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

The results of the Apidulcis study (*clinicaltrials gov. Identifier: NCT03678506*), recently published in Blood Advances,[1] confirmed the high efficacy and safety of extended anticoagulant treatment with a reduced dose of Apixaban (2.5 mg 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 2 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: 6.2x100 patients/year; 95% confidence interval [CI]: 3.9-9.5). This incidence was not only higher than expected based on observations from previous studies,[2,3] but also higher if compared with results obtained in a similarly designed study (3.0x100 patients/year; 95% CI: 2.0-4.4).[4] Furthermore, the incidence of VTE events was much higher than that recorded in patients who continued anticoagulation with reduced-dose Apixaban (0.9x100 patients/year; 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 VTE events in patients with persistently negative D-dimer results and, after the publication of the main report, we explored potential reasons which may have contributed to these findings.

We hypothesized that SARS-CoV-2 infection, which became widespread in Italy while the Apidulcis study was ongoing, might have influenced the above-mentioned results. The recruitment of patients in the study began in August 2018 (see Figure 1); however, much of the study was concomitant to the initial phase (the first affected patient in Italy was diagnosed at the end of February 2020) and the SARS-CoV-2 infection spread during the subsequent months, through all of 2021. As shown in Figure 1, only three thrombotic events (red bars) occurred before the pandemic, while the 16 remaining events occurred during the pandemic. As reported in Table 1, the incidence of recurrences was significantly higher in the last year of the study period, concomitant with the spread of the virus. We also invited all participant investigators to collect information from the patients who had a negative serial D-dimer test at inclusion about possible SARS-CoV-2 infection occurring during the follow-up. Information was gathered from n=258 (90.2%) patients of the 286 with a negative D-dimer test, including all 16 patients who had recurrent events during the pandemic. Three recurrences occurred among the 32 patients who had a positive COVID-19 test during follow-up; while 13 events occurred in the 226 who tested negative. The incidence was 10.3% patients/year; 95% CI: 2.1-30.3 and 6.1% patients/year; 95% CI: 3.2-10.4, respectively.

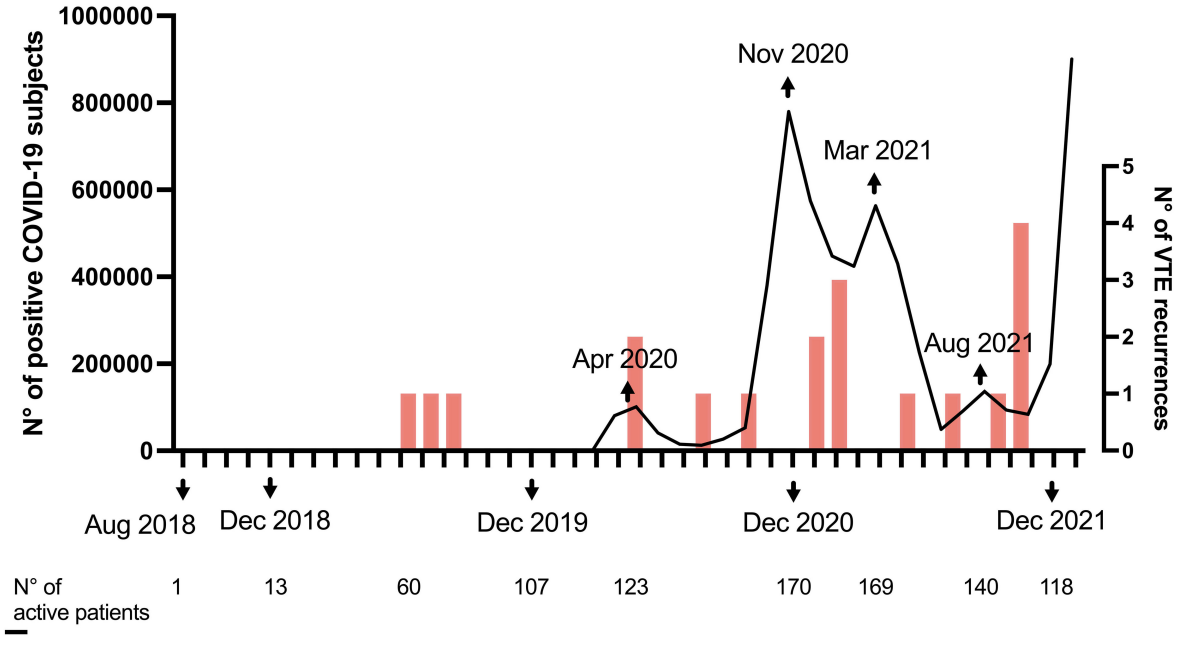

Figure 1. Recurrent venous thromboembolic events in relation to the number of COVID-19 patients in Italy during the time course of the Apidulcis study. Patient inclusion started in August 2018 and stopped in December 2021. The graph shows recurrent venous thromboembolic events (VTE) (marked as red bars), in relation to the number of COVID-19-positive subjects in Italy (data from Italian "Protezione Civile"; accessed July 31, 2022; *https://lab24.ilsole24ore.com/coronavirus/#*).

