative D-dimer results and, after the publication of the main report, we explored potential reasons that may have contributed to these findings.

We hypothesized that the SARS-CoV-2 (COVID-19) infection, which became widespread in our country while the Apidulcis study was ongoing, might have influenced the above results. The inclusion of patients in the study began on August 2018 (see Figure); however, much of the study was concomitant to the initial phase (the first affected patient in our country was diagnosed at the end of February 2020) and COVID-19 infection spread during the subsequent months, through all the 2021. As shown in the Figure, only 3 thrombotic events (red bars) occurred before the pandemic, while the 16 remaining events occurred during the pandemic. As reported in the Table, the incidence of recurrences was significantly higher during the last year of the study activity, in concomitance with the spread of viral infection. We also invited all participant investigators to collect information from the patients who had negative serial D-dimer testing at inclusion about possible COVID-19 infection occurring during follow-up. Information was gathered from n. 258 (90.2%) out of the 286 with negative D-dimer testing, including all the 16 patients who had recurrent events during the pandemic. Three recurrences occurred amongst the 32 patients who had positive COVID-19 testing during follow-up; while 13 events occurred in the 226 who tested negative [the incidence was 10.3% pt-y (95%CI: 2.1-30.3) and 6.1% pt-y (95%CI: 3.2-10.4), respectively].

The present data from a post-hoc analysis of Apidulcis results, lead us to hypothesize that the pandemic has affected the Apidulcis study results, directly or by various mechanisms, contributing to an increased risk of recurrences that could not be predicted by negative D-dimer assay performed at the time of patient

enrollment in the study. It is well known that COVID-19 pandemic is associated with an increased rate of VTE events, which is not limited to the patients more seriously affected^{5,6}. Furthermore, an impact of the pandemic on increasing VTE occurrence has been described even in non-COVID-19 populations^{7,8}, likely due to indirect pandemic effects, such as the various restrictions and lockdown, with a general reduction in physical activity⁹, a subsequent trend to obesity, and - among others - an increase in smoking¹⁰.

The present data suggest that the pandemic may have influenced the Apidulcis study results. This observation has two important implications.

First and more important, it adds further value to the remarkable efficacy and safety of reduced dose Apixaban, already described in the main report. As the recurrence rate in patients taking reduced dose Apixaban was comparable to that reported before the COVID-19 pandemic¹¹, it is tempting to speculate that the reduced dose Apixaban was consistently effective even in the patients experiencing increased pro-thrombotic effects associated with the pandemic. Secondly, the results of this post-hoc analysis illustrate the pitfalls associated with clinical prediction rules. During the conduct of the Apidulcis study, an unexpected event led to an increase in the baseline recurrence risk, thus substantially changing the targeted study population. We are still convinced that negative D-dimer testing may have a predictive ability for a patient population with a baseline recurrence risk of 3 to 5% pt-y (i.e., as our study population in the pre-COVID-19 era).

Finally, we would like to warn the researchers who plan to investigate the risk of recurrence after VTE, that the COVID-19 pandemic likely influences the natural history of VTE.

Apidulcis study group

(in order of decreasing cases recruited)

- Poli Daniela, Lotti Elena, Crudele Felice - Firenze
- Ageno Walter, Abenante Alessia, Caiano Lucia, Colombo Giovanna, Guarascio Matteo - Varese
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- Lessiani Gianfranco - Città Sant'Angelo (PE)
- Parisi Roberto, Bortoluzzi Cristiano, Vo Hong Ngoc - Venezia
- Chiarugi Paolo, Casini Monica - Pisa
- Violo Caterina, Nuti Marco - Pisa
- Angeloni Lucia - Ospedale "G. Dossetti" - Valsamoggia (BO)
- Carrozzi Laura, Pancani Roberta, Chimera Davide, Conti Valentina, Meschi Claudia - Pisa
- Cattaneo Marco, Podda Gianmarco, Birocchi Simone - Milano
- Cuppini Stefano, Marzolo Marco, Milan Marta - Rovigo
- Martini Giuliana, Merelli Sara, Pontoglio Sara, Portesi Nicola - Brescia
- Villalta Sabina, De Lucchi Lara, Sponghiado Alessandra - Treviso
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- Mumoli Nicola, Capra Riccardo, Orlando Mariantonia, Porta Cesare, Rotiroti Giuseppe - Magenta (MI)
- Demarco Monica, Petrillo Paola - Castellanza (VA)
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- Santoro Angelo, De Carlo Armando - Brindisi
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- Ria Luigi, Spagnolo Marina - Gallipoli (LE)
- Rupoli Serena, Federici Irene, Morsia Erika, Scortechini Anna Rita, Torre Elena - Ancona
- Franchini Massimo, Montorsi Paolo - Mantova
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- Pengo Vittorio, Denas Gentian - Padova
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Table Incidence of recurrent VTE events during the running periods of the Apidulcis study

	A Aug. 2018 - Dec. 2019	B Jan.2020 - Dec. 2020	C Jan. 2021 - Dec. 2021
VTE recurrences, n	3	4	12
Follow-up, y	60	138	137
Incidence, % pt-y (95% CI)	5.0 (1.0-14.6)	2.9 (0.8-7.4)	8.8 (5.4-15.3)

Figure

Time course of the Apidulcis study (the patient inclusion started in August 2018 and stopped in December 2021), recurrent VTE events (red bars), and curve of the subjects resulted positive to COVID-19 infection in Italy (data from Italian “Protezione Civile”; accessed July 31, 2022;

https://lab24.ilsole24ore.com/coronavirus/?refresh_ce=1.

