SSC Subcommittee Project/Collaborative Project

Towards precise and rapid diagnosis of heparin-induced thrombocytopenia: a prospective, multicentre cohort study (“TORADI-HIT”)

Subcommittee Platelet immunology

Person responsible (Chair / Principal Investigator):

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Design

We plan to conduct a prospective, multicentre cohort study involving 750 patients; the design is illustrated in Figure 1. Consecutive patients evaluated for suspected HIT will be included and no active diagnostic or therapeutic intervention applied. At the time of diagnostic work-up, we will record a number of clinical data and laboratory results obtained through routine clinical practice in assessing HIT. The new diagnostic tool will then be applied using the data so obtained. Residual serum (or plasma) samples will be stored and a heparin-induced platelet activation test (HIPA) conducted as reference standard. We will conduct a second follow-up on discharge (day 14 to day 21) recording information on treatment, clinical outcomes as well as the course of important laboratory parameters (platelet count, D-dimers).
**Figure 1:** Design of a multicentre cohort study to investigate the accuracy of an integrated diagnostic approach to assess HIT compared to routine procedures. The reference standard is a functional heparin-induced platelet activation assay (HIPA); clinical outcomes will be additionally assessed.

**Rationale**

Heparin-induced thrombocytopenia (HIT) is a life-threatening complication of heparin treatment, which affects a significant number of patients. If missed and untreated, HIT often leads to very serious consequences. Available diagnostic tests, however, are associated with important drawbacks. In clinical practice, we not only miss patients suffering from HIT but also unnecessarily treat many patients without HIT with costly and risky alternative anticoagulants. Hence, many authors consider current diagnostic approaches to be inadequate in clinical practice. Integrated diagnostic approaches, incorporating relevant clinical and laboratory information have the potential to significantly improve clinical decision-making.
Aims and objectives

We hypothesise that an integrated diagnostic approach taking personalised patient characteristics as well as quantitative results of individual immunoassays into account will allow the accurate determination of the probability of HIT in individual patients.

1. We aim to compare the diagnostic accuracy of a new integrated diagnostic tool, combining clinical characteristics and immunoassay test results using Bayes’ theorem, with current clinical practice in a multicentre prospective cohort study.
   a. The probability of HIT according to the proposed approach will be assessed using a variety of immunoassays and the diagnostic accuracy determined in relation to the reference (gold) standard (heparin-induced platelet activation assay, HIPA).
   b. Additionally, clinical outcomes (bleeding events, thromboembolic events) will be compared in categories determined by current practice with outcomes determined in categories defined by the proposed test.

2. Using the data of the proposed cohort study, we aim to develop a second integrated diagnostic tool using a multivariable prevalence function as calculated by logistic regression analysis.
   a. The predictive value (or diagnostic accuracy respectively) of this model will be compared with the diagnostic accuracy of the Bayes’ based model as well as clinical practice.

METHODOLOGY

Study centers

Patients will be included via an established Swiss study group as well as an international group of reference centres for HIT (members of the SSC subcommittee platelet immunology). The Swiss study group consists of all major haemostasis laboratories in Switzerland. Implementation of the cohort study in a number of large-scale international centres ensures inclusion of a large number of patients with different characteristics and guarantees applicability of the study results across different settings.

Predictor and outcome variables

The schedule of events is shown in Table 1; illustrating a number of clinical characteristics and laboratory test results recorded as diagnostic predictor variables. The four domains of the 4Ts score (Degree of thrombocytopenia, timing of thrombocytopenia, presence of thrombosis and presence of other reasons for thrombocytopenia) will be assessed by a member of the consultancy team, the referring physician or both. The type and quantitative result of the
immunoassay used in the individual study centre will additionally be recorded. Using these
data, the new developed diagnostic tool will be applied and a probability of HIT estimated. The
HIPA test will be conducted in the central laboratory as reference (gold) standard using
residual serum sample. The diagnostic accuracy of the new diagnostic tool and the standard-
of-care diagnostic pathway represents the primary outcome. Clinical outcomes
(thromboembolic events, bleeding events, and deaths) will be used as secondary outcome
variables.

Statistical analysis

Numbers of true positives, false positives, false negatives and true negatives of the new
diagnostic tool will be recorded with regard to the reference standard and diagnostic accuracy
measures calculated, in-line with confidence intervals: sensitivity, specificity, likelihood ratios
and post-test probabilities. The accuracy of the above mentioned new test will be compared
with current clinical practice (considering confidence intervals and test statistics). Clinical
outcomes will be additionally compared in categories obtained with the new diagnostic tools
and current clinical practice.

Power analysis

We aim to investigate differences in diagnostic accuracy of a new integrated diagnostic tool in
comparison to clinical practice. For the purpose of power analysis, we will focus on specificity,
rather than sensitivity, because “over-diagnosis” is regarded as the major issue associated with
current approaches. The power analysis has been conducted according to a method by Alonzo
et al. aiming for confidence intervals narrow enough to reject or keep the null hypothesis (null-
hypothesis: the diagnostic accuracy of the new diagnostic tool is similar to the current
approach). As long as appropriate diagnostic accuracy measures of current diagnostic
algorithms (sequential determination of 4Ts score and consecutive immunoassay if 4Ts score is
intermediate to high) are not available, we used measures of a recently published meta-
analysis of immunoassays. We consider a significance level of 0.05, a two-sided distribution, a
power of 0.9 and a difference in specificity of 5% as clinically relevant. The resulting number of
patients (n=701) was additionally increased to account for any sampling variability with regard
to the prevalence. Thus, we have calculated that a sample size of 750 patients with suspected
HIT is necessary. This number of patients is also considered to be sufficient for the
development of a prediction model using logistic regression (75 cases; 7 to 8 predictor
variables).