Table 1. Incidence of recurrent venous thromboembolic events in patients during the 3-year running period of the Apidulcis study.

	Aug. 2018 - Dec. 2019	Jan. 2020 - Dec. 2020	Jan. 2021 - Dec. 2021
VTE recurrences, N	3	4	12
Follow-up, patient years, N	60	138	137
VTE incidence, % pt/yr (95% CI)	5.0 (1.0-14.6)	2.9 (0.8-7.4)	8.8 (5.4-15.3)

Total number of patients with persistently negative D-dimer recruited in the Apidulcis study: 286. VTE: venous thromboembolic events; pt/yr: patients/year; CI: confidence interval.

The present data from a *post hoc* analysis of the Apidulcis study 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 the COVID-19 pandemic is associated with an increased rate of VTE events, which is not limited to patients who are more seriously affected.[5,6] Furthermore, an impact of the pandemic on increasing VTE occurrence has been described even in COVID-19-negative populations,[7,8] likely due to indirect effects of the pandemic, such as the various restrictions and the lockdown, resulting in a general reduction in physical activity,[9] a subsequent trend to obesity, and - among others - an increase in smoking.[10]

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

First and more importantly, 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 pandemic,[11] it is tempting to speculate that the reduced-dose Apixaban was consistently effective even in the patients experiencing increased prothrombotic 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 3-5% patients/year (i.e., as our study population in the pre-COVID-19 era).

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

Authors

Gualtiero Palareti,[1] Cristina Legnani,[1] Daniela Poli,[2] Walter Ageno,[3] Vittorio Pengo,[4] Sophie Testa,[5] Alberto Tosetto,[6] Paolo Prandoni[1] and the members of Apidulcis study group

[1]Fondazione Arianna Anticoagulazione, Bologna; [2]Malattie Aterotrombotiche, AOU Careggi, Firenze; [3]UOC Pronto Soccorso, Medicina d'Urgenza e Centro Trombosi ed Emostasi, ASST dei Sette Laghi, Varese; [4]Clinica Cardiologica, Azienda Ospedaliera di Padova, Padova; [5]Centro Emostasi e Trombosi, UUOO Laboratorio Analisi chimico-cliniche e microbiologiche, ASST Cremona, Cremona and [6]Divisione di Ematologia, Ospedale S. Bortolo AULSS 8 Berica, Vicenza, Italy

Correspondence:
G. PALARETI - gualtiero.palareti@unibo.it

https://doi.org/10.3324/haematol.2022.282130

Received: October 10, 2022.
Accepted: November 16, 2022.
Early view: November 24, 2022.

Disclosures

No conflicts of interest to disclose.

Contributions

GP, CL, PP, DP, ST, AT, VP and WA developed the concept and design of the study; GP, CL, PP, DP, ST, AT, VP and WA analyzed and interpreted the data; GP drafted the article; GP, CL, PP, DP, ST, AT, VP and WA critically revised the article for important intellectual content. All authors gave the final approval of the article.

Data-sharing statement

For original data, please contact the corresponding author.

