Lessons learned from COVID-19: the need for better thrombosis management

ETHA statement on the European Union's response to the pandemic, lessons learned, and recommendations for the future

In the context of World Thrombosis Day, the European Thrombosis and Haemostasis Alliance (ETHA) calls on the European Parliament Special Committee on the COVID-19 pandemic to consider the need for better management of thrombosis as a lesson learned from the pandemic.

Thrombotic complications, such as deep vein thrombosis (DVT) and pulmonary embolism (PE), have been key causes of mortality in patients with COVID-19. Although healthcare systems improved management of thrombotic complications during the pandemic, hypercoagulability is still a serious concern when treating COVID-19 patients as well as negatively affecting the quality of life of long-COVID sufferers.

Given that COVID-19 is inherently a pro-thrombotic disease, more basic and clinical research is needed to understand the relationship between blood clot formation and infectious diseases like COVID-19.

With more than 255 million confirmed cases and over 2 million deaths in Europe (as of October 2022)[1], the COVID-19 pandemic is the most significant healthcare crisis of our time. This pandemic has also led to a disruption of other health services which has taken a huge toll on European citizens and health systems.

When looking ahead to formulate recommendations for the future, it is essential that EU policy-makers take into consideration the importance of patient safety interventions, such as thrombotic risk-assessments, that are effective in multiple settings.

1. The link between thrombosis and COVID-19

Emerging research indicates that people with COVID-19, particularly those who are hospitalised with moderate and severe COVID-19 pneumonia, have a high incidence of venous thromboembolism (VTE). COVID-19 pneumonia is associated with an increased tendency for blood to clot (hypercoagulability) and with the development of micro-clots in the

[1] WHO Coronavirus (COVID-19) Dashboard, retrieved 6 October 2022

lungs[2]. Recent findings published in the British Medical Journal[3] also suggest that catching COVID-19 is associated with a fivefold increase in the risk of deep vein thrombosis and a 33-fold increase in risk of pulmonary embolism in the 30 days after becoming infected – with increased risk persisting for up to six months. Another new study, published in Circulation[4], shows that COVID-19 infection increases the incidence of blood clots for up to almost a year post-diagnosis and suggests that the COVID-19 pandemic may have led to an additional 10,500 cases of heart attacks, strokes, and other blood clot complications - such as deep vein thrombosis - in England and Wales in 2020 alone.

This hypercoagulability is also potentially implicated in long COVID. Although the cause remains undetermined, one theory[5] suggests that these symptoms are due to persistent micro clots that reduce blood flow. There is a hypothesis[6] that fibrin amyloid blood clots, resistant to normal processes that prevent problematic blood clot growth, cause reduced blood flow in small vessels. In turn, this reduces gas exchange and generates symptoms commonly found in long COVID patients: fatigue, brain fog and shortness of breath.

Given COVID-19's tendency to cause blood clots, the association[7] between infections and temporary increased incidence of arterial thromboses and VTE, and the possible role of micro clots in long COVID, future pandemic preparedness must include the lessons learned from investigating the relationship between blood clotting mechanisms and novel viruses. The Based on these discoveries, the ETHA recommends that the **EU institutions invest in research into the fundamental underlying mechanisms of blood clotting**. Such improved understanding of blood clotting could help improve the lives of patients living with long COVID-19, and potentially reduce morbidity and mortality of thrombotic disease complications. This would not only be of use in addressing future novel diseases, but also in addressing existing diseases – such as cancer – that are co-morbid with thrombosis.

2. The need for better clinical management of thrombosis and harmonized European approach to VTE risk-assessment

Pulmonary embolism (PE)-related mortality is also likely to increase[8] as a result of COVID-19 due to its potential blood clot-related complications. Cooperation at the EU level on this topic could ensure consistent measurement of VTE prevalence and access to prophylaxis across

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[2] A Systematic Approach for Managing Venous Thromboembolism in Patients with COVID-19:. International Society for Thrombosis and Haemostasis.

[3] Katsoularis I, Fonseca-Rodríguez O, Farrington P, Jerndal H, Lundevaller E H, Sund M et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study BMJ 2022; 377 :e069590 doi:10.1136/bmj-2021-069590

[4] Knight R, Walker V, Ip S, Cooper J A, Bolton T, Denholm R et al. Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales, Circulation 2022;

[5] Couzin-Frankel J. Clues to long COVID, Science 2022; 376

[6] Moiseiwitsch, N., Zwennes, N., Szlam, F., Sniecinski, R. and Brown, A. (2022), COVID-19 patient fibrinogen produces dense clots with altered polymerization kinetics, partially explained by increased sialic acid. J Thromb Haemost. Accepted Author Manuscript.

