A re-appraisal of thrombogenesis in COVID-19, seen as a multiple Complex System

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ABSTRACT
The aim of this essay is to re-consider the peculiar type of thrombogenesis observed in severe cases of COVID-19 infection, focusing on the multiple interconnected networks involved, such as inflammation, blood coagulation, fibrinolysis, and immune responses. These linked mechanisms can be assimilated to the “Complex Systems” (CS), that play a capital role in various domains: from physics to chemistry, biology and medicine, to social and behavioral sciences. CS are characterized by eliciting variable responses: their final results can be contradictory and often unpredictable. In fact, in severe COVID-19 various outcomes can occur, such as macro- and micro-thrombosis, vasculitis, hemorrhage, hyper and hypo fibrinolysis, distorted inflammatory and immune response, and others. The insight supplied by the CS theory in understanding thrombogenesis in COVID-19 can be useful in several ways. It recalls the importance of a “holistic” view of multiple patterns of signs, symptoms and biomarkers; stresses the added value of global versus mechanistic tests, particularly in coagulation and fibrinolysis; suggests building up small trials of selected patients in a perspective of precision medicine; discourages passive transfer of therapeutic choices from non-COVID to COVID patients; and finally indicates that some treatments, as the anti-inflammatory and the anti-coagulant ones, should be initiated as early as possible, so to avoid worsening of the condition by repetitive feedback and shortcut mechanisms.

INTRODUCTION
The outstanding scientist Giorgio Parisi, recently awarded the 2021 Nobel Prize for Physics, has been for years a committed supporter of the theory of the so-called “Complex Systems” (CS), applied to many domains of science. CS possess peculiar properties due to the involvement of a great number of interconnected factors. In fact, they display high variability, randomness, disorder, and hence unpredictable effects bound to the contradictory nature of the crosstalk among multiple factors, thus leading to the non-linearity of responses. Although the terms “complex” and “complexity” have often been misused and seem to be in some cases repetitive and worn out, they can regain their full meaning provided they correspond to precise scientific criteria.

In biological and medical science, we are confronted with many CS of different degrees. Thrombogenesis can be defined as a complex system, as it recruits activators and inhibitors of blood coagulation, platelet function and fibrinolysis, leading to an unstable balance between pro-thrombotic, anti-thrombotic, and pro-hemorrhagic states. What is more, in a context of heavy inflammatory and immune activation, as occurring in severe COVID-19, the mechanisms of thrombogenesis are implemented by factors that include unusual pathways of activation, giving rise to different phenotypes of vascular and thrombotic response. This condition deserves the definition of “multiple complex system” (MCS).

This paper aims to make the mechanisms of interactions between coagulation, inflammation and immune responses as clear as possible for readers involved in clinical and research activities.

The various systems recruited in COVID-19-induced thrombogenesis are described, with special regard to their mutual interconnections, that may cause “collective effects” not predictable by any of the single factors involved. Finally, the problems of transmission to wider
Entry of the virus and binding to the receptor

At first entry into the organism along proximal and distal airways, the “spike” protein of the SARS-COV2 virus makes use of a receptor that otherwise binds angiotensin 2 (ACE2), an enzyme that down-regulates effects of the renin-angiotensin-aldosterone system (RAAS) and particularly the balance between vasoconstriction and vasodilation. This receptor is ubiquitous, but mainly concentrated in airways, lungs, kidneys, and in platelets and other blood cells.

The binding of the spike protein of the virus to the ACE2 receptor is driven by a proteolytic chain potentiated by heparan sulphate (HS), a precursor of endogenous heparin, responsible for the synthesis of the endothelium protecting layer known as glycocalyx. Impoverishment in HS in fact contributes to damage of endothelial and blood cells.

Occupancy of the receptor by the SARS-COV2 virus results in a distorted hyper-production of angiotensin II, which has marked vaso-constrictive and endothelial damaging properties, and is linked to thrombogenesis through the release of the potent inhibitor of fibrinolysis PAI I by endothelial and blood cells (Table 1).

