

COVID-19 Early Stage Disease Progression and Anticoagulants: Investigation Rationale, Challenges and Difficulties

Krankheitsprogression in frühen Stadien COVID-19 und Gerinnungshemmer: Die Möglichkeiten und Schwierigkeiten einer sinnvollen Untersuchung

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ZUSAMMENFASSUNG

Die Covid-19-Pandemie hat die Welt verändert, und wird sie noch für eine geraume Zeit in Schach halten. Ziemlich bald nach der Verbreitung der Erkrankung in Wuhan und dann in Italien und Spanien wurde klar, dass Thrombosen in Venen und Arterien eine Rolle bei den tödlich verlaufenden Fällen spielen.

Der Artikel stellt die Hypothese auf, dass Patienten mit COVID-19 in einer frühen Phase (Leichte Symptome, ohne Atemnot) von Heparin in prophylaktischer Dosierung oder ASS profitieren könnten, wenn der Krankheitsprogress Thrombose-getriggert wäre. Verschiedene Studienmodelle, dies zu beweisen werden vorgestellt. Aber auch die Schwierigkeit, eine derartige Studie durchzuführen, vor allem vor dem Hintergrund, dass die eingesetzten Medikamente sehr günstig sind, und daher kein finanzielles Interesse seitens der Industrie besteht.

Die meiste Forschung rund um COVID-19-Patienten geschieht nach der stationären Aufnahme wegen einer Symptomverschlimmerung – Studien zum Vorbeugen dieser Verschlimmerung sind nicht abgeschlossen. Vielleicht wäre aber – auch ohne Studien – eine generelle Testung der D-Dimere (quantitativ) von Patienten mit SARS-CoV-2 und Symptomen zielführend, um bei Erhöhung der D-Dimere eine Prophylaxe einzuleiten, die von der Gesellschaft für Thrombose und Hämostaseologie (GTH) auch großzügig gefordert wird.

ABSTRACT

COVID-19 pandemic has changed the world and will keep us breathless for some time, still. Soon after the start of the disease in Wuhan and later in Italy and Spain, it became clear, that thromboses of arteries and veins played an important role in the severe cases.

The present article parts from the hypothesis, that patients suffering from COVID-19 could benefit from low molecular weight heparin (LMWH) in prophylactic dose or aspirin, if applied in early stages of the disease. LMWH prevent venous and ASS arterial thromboses. Different study approaches are proposed in the article. The difficulties to run a study like this, applying anti aggregation or anticoagulation to patients in early stages of SARS-CoV-2 infection are discussed, especially considering, that the medicaments are cheap and no industry will have any interest in sponsoring.

Most of the studies in corona disease are run in hospitals, where everybody fights to save critically ill patients. Very little investigation was done until now in pre-clinic patients. Mostly, because in lot of countries the testing was performed when admitted to hospital. Perhaps – even without a study – the evidence of thrombosis in the disease progression should lead to a D-Dimer testing after infection. The German Society of Thrombosis and Haemostasis Research (GTH) has recommended to consider administering heparin generously in COVID-19 ambulatory patients already in April 2020. Thus, in patients with little symptoms it would be possible to start early with LMWH in prophylactic dose in case of increased D-Dimer.

Background

Since February/March 2020, the COVID-19 pandemic has held the world in thrall, with far-reaching consequences for humanity and the economy. Although the exact pathogenesis of the disease is still unknown, it has become clear since the start of the pandemic that increased coagulation activity plays a part. As early as March, a study in an intensive care unit in Wuhan showed that the mortality was lower in patients, who had been given prophylactic heparin (for seven days) [1].

Further studies, initially from Italy, later from the USA [1–10] and then at the end of April also from Germany, have shown that the coronavirus infection is associated with a higher incidence of thrombosis, not only in the leg veins with pulmonary embolism, but also affecting the arteries of various organs, such as the lungs, kidneys and liver, leading to organ failure. In the middle of April, the German Society of Thrombosis and Haemostasis Research [GTH] recommended the use of heparin as prophylaxis and has since updated these recommendations to emphasise a generous approach especially also for ambulatory patients in the early stages of the disease [11].