[7] Knight R, Walker V, Ip S, Cooper J A, Bolton T, Denholm R et al. Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales, Circulation 2022;

[8] Barco S, Valerio L, Gallo A et al. Global reporting of pulmonary embolism–related deaths in the World Health Organization mortality database: Vital registration data from 123 countries. Res Pract Thromb Haemost. 2021;5(5). doi:10.1002/rth2.1 2520

all 27 Member States, including action directed at tackling health inequalities within and between countries, given that access to VTE risk assessment remains inconsistent and highly dependent on which Member State a patient is in. Although VTE risk assessment is often used or mandated in European countries, very few (Belgium, North Macedonia, United Kingdom) have national guidelines[9] in place recommending the use of VTE risk assessment.

To decrease mortality, it is therefore essential to adopt a more harmonised approach to preventing, diagnosing and treating VTE among patients with COVID-19. This should follow the WHO guidelines on the clinical management of COVID-19 patients that advocate for consistent monitoring for symptoms of thromboembolism and set out guidance on thromboprophylaxis dosing. To avoid a potential increase in inequality of health outcomes in pulmonary embolism, we recommend that **EU Member States develop and enact plans to tackle the risk of a reverse in the decline of PE-related mortality rates** in the WHO European Region. Such plans should be accompanied by **adoption of national guidelines on VTE risk assessment in all Member States**, to secure consistent access to VTE risk assessment and prophylaxis as necessary.

3. Potential to achieve positive spillovers from addressing thrombosis

A key lesson learned from the COVID-19 pandemic has been that hospitals and health systems were initially unprepared to handle COVID-19 related complications such as thrombosis, but that mortality rates improved with use of existing technologies and better assessment of individuals at risk of thrombosis. In making recommendations for health system improvement, the ETHA urges the COVI Committee to **promote patient safety interventions – such as VTE risk assessment – that would be effective in multiple disease contexts as a key lesson learned from the pandemic**. This could improve overall survival from many other risk factors for blood clots, including cardiovascular, haematological, and pulmonary diseases – improving population health.

Summary

There is a clear link between COVID-19 and higher incidence of VTE. Although more research is needed, having national guidelines in place recommending the use of VTE risk assessment and systematically collecting data on COVID-19 and VTE would help to reduce the risk of developing blood clots, safeguard patient quality of life, avoid preventable deaths, and reduce the health budget pressures arising from VTE incidents. The EU should support these efforts by **providing sufficient research funding for this topic and promoting VTE risk assessment as a best practice at EU level**. Additionally, studying the link between COVID-19 and VTE provides an opportunity for the EU to learn lessons for future pandemics about understanding and treating the symptoms and aftereffects of novel viruses.

In order to create a Europe-wide basis for further research and health care actions, it is vital that the EU Member States collect consistent data on the incidence, death rate, and long-term burden of VTE. This will establish a solid, common understanding of the impact VTE has in Europe – including its differential impact on people from socioeconomically disadvantaged backgrounds. Additionally, such data is essential for implementing best practice and assessing effectiveness of prevention measures across the EU.

[9] Wendelboe A, Langenfeld H, Ageno W et al. Current practices of standardized risk assessment for venous thromboembolism: Results from a global survey from the World Thrombosis Day steering committee. Journal of Thrombosis and Haemostasis. 2021;20(2):532- 5

About ETHA:
The European Thrombosis and Haemostasis Alliance (ETHA) is made up of eminent clinicians and researchers from European national and international societies representing those working in the field of thrombotic and bleeding disorders. We have come together to give the European thrombosis and haemostasis community an allied voice and provide input to EU health and patient safety strategies; make recommendations on EU research programme funding and encourage sharing and adoption of best practices in the treatment and prevention of thrombotic and bleeding disorders across Member States. Learn more at etha.eu.

About Thrombosis:
Thrombosis, also known as blood clots, is the formation of potentially deadly blood clots in an artery (arterial thrombosis) or vein (venous thrombosis). It is the underlying cause of heart attack, thromboembolic stroke, and venous thromboembolism (VTE), the top three cardiovascular killers.

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