Hyper-inflammation

The mentioned loss of function of angiotensin, replaced by the more harmful angiotensin II, is responsible for acute damage of pulmonary microcirculation, and induces endothelial injury and vasculitis. The disordered RAAS system also combines with the cellular release of cytokines, a family of endogenous inflammatory agents that become massively activated (the cytokine storm), fuelling severe endothelial damage and hyper-inflammation. Various cytokines are involved in this reaction, as Interleukin (IL)1, IL6, IL18 and tumor necrosis factor, but IL6 is likely the main actor. At the same time, IL6 activates the parallel pathway of the (pre) kallikrein-kinin system, and produces an increase of bradykinin, a promoter of vasodilation and edema (e.g. in lungs).

Pre-kallikrein opens a further way towards coagulation, by involving coagulation Factor XII and other Factors as IX, X, and XI.

Besides inflammation, the virus induces a marked immune reaction by the host, through innate and adaptive immunity. The excessive and disordered immune response of the host is a capital factor for severe disease courses, often more dangerous than the viral burden itself.

The main factor of the immune system involved in thrombogenesis of COVID-19 is the complement complex. Complements are proteins produced and stored in the liver. Within the innate host defense, complement components (C2-C5) undergo cleavage and activation, giving rise to highly thrombogenic fragments. Multiple links between fractions of complement and various factors of coagulation and fibrinolysis have been described: Factors XIa, X, IXa, as well as thrombin and plasmin can in fact be activated by this pathway. The final product of activated complement, MAC (membrane attack complex) fosters thrombogenesis through multiple mechanisms such as up-regulation of tissue factor, platelet activation, increase of fibrinogen, and of PAI-I, with consequent hyper-coagulation and hypo-fibrinolysis. The rise of von Willebrandt factor (VWF) also occurs with production of ultra-large multimers responsible for destructive endothelial damage and cellular death (see later). Complement fractions and MACs also stimulate the formation of cellular traps that recruit neutrophils and pro-thrombotic factors, thus preparing convenient scaffolds for thrombogenesis. Finally, complement participates in the structure of diffuse microthrombi occurring in lungs and other organs: complement components have been identified by im-

Table 1. First steps of thrombogenesis in severe COVID-19.

1 Penetration of the virus (spike protein) into cells (favored by initial proteolytic state)
2 Binding of spike protein to receptor otherwise acting on the renin-angiotensin-aldosterone system (RAAS)
3 Occupancy of the receptor causes distorted production of angiotensin I in favor of the more noxious angiotensin II, a potent vaso-constrictor
4 Angiotensin II also impairs the degradation of bradykinin, which induces vasodilation, capillary leaking, and edema, and stimulates PAI I, the main inhibitor of fibrinolysis
5 Additionally, angiotensin II stimulates interleukins (cytokine storm), recruits Factor XII, and complement fractions (hyper-inflammation and Immuno-thrombosis)
6 Kallikrein, bradykinin and interleukin-6 also recruit blood coagulation factors (FXI, XII)
7 The involvement of complement and its cleavage fractions contribute to the activation of coagulation
munochemistry in the COVID-induced diffuse microthrombosis of lungs.\textsuperscript{13} These strict interactions have been defined as “complement-induced coagulopathy”.

A concurrent failure of “first line” innate defense is due to the fall of Interferon (IFN\textsubscript{1}), either caused by genetically reduced synthesis, or the development of IFN\textsubscript{1} auto-antibodies.\textsuperscript{14}

In conclusion, both innate and adaptive immune systems and particularly the complement, build up an early and sustained defense against viral aggression. Unrestrained hyper-activation of complement can however contribute to massive endothelial damage, hyper-coagulation and thrombogenesis, also favoring a marked inhibition of fibrinolysis.

Disordered immunity may in some cases induce autoimmune complications, interfering with the natural course of the infection and contributing to poor outcomes. A short list of autoimmune vascular and thrombotic complications of COVID-19 is reported in Table 2.\textsuperscript{15}

The “coagulation cascade” in COVID-19

The “coagulation cascade” includes two distinct and highly interconnected pathways. The extrinsic system undergoes activation directly at the viral attack on the endothelium,\textsuperscript{16} causing cellular damage of relevant degree, with externalization and release of tissue factor (TF). On the other hand, the “intrinsic” system is activated by the contact of blood with several surfaces, inorganic or organic, such as blood cells, bacteria, viruses, cellular traps, and other negatively charged (anionic) materials. This pathway starts with the involvement of Factor XII following contact with some of the above sets of surfaces. Activated Factor XII (Factor XIIa) in turn activates Factor XI, assembling a complex that activates Factor X (prothrombinase) responsible of the conversion of fibrinogen to fibrin.