Lockdown has had the result that we were not allowed to treat patients apart from emergencies and had more time to get to grips with world events. The author has many friends in Italy and Spain and has thus (unfortunately) been able to follow at close quarters the extent of the difficulties with ventilation and monitoring that were not previously known from the usual pneumonias. Then in April, post-mortem reports arrived from Italy, which revealed homogeneous thrombosis of the pulmonary arteries. And in international chats with phlebologists, the question arose as to why the mortality is proportionally much lower in Germany than in other countries.

One answer was clear to the author: in Germany, each patient admitted to hospital with an infection – and every case requiring mechanical ventilation – is routinely injected with a prophylactic dose of heparin. However, we were fairly alone with this worldwide, as, for reasons of cost, other countries were treating only those patients at high risk of thrombosis in this way. In the meantime, however, it is becoming routine throughout the world to give heparin to every patient with COVID-19 admitted to hospital (Phase c or higher, as shown in ► Table 1).

But how would it be, if patients with COVID-19 were to be treated with heparin even when they have only mild symptoms (in Phase b)? Would it be possible to prevent or attenuate its progression? Could we thereby remove some of the horror from this disease?

As early as March, studies on Phases c–f showed that the early administration of prophylactic doses of low molecular weight heparin (LMWH) on admission to hospital significantly lowered the mortality rate [6]. A cohort study from Italy that has not yet been published suggests that patients given LMWH in Phases a and b have fewer hospital admissions. However, not many patients have been enrolled in the study and they have not been randomised [10]. According to a press release dated 24 April 2020, a study on LMWH prophylaxis in Phase b without a placebo control has been started in Zurich.

► Table 1 Phases of COVID-19, according to WHO

a	not in hospital, no impairments
b	not in hospital, impairments
c	hospital, no oxygen required
d	hospital, supplemental oxygen required
e	hospital, non-invasive ventilation or high-flow oxygen therapy
f	hospital, invasive mechanical ventilation or ECMO
g	death

Protocol 1 – Low molecular weight heparin vs placebo

The first study protocol was drawn up with the idea of prospectively treating randomised groups of Phase b patients with heparin or placebo. As people over the age of 50 are particularly susceptible to develop symptoms after infection with the SARS-CoV-2 virus, only patients above this age would be included. The local health authority said it was prepared to provide information to patients, who had tested positive. The local swab test site should then perform the enrolment into the study by obtaining the patient's consent, performing a clinical examination, drawing blood to determine CRP and D-dimers as well as forwarding the information to the study centre.

According to the studies, clinical deterioration with admission to hospital usually occurs within a period of seven days. It was therefore decided to administer heparin for seven days. This eliminates the platelet count required after seven days.

The aim of the first study project was a prospective double-blind randomised placebo-controlled trial to determine whether prophylactic doses of low molecular weight heparin could prevent the symptoms in mild cases of COVID-19 from progressing to severe disease with admission to hospital. The heparin selected had to be one that was approved for the indication of COVID-19 in the outpatient treatment phase and a potent prophylactic. The only heparin to meet these criteria in Germany is dalteparin 5000 – as it has marketing authorisation for non-surgical patients with restricted mobility.

Hypothesis: LMWH reduces the occurrence of complications after infection with SARS-CoV-2 virus, if administered in the early stages of the disease.

Target group

- Persons in quarantine after positive COVID-19 swabs and clinically in Phase b (with cough, fever, anosmia, headache and/or diarrhoea)
- Aged over 50 years
- No contraindication to heparins (e. g. gastrointestinal bleeding)
- Not taking oral anticoagulants
- No signs of acute organ failure
- No clinical signs of thrombosis.

Endpoints

- Primary endpoints: Deterioration with admission to hospital, death
- Secondary endpoints: Duration of symptoms
Correlation between lab test results and progression

Timeline

- Recruitment (via swab test sites, corona app, health authorities, the media, etc.)
- Randomisation into two groups (heparin/placebo)
- The patient receives the study medication from the doctor and neither doctor nor patient knows the contents. Daily injection of placebo or a prophylactic dose of LMWH (dalteparin 5000 IU) for 7 days
- Laboratory tests (full blood cell count, D-dimers, C-reactive protein) and physical examination on the day of admission
- The trial centre contacts the patients by phone every seven days to enquire how they are. At least until day 28, at most until recovery/death.
- Procedure in the case of deterioration: unblinding
- Patients give their consent for their hospital discharge report to be sent to the trial unit.
- According to the power analysis based on published figures, between 300 and 500 patients in each arm of the trial would be necessary to achieve statistical significance, if progression from Phase b to Phase e/f/g were to be halved by the administration of heparin.

