PROTOCOL

Predictive value of suPAR and hsCRP on postoperative mortality in 951 patients undergoing elective on-pump cardiac surgery.

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PROJECT SUMMARY

Title: Predictive value of suPAR and hsCRP on postoperative mortality in 951 patients undergoing elective on-pump cardiac surgery.

The risk models currently used to predict outcome after cardiac surgery only explain a minor part of the observed variation in perioperative complications between patients. A recent trend in risk modelling has been the addition of various biomarkers to supplement clinical risk factors.

This study aims to investigate whether preoperative measurement of the inflammatory biomarkers soluble urokinase plasminogen activating receptor (suPAR) and High-sensitivity C-Reactive Protein (hsCRP) are associated with death after cardiac surgery. Further, to assess whether suPAR and hsCRP provides increased predictive accuracy of the clinical risk model EuroSCORE II. The purpose of the study is to gain knowledge on whether these inflammatory biomarkers might be able to reveal a pro-inflammatory disease state that represents a risk in patients undergoing cardiovascular surgery. Hence, these biomarkers may assist clinicians to gain more accurate risk identification and selecting compassionate treatment for high risk patients.

The study design is a retrospective observational cohort study conducted at The Department of Cardiothoracic Anaesthesiology, Rigshospitalet, in collaboration with University of Copenhagen and PERSIMUNE Centre of Excellence, Rigshospitalet.
Patients (≥18 years) undergoing elective on-pump cardiac surgery at the department of Cardiothoracic Surgery at Rigshospitalet, Denmark (isolated coronary artery bypass graft (CABG), single and multiple valvular procedures, combined CABG and valvular surgery, and others) and have given informed consent, is included. Exclusion criteria is; Peroperatively cancelling the surgery due to anatomic challenging findings, sudden change to off-pump coronary artery bypass (OPCAB) surgery, death prior to surgery and project blood samples not available.
Approximately 1000 patients will be enrolled in the biobank between 2012 and 2018 and will be included in the study. Data collection and analysis of the biomarkers is expected to be performed in 2019. The statistical analysis, writing of the manuscript and submission to a peer-reviewed journal is expected to be conducted in primo 2020. The study is approved by The Regional Committee on Health Research Ethics and the Data Protection Agency.

GENERAL INFORMATION

Protocol title: Predictive value of suPAR and hsCRP on postoperative mortality in 951 patients undergoing elective on-pump cardiac surgery.

Investigators:

Primary responsible:
Sebastian Roed Rasmussen, MD
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Senior responsible:
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Rigshospitalet, University Hospital Copenhagen
Dept. Cardiothoracic Anaesthesiology
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Rikke Vibeke Nielsen, MD, PhD, Dept. Cardiothoracic Anaesthesiology, Rigshospitalet
Sisse Ostrowski, MD, PhD, DMSc, Associate professor, Dept. Clinical Immunology, Rigshospitalet
Frank Eriksson, Ass. professor, Section of Biostatistics, University of Copenhagen.
Rasmus Møgelvang, MD, PhD, consultant, professor, centre director, the centre for cardiac, vascular, pulmonary and infectious diseases, Rigshospitalet

Collaborators:

PERSIMUNE, Department of Infectious Diseases, Rigshospitalet, Copenhagen University Hospital

The Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital

Section of Biostatistics, University of Copenhagen.

RATIONALE & BACKGROUD INFORMATION

Hypothesis

We hypothesize that biomarkers reflecting a pro-inflammatory disease state at baseline; the soluble urokinase plasminogen activator receptor (suPAR) and high sensitivity C-reactive protein (hsCRP), can be used as preoperative predictors of outcome after cardiac surgery.

Aim

This study aims to investigate whether preoperative soluble urokinase plasminogen activating receptor (suPAR) and High-sensitivity C-Reactive Protein (hsCRP) levels are associated with death from any cause during the study period following cardiac surgery. Further, to assess whether suPAR and hsCRP provides increased predictive accuracy of the clinical risk model EuroSCORE II, in predicting 30 days mortality. The purpose of the study is to gain knowledge on whether these inflammatory biomarkers might be able to reveal a pro-inflammatory disease state that represents a risk in patients undergoing cardiovascular surgery. Hence, these biomarkers may assist clinicians to gain more accurate risk identification and selecting compassionate treatment for high risk patients.

Background

The risk models currently used to predict outcome after cardiac surgery only explain a minor part of the observed variation in perioperative complications between patients. A recent trend in risk modelling has been the addition of various biomarkers to supplement clinical risk factors. By identifying predictive parameters of postoperative outcome such as biomarkers, future prevention- and treatment strategies for high risk patients may be developed and reduce morbidity and mortality after cardiac surgery. These are the first steps towards introducing personalized medicine on the patient level and improve cost utility.