In recent years, the mechanisms of the two pathways of blood coagulation have been partly revised and subtle differences between the formation of thrombotic versus hemostatic clots have emerged. In fact, Factor XI and Factor XII have been found as “indispensable” for thrombogenesis, but “dispensable” for hemostasis and prevention of bleeding, thus opening the way to therapeutic dissociation of antithrombotic effects versus bleeding risk.\textsuperscript{17} At the same time, a better understanding of the intrinsic pathway focused attention on the multiple links of Factor XII with other systems, such as inflammation and immunity. The crosstalk between coagulation, inflammation, and immunity is driven by Factor XII in the non-activated form.\textsuperscript{18,19} In COVID-19 peculiar changes of Factor XII are described, as the increase in the first phases of infection, and the sharp decrease in advanced stages, thus suggesting a consumption mechanism. This “wave” of Factor XII seems to indicate that both coagulation pathways (extrinsic and intrinsic) work simultaneously, and also that the intrinsic system, besides reinforcing blood coagulation, brings about inflammatory and immune changes thus explaining co-existence of macro-thrombosis, vasculitis, and micro-thrombosis.

Fibrinolysis

Fibrinolysis is an essential function of hemostasis that drives and controls the rate of formation and dissolution of fibrin. Similarly, to coagulation, fibrinolysis belongs to a complex system that includes many correlated factors, as activators and inhibitors of clot formation, strictly interconnected with activators and inhibitors of clot dissolution, through mechanisms of signaling, retroaction and feedback.

The effect of fibrinolysis should not be seen as limited to the dissolution of pre-existing clots or thrombi. It can be surmised that agents responsible for coagulation, anticoagulation and fibrinolysis are constantly working at a restrained pace, in order to maintain blood fluidity while being ready for fast clot activation, inhibition, or dissolution, thus giving rise to a fairly unstable equilibrium.

The main physiological agents of the fibrinolytic system are the tissue plasminogen activator (tPA) and the urokinase-type plasminogen activation (uPA). The first, tPA, is widely but unequally distributed among most organs and tissues, including the vascular walls,\textsuperscript{20} while uPA is mainly present in urinary organs and in airways and lungs, where it contributes with tPA to keeping broncho-alveolar surfaces viable and free from fibrin de-

| Table 2. Autoimmune complications of hemostatic or vascular nature related to COVID-19 (from 15, modified). |
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| 1 Immunologic thrombocytopenic purpura (ITP) |
| 2 Thrombotic thrombocytopenic purpura (TTP): due to disease or vaccine (VITT) |
| 3 Anti-heparin antibodies induced heparin resistance |
| 4 Antiphospholipid antibodies and lupus-like anticoagulant (LLA) |
| 5 Anti-interferon (FN1) autoantibodies |
| 6 Anti α1 antitrypsin autoantibodies |
| 7 Kawasaki-like disease with systemic vasculitis and shock syndrome (in children) |
A re-appraisal of thrombogenesis in COVID-19 as a multiple complex system

Both tPA and uPA are counteracted by one and the same inhibitor, PAI I. An additional factor for inhibition of fibrinolysis is available, the thrombin-activatable fibrinolysis inhibitor (TAFI), a peptidase that acts by removing specific binding sites for fibrinolysis activation, thus impairing the affinity of newly formed fibrin for fibrinolytic enzymes. This pathway works in fact as a feedback system to strengthen the stability of the clot (Figure 1).

The first action of the fibrinolytic system in COVID-19 is the activated proteolysis that favors the penetration of the virus and its binding to the receptor. Thereafter, distortion of RAAS system with suppression of angiotensin in favor of angiotensin II stimulates the production of PAI I, thus preparing the ground for vascular and alveolar thrombotic obstruction. But the inflammatory reaction (cytokine storm), and the concurrent involvement of kallikrein with coagulation Factor XII in reciprocal activation, also stimulate the production of the plasminogen activator tPA. The concurrent effects of tPA and PAI I give rise to an unstable equilibrium between fibrinolysis and anti-fibrinolysis. This over-regulated fibrinolytic balance (more activation and more inhibition) is subject to high instability with concomitant thrombotic, but also bleeding risk although less frequent (Figure 1).