As the case numbers in Germany are fortunately low, it would have to be a multinational study. All the actors involved – the industry as well as colleagues at home and abroad – were absolutely convinced by this pragmatic idea. However, the patent for dalteparin expired long ago and the manufacturer sees no possibility of financing studies. LEO Pharma considered the possibility of testing this indication for tinzaparin 4500 (marketing authorisation study), but then sadly abandoned the idea. In most other countries with higher case numbers, patients were not tested in April/May until they were admitted to hospital, so the studies could not be carried out there.

The situation is interesting in Egypt, where patients who test positive or their relatives are accommodated in hospitals or hotels to ensure that they observe quarantine. These conditions would therefore be optimal for conducting the study. With great enthusiasm on the part of our colleagues there and the hospitals also showing great interest, the project was put forward to, but eventually not financed by the administration. Even so, it was established that from the end of May onwards all patients with symptoms and who tested positive would be given heparin and studied prospectively. They would then be compared with earlier cases not treated with heparin. In Germany, case numbers were falling progressively and a sponsor could not be found ...

Protocol 2: Retrospective evaluation of patients on oral anticoagulants (OAC)

As the study with heparin seemed to be falling apart, Joseph Grace (a colleague from Sydney) proposed a retrospective evaluation of patients, who had already been treated. The idea behind his suggestion was that many people are already taking oral anticoagulants. If some of the clinical picture of COVID-19 is triggered by thrombosis, patients taking OACs should be protected.

There would therefore be a smaller number of patients on OACs amongst those admitted to hospital or dying from COVID-19 than would be expected from the comparable general population.

Hypothesis: Oral anticoagulation protects against the development of symptoms after infection with SARS-CoV-2.

Endpoint: proportion of patients on OACs in the general population compared with the proportion in patients with COVID-19.

Outline of study:

- Determination of the number of persons on anticoagulation in the general population
- Determination of the number of persons on anticoagulation under the patients, who were admitted to intensive care due to COVID-19 or died from it

The comparison would be very easy to carry out with a χ^2 test:

Persons aged over 70 years	General population	Admitted to intensive care	Death	
with OAC				
without OAC				
				100 %

This study protocol was proposed to various health insurance companies in Germany (who had informed the author that they might have this data). Unfortunately, they did not consider this evaluation to be a priority. Manufacturers of oral anticoagulants showed interest in conducting a study of this nature by asking the general population to participate in a survey. Admittedly the reservations were also (justifiably) considerable: would only particularly ill or particularly healthy people react? Can a data collection of this nature actually be statistically relevant? Because of this, they ultimately decided against financing.

The author consequently contacted countries that were particularly affected by the epidemic. Most of the hospitals could not process the data, as they were under too much pressure having to care for the patients. The RIETE registry in Spain found the idea interesting and wanted to perform the analysis, but unfortunately has not yet come back to us on this (two months later).

Protocol 3

The evidence for thrombosis also occurring in the arterial branch of the organ circulation prompted the author to consider investigating not only heparin, but also antiplatelet aggregation (acetyl-

salicylic acid = ASA). In the meantime, some countries have introduced the approach of testing patients with symptoms for D-dimer levels and treating them immediately with heparin, if these are raised. In line with Protocol 1 (see above), the procedures would be as follows:

Patients with COVID-19 and exhibiting symptoms (Phase b) will have a blood sample taken (something which, in the author's opinion, is worthwhile in all patients) with full blood count, C-reactive protein and D-dimers.