One of the most important contributors to morbidity after cardiac surgery is the systemic inflammatory response syndrome (SIRS). All patients have an inflammatory response after cardiac surgery, but in about 30% of all patients it may lead to shock, vital organ failure, poor outcome and death (Laffey et al. 2002). The inflammation most likely plays a central role in the development of failure in all vital organs postoperatively (Laffey et al. 2002, Karkouti et al. 2009, Kertai et al. 2015). Further, patients with pro-inflammatory disease states preoperatively, such as coronary heart disease, heart failure and diabetes are at increased risk of SIRS and poor outcome after cardiac surgery.

The ability to predict patients at high risk of postoperative complications is essential to reduce patient morbidity and mortality after cardiac surgery. The fundamental role of inflammation in cardiovascular disease has prompted interest in the predictive capability of numerous biomarkers to detect subclinical levels of inflammation. Formation of atherosclerotic plaques is proven to be influenced by inflammation and suPAR and CRP highlight different element of inflammatory biochemical pathways linked to cardiovascular risk (Desmedt et al., 2017). CRP is involved in the trigger process of vascular remodelling and is positively associated with anthropometric measures where suPAR is linked to endothelial dysfunction, subclinical organ damage and atherosclerotic disease burden. SuPAR and hsCRP have been studied in infectious disease as well as in cardiovascular disease but the relationship to cardiovascular surgery outcome has only recently been explored. CRP is an acute phase protein produced by the liver in response to several cytokines released from leukocytes during inflammation in response to infection or trauma. HsCRP measures low levels of CRP with

increased sensitivity. SuPAR is a novel biomarker that correlates with cardiovascular events and outperforms traditional markers of inflammation in prognosticating a range of cardiovascular events. SuPAR is released into the circulation by cleavage of the membrane-bound urokinase-type plasminogen receptor (uPAR) from various cells, including inflammatory and endothelial cells (Hodges et al. 2015). Patients with preoperative pro-inflammatory disease states, such as coronary heart disease, heart failure and diabetes are at increased risk of SIRS and poor outcome after cardiac surgery. New studies have indicated that patients with elevated suPAR undergoing aortic valve replacement surgery are at increased risk of postoperative complications and mortality (Hodges et al. 2018). Increased circulating concentrations of suPAR are also strongly associated with increased risk of cardiovascular disease, diabetes, cancer and mortality in the general population, with poor outcomes in critically ill patients, in non-ST-elevation myocardial infarction (NSTEMI) patients, and with recurrent myocardial infarction and mortality in patients with STEMI undergoing primary percutaneous coronary intervention (Hodges et al. 2015). Further, suPAR improves risk stratification beyond traditional risk variables in patients with acute ischemic cardiac events (Hodges et al. 2015). Results from our own research group support these findings of suPAR as a predictor for patients with acute chest pain and patients with STEMI undergoing primary percutaneous coronary intervention (Lyngbaek et al. 2012, Lyngbaek et al. 2013).

HsCRP has received a lot of attention regarding screening, reclassification and prediction of treatment response in patients suffering from cardiovascular disease, and elevated levels of hsCRP preoperatively was found to be associated with increased risk of postoperative cardiovascular events after on-pump coronary artery bypass grafting surgery (Yousuf et al. 2013, Balciunas et al. 2009). A Danish study from 2018 has revealed, that elevated suPAR and CRP were associated with cardiovascular risk and had predictive value among the 60-year old, and suPAR was of particular importance among women (Diedrichsen et at. 2018). Hence, these inflammatory biomarkers might be able to reveal a pro-inflammatory disease state that represents a risk in patients undergoing cardiovascular surgery, leading to a stronger inflammatory response with subsequent increased morbidity and mortality.

STUDY GOALS AND OBJECTIVES

The goals of this study are to assess how a high pro-inflammatory disease state at baseline reflected by the biomarkers suPAR and hsCRP, is associated with adverse outcome after cardiac surgery. We also expect that suPAR and/or hsCRP can provide increased predictive accuracy of the risk model EuroSCORE II which is currently being used for risk stratification in many hospitals.