The course of such an unstable fibrinolytic balance may lead to a condition called fibrinolysis shutdown. This expression indicates a profound, acute condition of hypofibrinolysis, detectable by global tests such as thromboelastography (TEG) or rotational viscoelastometry (ROTEM). Fibrinolytic shutdown (FS) defines a situation clinically correlated with a high incidence of macro or micro-thrombosis. FS has been reported in about 40% of severe COVID-19 patients, and also in other conditions such as liver transplantation, severe trauma, multiple organ failure, and severe cardiac damage involving extensive tissue injury. At first approach, FS seems to be a situation of total and persistent fibrinolysis inhibition due to a prevailing effect of PAI I. However, it is known that even in this apparent condition of fibrinolytic blockade, a previous increase in D-dimer may persist. This “D-dimer paradox” discloses a concomitant, discreet fibrinolytic activity, probably mainly localized in microthrombi and/or in tissues and organs rich in tissue plasminogen activator (t-PA).

To summarize, in COVID-19 fibrinolysis undergoes initial activation, inducing proteolysis that favors viral penetration. Afterwards, the situation can be overturned by PAI I and tPA concurrent hyperproduction. In severe cases, a fibrinolytic shutdown may occur, giving rise to intra-alveolar micro-thrombosis and hemorrhage, with heavy respiratory insufficiency, that can be lethal or may favor chronic alveolar fibrosis.

\[\text{PLG, plasminogen; tPA, tissue Plasminogen Activator; uPA, urokinase type Plasminogen Activator; TAFI, Thrombin Activatable Fibrinolytic Inhibitor.}\]

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**Figure 1.** The fibrinolysis balance. The balance between activators and inhibitors of fibrinolysis includes a positive feedback mechanism: fibrinolytic activators and plasmin are very active on fresh fibrin, but thrombin moderates this effect by activating TAFI, thus strengthening stability of the clot.

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Platelets

During viral infections, circulating platelets may undergo alterations in number and functional activities. In COVID-19 platelets count may be increased, normal, or even severely decreased, indicating either an abnormal rate of production and/or an excessive rate of consumption and cellular death. It is well known that sera from severe COVID-19, added to normal platelet-rich plasma, induce apoptosis and destruction of platelets.

Like other cells, platelets contain the receptor for spike protein of the COV-SARS2 virus, thus concurring to early endothelial damage and inflammatory plus immune reactions. Thrombocytopenia or thrombocytosis may coexist with inflammation, immuno- thrombosis, and intra-alveolar microthrombi and hemorrhages.26

Infected platelets also show increased adhesion to substrates like fibrinogen, fibrin, and collagen, and form structures as platelet-neutrophil aggregates27 producing extracellular traps (NETs). These multiple roles of platelets comply with the properties of variability and unpredictable response appropriate for Complex Systems.

An alternative (or additional?) mechanism for micro-thrombosis

A different look at endothelial injury leading to diffuse micro-thrombosis entails activation of a pathway of cellular damage and disruption caused by extra-large multimers of von Willebrand Factor, found in the blood during severe COVID-19.

Usually, such multimers are cleaved and suppressed by a coenzyme known as ADAMTS-13, but in case of over-activation of VWF and/or absolute or relatively low levels of ADAMTS-13, they produce high-degree damage to platelets and endothelial cells.27

This condition was suggested to mimic a spontaneous disease, “Thrombotic Thrombocytopenic Purpura (TTP)”, and was therefore labeled as “TTP-like syndrome” of severe COVID-19.

It seems however reasonable to surmise that the TTP-like syndrome may coexist in various proportions with classic activation of the coagulation cascade. The TTP-like pathway could represent an additional thrombosis mechanism, or a biomarker, rather than an alternative phenotype of thrombogenesis.28 However, the role of the above mechanism and the related clinical presentation are still discussed. Some authors29 argue in fact that the described TTP-like syndrome is the specific mechanism responsible for micro-thrombosis, while macro-thrombosis would depend on the classic activation of blood clotting.