- **In the case of elevated D-dimer levels:** Automatic administration of heparin (only dalteparin 5000 is approved for this use in Germany) and randomisation into two groups:
 - ASA 100 once daily for four weeks
 - Placebo tablet once daily for four weeks
- **In the case of normal D-dimer levels:** Randomisation into four groups
 - Heparin once daily for seven days plus placebo tablet for four weeks
 - Heparin once daily for seven days plus ASA tablet for four weeks
 - ASA 100 once daily for four weeks
 - Placebo tablet once daily for four weeks

For all subsequent steps, see Protocol 1.

Is a study of this nature even possible?

During the past three months, the author has contacted an incredible number of people in a wide range of positions and held some very interesting conversations. Professorial staff at universities could not contemplate taking part in such a study outside of a hospital setting. But, by definition, inpatients would not be enrolled in the study. For a practice to "conduct" such a study does not seem to lie within the realms of possibility in this country. The costs of carrying out Protocol 1 would be about EUR 80 000–130 000 (Ethics committee approval, printing costs, costs of staff for telephone calls, data entry, lab costs, reimbursement of swab test sites, statistics). This is very little for a study of this size. The author presumed that regulatory approval would not be necessary for the study on a drug that already has marketing authorisation.

However, as the ethics committee informed the author a few days before submission of this article, the study is subject to the German Medicinal Products Act (AMG). A study on an approved drug against placebo and the associated randomisation is an (interventional) Phase IV clinical trial that falls under Sections 40 to 42b AMG.

The Association of the Scientific Medical Societies in Germany (AWMF) made the following comments on the amendment of the law on clinical drug trials:

'The AWMF views the negative effects of this law on the academic clinical research in Germany with great concern'.

The AWMF justifies this opinion as follows:

The law globally regulates the technical course of clinical trials without distinguishing between the different types of study. In particular, there is no differentiation between industry-initiated and sponsored trials on the one hand and purely scientifically driven clinical studies on the other. The latter are made considerably more difficult by the new law, if not impossible. While marketing authorisation studies are usually prompted and financed by companies in the pharmaceutical industry, treatment optimisation studies, the development of new therapeutic principles and starting points for therapeutic agents, the prevention of widespread diseases, the discovery of possible adverse effects or the extension of the indications for a particular drug are frequently carried out by university hospitals, non-university research facilities or other hospitals and healthcare facilities alone, i. e. without the involvement of an industrial partner.

[...]

These stipulations in the new AMG will greatly hinder academic clinical research. This will mean that, in future, the development of therapeutic agents in clinical research will be predominantly, if not exclusively, driven by the industry. This cannot be the point of a law that, under Section 1 of the Ordinance on Good Clinical Practice of 09.08.2004, aims to ensure "...that the rights, safety and well-being of the trial subject are protected and that the results of the clinical trial are credible". (Source: <https://www.awmf.org/forschung-lehre/stellungnahmen/wissenschaft-forschung/auswirkungen-des-neuen-amg-auf-die-forschung.html>)

Conclusions

Unfortunately, it seems that any research into these important questions is no longer possible in Germany. The requirements push up the costs, insurance policies have to be negotiated – aspects that lie way beyond the possibilities of a practice or an initiative. Heparins and ASA do not generate enough profit for the pharmaceutical industry to make a study of this nature worthwhile. That it would reduce the number of deaths and admissions to hospital due to COVID-19 – as is certainly to be expected, given the current research findings – and thus not only have humanitarian benefits in reducing suffering, but also bring about considerable financial savings, is ultimately irrelevant in this development. If anticoagulation or antiplatelet aggregation could halve the number of infections progressing from mild disease to requiring intensive care, the lockdown measures with all their economic consequences would not need to be so strict. Not only would the direct costs be lowered by the reduced need for expensive medical treatment on intensive care units, but considerably lower macroeconomic follow-up costs would also be expected.

Conflict of Interest

Die Autorin wurde von Bristol-Myers Squibb 2019 eingeladen, einen Vortrag zum Ultraschall der tiefen und oberflächlichen Beinvenenthrombose zu halten und wurde dafür honoriert. Sowohl Bristol-Myers Squibb als auch Leo-Pharma unterstützen von der Autorin organisierte Tagungen mit Industrie-Ständen (keine direkte Bezahlung an die Autorin). Diese Aktivitäten haben keinen Einfluss auf den vorliegenden Artikel.

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