Study population

We defined “patients with suspected HIT” as the study population, because such patients
represent the intended target population for which the new diagnostic tool would be applied.
This definition is equivalent to most previous cohort studies investigating current diagnostic
tests, as well clinical assessment tools such as immunoassays. We decided against a study
population “all patients with heparin exposure” or “all patients with thrombocytopenia” because they do not represent the intended target population which would be assessed with the proposed diagnostic tool. In addition, the prevalence of HIT would be low in this population (between 1 and 3%), leading to particular problems in the interpretation of results. Exclusion criteria are: age below 18 years and consent refusal.

**Expected timeline:**

<table>
<thead>
<tr>
<th>Time period</th>
<th>Activities</th>
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<tbody>
<tr>
<td>Apr 2017 – Jun 2017</td>
<td>Gaining ethical approval at all study centres</td>
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<tr>
<td></td>
<td>Setup and implementation of e-CRF</td>
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<tr>
<td>Jul 2017</td>
<td>Initiation of study at study centres</td>
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<td>Jul 2017 – Dec 2018</td>
<td>Recruitment of patients</td>
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<td></td>
<td>Determination of HIPA assay</td>
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<tr>
<td>Dec 2019</td>
<td>Determination of remaining immunoassays</td>
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<tr>
<td>Jan 2019</td>
<td>Data cleaning and analysis</td>
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<tr>
<td>Jan 2019 – Mar 2019</td>
<td>Presentation and manuscripts</td>
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**Expected outcomes:**

The results of this project will be presented in several original articles and possibly consecutive guidance documents. The members of the SSC subcommittee will co-author these publications, demonstrating the joint work of the group.

With the present project, we aim to investigate the merits of an integrated diagnostic approach taking into account several patient characteristics, quantitative immunoassay results as well as the type of the individual immunoassay. With the help of this tool, the probability of HIT can be estimated considering all relevant information available at the bedside. If confirmed in our prospective, multicentre cohort study, diagnosis of HIT will be markedly improved and decisions on treatment can be made objectively rather than subjectively. With an improved diagnostic approach, the number of patients not requiring treatment with alternative anticoagulants can be anticipated to decrease, preventing a significant number of bleeding complications. In addition, the number of patients with missed HIT might be reduced. Thus, our research may not only help to improve patient care but also to limit health costs in this vulnerable patient population.

**Project setup and management**

As head of the haemostasis laboratory Inselspital University Hospital Bern, I am able to use the infrastructure of a large, specialised haemostasis laboratory with extensive experience conducting large-scale studies. A number of immunoassays for the detection of H/PF4 (HIT) immunoassays are in routine use (ELISA, PaGIA, chemiluminescent immunoassay). The
heparin-induced platelet aggregation test (HIPA) was implemented with the help of Prof. A. Greinacher (Greifswald University, Germany). Prof. Angelillo-Scherrer, head of Department of Haematology, fully supports this application and is already engaged with this study through the provision of expertise, infrastructure and working time.

An international team of well-recognised experts in HIT, epidemiologists, physicians and laboratory specialists support the proposed project. Most importantly, many world renowned experts in HIT, forming the SSC subcommittee of the ISTH, support this study: Prof. A. Cuker (University of Pennsylvania, US), Prof. A. Greinacher (Greifswald University, Germany), Prof. L. Alberio (Lausanne University, Switzerland), Prof. T. Bakchoul (University of Tübingen, Germany), Prof. F. Mullier (Université catholique de Louvain, Belgium), and Prof. D. Arnold (McMaster University, Canada). All have published a large number of studies focused on HIT diagnosis. Prof. L.M. Bachmann (Zürich University, Switzerland) is an epidemiologist with an impressive track record in clinical research with a particular interest in diagnostic research and meta-analysis. Prof. A. Angelillo-Scherrer is a distinct expert in experimental haemostasis and has led several large projects. She has particular expertise in establishing large biobanks.

The national study group, the Working Party Haemostasis (WPH) of the Swiss Society of Haematolog, joined by all heads of major haemostasis laboratories in Switzerland, is an ideal national partner to conduct the mentioned cohort study on HIT patients. By far the most antibody tests in Switzerland are conducted in one of these laboratories (estimated at 500 per year) and above-mentioned colleagues are consultants for HIT treatment in their hospitals. Collaboration with WPH ensures recognition of all eligible patients, fast mobilisation of the study team, and high quality data collection. All members have already agreed to participate.

References:


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100. Nagler M, Alberio L, Angellillo-Scherrer A, et al. Measuring rivaroxaban plasma levels with anti Xa assays: accuracy and reproducibility in a prospective, multicenter evaluation study employing different reagents and analyzers. 60th Annual Meeting of the Society of Thrombosis and Haemostasis Research; 2016; Münster, Germany.