In this perspective, the so-called “von Willebrand” axis has been thoroughly investigated in severe COVID-19 patients. All different forms of the Factor VIII – von Willebrand factor were found to be markedly increased,30 while levels of ADAMTS13 were correspondently decreased. It was also confirmed that the activity of ADAMTS13 enzyme, responsible for cleavage of the extra-large multimers, is generally reduced in severe patients, and associated with poor prognosis.31

Genetic influences

As only a fraction of COVID-19 infected subjects develops severe disease and thrombosis, it seems likely to surmise that genetic factors may predispose to an excessive or defective response.

In a large study, genome-wide significant associations with severe COVID disease were identified in various chromosomes, and especially in a cluster of genes encoding control of proteolytic enzymes that play an important role in early viral penetration and binding to the receptor.32 Also, low expression of the gene for the synthesis of interferon, and high expression of the gene for receptors of macrophages have been described as associated with severe disease.33

Genetic control of alpha-1 antitrypsin (AAT), a serine-protease with antithrombin and antiplasmin activities, is thought to be an important factor in the control of initial proteolysis. AAT also exerts a protective activity against intra-alveolar deposition of fibrin, and loss of functional polymorphisms of the genes for AAT have been forwarded as possible causes of severe respiratory insufficiency and pulmonary fibrosis.34 These views were supported by studies describing concordance between the geographic distribution of the AAT polymorphisms and the frequency of severe cases of COVID-19. However, a recent study suggests that polymorphisms bound to mild AAT deficiency do not influence the clinical course of respiratory failure, but no data for severe “loss of function” polymorphisms are available.35

A further clinical question is whether genetic thrombophilias affect thrombogenesis in COVID-19. Genetic thrombophilias are not rare diseases and constitute a highly heterogeneous cohort of subjects with a variable predisposition to thrombosis, according to the type of defect, its homozygote or heterozygote nature, and its role as main or accessory cause or concause of thrombosis. This wide variability of the prothrombotic effects curtails the possibility of a simple answer to the question.

Some authors consider pre-existing “thrombophilic risk profiles” to be co-responsible for thrombotic events occurring during COVID-19. But, in a study of patients with generic sepsis,36 only fibrinogen and PAI 1 genotypes were found associated with septic shock and mortality. Conversely, another study ruled out any statistical association between the common thrombophilic polymor-
DISCUSSION

Complex Systems are sets of entities of various types (e.g. elementary particles, molecules, cells, bacteria, viruses, antibodies, enzymes… etc.) that drive and control relevant functions in different domains of science. CS have been described in physics, chemistry, mathematics, statistics, but also in biology, medicine, anthropology, sociology, economics, informatics and other domains. In biological and medical sciences CS acquire a capital role in clarifying the highly interconnected mechanisms related to the control of human variability in health and disease.

CS are characterized by several properties. First of all, their final outcomes are of collective nature and often do not correspond to the effects of single components. Outcomes are variable or even contradictory according to time, phase, activation and inhibition, thus inducing a disproportion of responses versus inputs (non-linearity of response). CS also present a co-existence of deterministic (causal) and non-deterministic behaviors (randomness), and in consequence unpredictability of final outcomes as a result of even small, but multiple modifications.

In this paper, it is assumed that a system like that of blood coagulation, due to its multiple complex interactions, internal and external information mechanisms, retro-actions, feedbacks and shortcuts, may produce different or even contradictory outcomes (e.g. hemostasis, thrombosis, hemorrhage, activation or inhibition of fibrinolysis, fibrosis, etc.), and could be seen as a CS. Moreover, in the case of thrombogenesis of COVID-19, the recruitment, beyond the coagulation system, of other complex mechanisms such as inflammation and immune responses, may allow to define this condition as a multiple complex system, MCS (Table 3).

It can be noted that biological and medical CS share many properties with CS of physics, in terms of variability, instability, and unpredictable final outcomes. For instance, in the MCS discussed here, the outcome of thrombosis generally prevails, but bleeding may also appear either associated or consecutive.

Already at the early binding of the virus to the ACE2 receptor, these contradictory effects may occur, inducing vasodilation or vasoconstriction; inflammation is enhanced but also disordered, and auto-immune responses can be observed. To increase variability, changes directly caused by the viral burden coexist with deranged effects by the host response, as influenced by genetic factors, immunologic status and individual biological memory.