Apidulcis study group members:
(in order of decreasing cases recruited): Poli Daniela, Lotti Elena, Crudele Felice – Firenze; Ageno Walter, Abenante Alessia, Caiano Lucia, Colombo Giovanna, Guarascio Matteo – Varese; Testa Sophie, Cancellieri Emilia, Morandini Rossella, Paoletti Oriana, Zambelli Silvia – Cremona; Bucherini Eugenio, Martini Sauro, Vastola Monica – Ravenna; Chistolini Antonio, Serrao Alessandra - Dipartimento di Medicina Traslazionale e di Precisione Sapienza Università di Roma – Roma; Martinelli Ida, Bucciarelli Paolo, Abbattista Maria, Artoni Andrea, Capecchi Marco, Gianniello Francesca, Scimeca Barbara – Milano; Falanga Anna, Barcella Luca, Gamba Sara, Lerede Teresa, Maggioni Anna, Schieppati Francesca, Russo Laura, Zunino Federica – Bergamo; Tosetto Alberto, Artuso Anna, Bellesso Stefania, Cadau Jessica, Carli Giuseppe, Nichele Ilaria, Perbellini Omar – Vicenza; Sarti Luca, Caronna Antonella, Gabrielli Filippo, Lami Francesca, Nicolini Alberto, Scaglioni Federica – Modena; Mastroiacovo Daniela, Pinelli Mauro, Desideri Giovambattista - Avezzano (AQ); Cosmi Benilde, Borgese Laura, Favaretto Elisabetta, Libra Alessia, Migliaccio Ludovica, Sartori Michelangelo – Bologna; Visonà Adriana, Panzavolta Chiara, Scandiuzzi Tatiana, Zalunardo Beniamino - Castelfranco Veneto (TV); Santoro Rita Carlotta, Ierardi Antonella, Leotta Marzia, Strangio Alessandra – Catanzaro; Zanatta Nello, Guzzon Samuele - Conegliano (TV); Grandone Elvira, Colaizzo Donatella, Favuzzi Giovanni - San Giovanni Rotondo (FG); Lombardi Maria, Rosa, Ferrini Piera Maria, Tassoni Maria Ilaria – Parma; Corradini Sara, Iotti Matteo, Lambertini Isabella, Veropalumbo Maria Rosaria - Reggio Emilia; 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; Becattini Cecilia, Giustozzi Michela, Vinci Alessandra – Perugia; Pignatelli Pasquale, Bucci Tommaso, Menichelli Danilo, Pastori Daniele – Roma; Pomero Fulvio, Casalis Sara, Galli Eleonora - Alba (CN); Ciammaichella Maurizio, Maida Rosa – Roma; De Cristofaro Raimondo, Alberelli Maria Adele, Basso Maria Rosaria, De Candia Erica, Di Gennaro Leonardo – Roma; Mumoli Nicola, Capra Riccardo, Orlando Mariantonia, Porta Cesare, Rotiroti Giuseppe - Magenta (MI); Demarco Monica, Petrillo Paola - Castellanza (VA); Rossi Elena, Bartolomei Francesca, Soldati Denise - Roma -Russo Umberto, Burgo Ilaria – Milano; Ziliotti Maurizio, Pataccini Corrado, Terroni Lorenza, Ugolotti Maria Chiara - Fidenza (PR); Di Giorgio Angela – Roma; Cavagna Laura, Mete Francesca / Gino Miriam - Rivoli (TO); Santoro Angelo, De Carlo Armando – Brindisi; Cappelli Roberto, Bicchi Maurizio, Dyrmo Lediona – Siena; Grifoni Elisa, Masotti Luca - Empoli (FI); Ria Luigi, Spagnolo Marina - Gallipoli (LE); Rupoli Serena, Federici Irene, Morsia Erika, Scortechini Anna Rita, Torre Elena – Ancona; Franchini Massimo, Montorsi Paolo – Mantova; Galgano Giuseppe, De Luca Anna - Acquaviva delle Fonti (BA); Muiesan Maria Lorenza, Paini Anna, Stassaldi Deborah – Brescia and Pengo Vittorio, Denas Gentian, Pesavento Raffaele, Ceccato Davide – Padova, Italy.

References

1. Palareti G, Poli D, Ageno W, et al. D-dimer and reduced dose apixaban for extended treatment after unprovoked venous thromboembolism: the Apidulcis study. Blood Adv. 2022;6(23):6005-6015.
2. Douketis J, Tosetto A, Marcucci M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. BMJ. 2011;342:d813.
3. Prandoni P, Vedovetto V, Ciammaichella M, et al. Residual vein thrombosis and serial D-dimer for the long-term management of patients with deep venous thrombosis. Thromb Res. 2017;154:35-41.
4. Palareti G, Cosmi B, Legnani C, et al. D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study. Blood. 2014;124(2):196-203.
5. Kerbikov O, Orekhov P, Borskaya E, Nosenko N. High incidence of venous thrombosis in patients with moderate-to-severe COVID-19. Int J Hematol. 2021;113(3):344-347.
6. Zuin M, Engelen MM, Barco S, et al. Incidence of venous thromboembolic events in COVID-19 patients after hospital discharge: A systematic review and meta-analysis. Thromb Res. 2022;209:94-98.
7. Qian C, Lyu X, Zhu HD, et al. Venous thromboembolism in non-COVID-19 population during the pandemic: a nationwide multicenter retrospective survey. J Thromb Thrombolysis. 2021;52(4):1094-1100.
8. Tankere P, Cottenet J, Tubert-Bitter P, et al. Impact of COVID-19 and lockdowns on pulmonary embolism in hospitalized patients in France: a nationwide study. Respir Res. 2021;22(1):298.
9. Curtis RG, Olds T, Ferguson T, et al. Changes in diet, activity, weight, and wellbeing of parents during COVID-19 lockdown. PLoS One. 2021;16(3):e0248008.
10. Alla F, Berlin I, Nguyen-Thanh V, et al. Tobacco and COVID-19: a crisis within a crisis? Can J Public Health. 2020;111(6):995-999.
11. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013;368(8):699-708.