Innovative applications of global assays of hemostasis

Addendum

Valorization

This chapter describes the scientific and social relevance, target populations, innovation, and future directions of the key findings presented in this thesis.[1] The studies in this thesis explored multiple applications of global assays of hemostasis with the aim to ultimately improve hemostasis patient care.

Research field

In recent years, a shift has been initiated from traditional uni-dimensional assays towards more global assays of hemostasis. Previously acknowledged limitations of traditional assays of hemostasis inspired the search for measurements that better represent the *in vivo* hemostatic status in a patient. These global assays of hemostasis have the potential to address unmet laboratory challenges in patients with complex hemostatic pathologies. This thesis evaluates two high-risk patient cohorts to illustrate the potential of global assays of hemostasis in the clinic.

COVID-19 patients admitted to the ICU

The SARS-CoV2 virus causes a spectrum of disease pathologies, ranging from mild upper airway disease to life-threatening coronavirus 2019 (COVID-19) pneumonia. The COVID-19 pandemic, that held the world in its grip for over two years, has caused over six million deaths worldwide.[2] The frequent occurrence of thrombotic complications in hospitalized patients revealed that hemostatic disruption plays a crucial role in COVID-19 morbidity and mortality.[3] In response, clinicians called for the urgent need to develop tools to better characterize COVID-19 associated coagulopathy and to identify patients at risk for thrombotic complications and mortality. The studies in this thesis were performed to address the potential of global assays of hemostasis in this regard.

High-risk post-PCI patients

The second population consists of vulnerable patients with coronary artery disease at high clinical risk for hemorrhagic complications and/or major adverse cardiovascular events following percutaneous coronary intervention (PCI). The availability of a larger spectrum of antithrombotic treatment options allows for more tailored treatment strategies in the post-PCI setting. However, a delicate balance emerges between limiting ischemic risk, while preventing hemorrhagic complications, challenging clinicians to prescribe the optimal antithrombotic strategy. One of the aims of the outpatient clinic for high-risk patients was to improve long-term risk assessment using established laboratory assays and to explore the potential of novel assays, including global assays of hemostasis.[4]

Relevance of key findings

This thesis illustrates the potential of global assays of hemostasis, predominantly rotational thromboelastometry (ROTEM), in these two different patient settings.

Characterizing complex hemostatic pathologies

Traditionally an elaborate panel of hemostatic assays is required to gain a full overview of the hemostatic status in a patient. This thesis demonstrates the ability of ROTEM to characterize hemostasis and fibrinolysis in two different complex hemostatic pathologies. E.g. the tissue plasminogen activator (tPA) ROTEM assay was able to detect fulminant hypofibrinolysis in severe COVID-19 patients, but was also sensitive to the subtle decrease in fibrinolytic potential in a cohort of coronary artery disease patients. In addition to informing the clinician, providing a global overview of hemostasis in patients may uncover therapeutic targets and could help guide therapeutic intervention. In this regard, the tPA ROTEM assay may prove a promising tool to identify and monitor COVID-19 patients benefitting from treatment with profibrinolytic agents. The findings in this thesis lay the foundation for further exploration of the effect of (hemostatic and immunologic) therapeutic interventions on hemostasis and fibrinolysis as measured by viscoelastic assays.

The presented findings further expand the existing evidence by exploring clinical endpoints in relation to ROTEM measurements. We demonstrated that ROTEM may be of interest to predict future bleeding episodes in post-PCI patients on dual antithrombotic therapy. However, the considerable overlap between patients with and without bleeding challenge its introduction in the laboratory workup. Though the findings were considered unsuitable to improve risk assessment in our post-PCI setting, they do have the potential to increase awareness of the knowledge gaps in this high-risk population, guiding further exploration of hemostatic laboratory biomarkers. In COVID-19 patients, the observed trajectories of ROTEM parameters over time in non-survivors are in line with the current dogma that further deterioration of hemostasis is a driver of mortality in severe COVID-19. Moreover, we demonstrate ROTEM's value for the prediction of 45-day intensive care unit (ICU) mortality, thus providing the aim for a next step in prognostic factor research.[5,6] Ultimately, early identification of patients at risk for worse disease course may help guide treatment strategy. Taken together, the presented studies provide a solid base in support of the implementation of viscoelastic measurements in routine COVID-19 ICU patient monitoring. Follow-up studies establishing the clinical benefit of viscoelastic assays are required.

Antithrombotic drug monitoring

Global assays of hemostasis are promising tools to detect and monitor heparins and anticoagulant drugs (vitamin K antagonists and direct oral anticoagulants). The results presented in this thesis provide some preliminary evidence for the use of adapted thrombin generation assays and ROTEM to monitor heparins in COVID-19 patients. Mainly the potential of these assays to better illustrate the *in vivo* heparin anticoagulant effect is of interest. However, future studies focusing on the association with clinical outcomes and optimizing the heparin therapeutic range are fundamental to determine their clinical relevance.

Alternatively, there is an unmet clinical need for a global screening assay to identify the presence of antithrombotic medication in emergency situations, where patients are unavailable for anamnestic evaluation (e.g. intracranial hemorrhage). We demonstrate that ROTEM has excellent discriminative ability to detect the presence of anticoagulant drugs in an ambulatory patient setting. This observation, in combination with the whole-blood and point-of-care characteristics of viscoelastic assays, highlight the potential for the detection of clinically relevant anticoagulant concentrations in acute patient settings. However, validation and optimization of cutoffs are required to further establish the diagnostic performance of viscoelastic assays in an acute setting.

Knowledge dissemination

The COVID-19 pandemic took healthcare workers by surprise and no guidelines or evidence-based treatment strategies were available when the first surge of patients were admitted to hospitals in the Netherlands. Many research questions quickly arose, ranging from the underlying pathophysiology to the optimal treatment strategy of this novel disease. A collaboration across many disciplines emerged to find answers to these knowledge gaps. Therefore, the COVID-19 findings presented in this thesis must be attributed to the combined efforts of clinicians, laboratory analysts, nurses, clinical chemists, data engineers, epidemiologists, statisticians, and (fundamental) researchers. Throughout the pandemic, results were continuously shared in multidisciplinary meetings to inform and guide healthcare workers providing COVID-19 patient care. These experiences serve as a roadmap for the organizational structures required between researchers, laboratory specialists and clinicians to implement and optimize laboratory-guided patient management when confronted with a new pandemic.

Results presented in this thesis have been, and will be, published in international peer-reviewed journals. Furthermore, the findings were presented at several (inter)national congresses and a live World Thrombosis Day webinar aimed at (family of) patients with thrombosis.[7] This way, the results reached a broad audience of researchers, clinicians and the patient community. The impact of this thesis can be considered primarily scientific within the field of laboratory hemostasis testing, but it is also of importance to clinicians within the fields of hematology, cardiology, clinical chemistry and critical care medicine. We aim to inspire others to continue to explore the value of global assays of hemostasis in the presented and novel clinical settings. This will further aid the shift from a large amount of unidimensional laboratory assays towards a more global approach in patient hemostasis care.

References

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