The instability of fibrinolysis due to concurrent high levels of activators and inhibitors is likely responsible of the co-existence of intra-alveolar micro-thrombosis with hemorrhages. Fibrinolytic shutdown in advanced cases also favors thrombosis but does not prevent bleeding, or late alveolar fibrosis.

In the presence of so many available pathways of activation and inhibition of coagulation, fibrinolysis, and inflammatory and immune mechanisms, a preliminary question arises: are we sure that all mechanisms described mainly in experimental conditions, do really participate in the pathophysiological course of the disease? The only possible answer at this state of knowledge seems to be that all these links, feedbacks, and retroactions “are available”: perhaps inactive in mild cases, they could be exploited in severe cases especially depending on viral load and intensity of response.

The “choice” among the numerous practicable pathways and shortcuts may occur by the selection of the “fittest mechanism” (“Darwinian” hypothesis) or by chance (random hypothesis).

Table 3. Retroactions, feedbacks and short-cuts in thrombogenesis of severe COVID-19 (in ten points).

| No.  | Description                                                                 |
|------|-----------------------------------------------------------------------------|
| 1    | Angiotensin II stimulates synthesis and release of PAI I                     |
| 2    | Angiotensin II recruits Factor XII and complement                            |
| 3    | Cytokines, mainly Interleukin 6, release tPA from tissues and cells          |
| 4    | Kallikrein and bradykinin activate clotting Factors XI and XII (essential for thrombogenesis) |
| 5    | Complement in turn retro-activates blood coagulation and fibrinolysis       |
| 6    | Products of complement cleavage, as MAC stimulate tissue factor, platelets, fibrinogen, and PAI I |
| 7    | Concurrent activation of both extrinsic and intrinsic clotting pathways overstimulates coagulation and the immune system |
| 8    | Large multimers of von Willebrand factor destroy platelets and severely damage endothelial cells |
| 9    | Fibrinolysis can be blocked (fibrinolytic shutdown); however, previously increased D-dimer can persist (D-dimer paradox) |
| 10   | The two main proteolytic enzymes, thrombin and plasmin, are self-regulating through feedback mechanisms: thrombin also produces the clotting inhibitor Prot. C, and plasmin can mitigate fibrinolytic effects, by TAFI |
Anyway, the viral aggression will resemble a tsunami that, while bursting into dryland, outruns any preformed or non-preformed stream (Table 3).

**Communication of complexity**

The multilateral complexity of thrombogenesis in COVID-19 would be obviously tough for general audiences, including the press and social media. In fact, communication of complexity has always been avoided, or too often transmitted through oversimplification. Any excess of simplification can be misleading, and favors apparently conflicting opinions even in the presence of basic common thought.

The growing habit of a binary type of reasoning, fostered by informatics, algorithms and artificial intelligence, has prompted the conviction that science, medicine, and related domains cannot be popularized without losing significance. But the theory of CS suggests that the time has come for seriously introducing concepts as complexity, variability, and even uncertainty that are peculiar to biological and medical sciences. 40 Dependable divulgation of complexity should be the objective, and coarse over-simplification should be avoided. Thus, examples of complexity as those supplied by the CS should be gradually outlined and explained, with a new language preventing the suspicion that we are trying to conceal our legitimate uncertainties.

Thus, the ever-growing audiences should be enabled to accept the idea that dogmatic truths do not dwell in science. 40 The major steady point to be transmitted is the scientific method, which produces dynamic truths that, although deserving practical applications, ever remain subject to discussion, doubt, adjustment, and sometimes overturning.

**CONCLUSIONS**

Thrombogenesis in severe COVID-19 has been discussed stressing, in particular, some significant aspects. A few hints of practical nature, suggested by the present approach, can be proposed.

- It is important to consider this succession of biological events with a global look, thus introducing a “holistic” vision, but without abandoning the necessary “reductionistic” approach.
- Global tests, particularly for fibrinolysis and coagulation, should be re-introduced, together with the specific mechanistic ones
- The high variability described here should suggest small trials on groups of patients selected for relevant properties, in the perspective of precision medicine.  
- The efficacy of any drug or therapy proved effective in usual conditions, should not be taken for granted in this peculiar model of thrombogenesis.

- Considering the very early involvement of inflammation, blood coagulation and fibrinolysis, appropriate therapy should be initiated as soon as possible, in order to block the repetitive pathways, feedback and shortcuts available. 41

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