Primary objective

1. Association of preoperative suPAR values in relation to the censored time-to-event outcome "death from any cause" [Time Frame: from index surgery to date of data collection]

Secondary objectives:

1. Association of preoperative hsCRP values in relation to the censored time-to-event outcome "death from any cause" [Time Frame: from index surgery to date of data collection]
2. Assess whether adding suPAR, hsCRP or combined suPAR+hsCRP measurements improves predictive accuracy of EuroSCORE II [Time Frame: from index surgery to 30 days postoperative]
3. Sensitivity of the models; EuroSCORE II, suPAR, hsCRP, suPAR+hsCRP, EuroSCOREII+suPAR, EuroSCOREII+hsCRP and EuroSCOREII+suPAR+hsCRP in relation to the time-to-event outcome "death from any cause" [Time Frame: from index surgery to 30 days postoperative]
4. Specificity of the models; EuroSCORE II, suPAR, hsCRP, suPAR+hsCRP, EuroSCOREII+suPAR, EuroSCOREII+hsCRP and EuroSCOREII+suPAR+hsCRP in relation to the time-to-event outcome "death from any cause" [Time Frame: from index surgery to 30 days postoperative]
5. Asses association between suPAR and hsCRP measurements

Other outcome measures:

1. 30 days mortality measured by a yes/no question of "all-cause mortality" [Time Frame: from index surgery to 30 days]
2. 1-year mortality measured by a yes/no question of "all-cause mortality" [Time Frame: from index surgery to 1 year]

STUDY DESIGN

Study design:

Retrospective observational cohort study.

Place of conduction:

Dept. Cardiothoracic Anaesthesiology 4141, Rigshospitalet, Copenhagen University Hospital, Denmark.

Data concerning outcome measures will be obtained in collaboration with PERSIMUNE Datawarehouse and Biobank.

Research population:

The population includes adult patients (≥18 years) undergoing cardiac surgery at department of Cardiothoracic Surgery at Rigshospitalet, University hospital Copenhagen, Denmark.

Inclusion Criteria:

- Patients undergoing elective on-pump cardiac surgery (isolated coronary artery bypass graft (CABG), single and multiple valvular procedures, combined CABG and valvular surgery, and others) and have completed informed consent on delivering a blood sample for the biobank.

Exclusion Criteria:

- Peroperatively cancelling the surgery due to anatomic challenging findings, sudden change to off-pump coronary artery bypass (OPCAB) surgery, death prior to surgery and project blood samples not available.

METHODOLOGY

The following clinical information will be obtained from the electronic databases listed:

PATS: BMI, procedure codes, CPB time and aorta clamp time, procedure date, date and time for admission and discharge ICU.

ICCA: length of stay ICU (if missing in PATS)

Biochemical data: creatinine

The Danish National Patient Register: age, sex, date of death

Perfusionist charts: CPB time and aorta clamp time (if missing in PATS)

Sundhedsplatformen: type of surgery, previous PCI, AMI within 90 days of surgery, hypertension, diabetes mellitus, smoking status, left ventricle ejection fraction (LVEF), NYHA, CCS, date of discharge hospitalisation, length of stay ICU (if missing in PATS), and the following defined according to the EuroSCORE II; extracardiac arthropathy, mobility status, previous cardiac surgery, chronic lung disease, active endocarditis, critical preoperative state and pulmonary hypertension,

The blood samples for the study were drawn preoperatively or within the first 24 hours of surgery (only preoperative data for hsCRP included), and stored in the Persimune Biobank or two other biobanks at Dept. Cardiothoracic Anaesthesiology and Dept. Cardiothoracic Surgery, Rigshospitalet (registered with Katrine Buggeskov, MD, PhD and Anne Vedel, MD, respectively). The blood samples from the established biobanks were obtained in relations to research projects on patients undergoing cardiac surgery. When the patients were giving informed consent to participate in the study they were informed about, they were also at the same time giving consent to the blood samples to be obtained for future research (see attached participant information). Blood samples stored in Persimune Biobank from patients undergoing cardiothoracic surgery has continuously been included by MD, PhD Rikke V. Nielsen and MD Maria Dons at the Dep. of Cardiothoracic Anaesthesiology. The study has been approved by the executive committee of the PERSIMUNE Centre of Excellence.

In this study we will use 850 µL EDTA-plasma in matrix tubes for each patient from a total of ~1000 patients from all three biobanks. All tubes will be transported directly from the respective biobank to the Dep. of Clinical Immunology for suPAR analysis. The tubes will be kept at the Dep. of Clinical Immunology for two days while conducting the analysis and after analysis the tubes including excess biological material will be discarded. Likewise, 850 µL EDTA-plasma in matrix tubes from the ~1000 patients from all three biobanks will be transported directly from the respective biobank to the Dep. of Clinical Biochemistry for hsCRP analysis. They will be kept here for two days while conducting the analysis, and after analysis the tubes including excess biological material will be discarded as well. The analysis will be performed using commercially available analyses (suPARnostic® kit (validated to measure suPAR concentrations between 0.6 and 22 ng/mL) (ViroGates)). HsCRP will be measured by high sensitivity CRP assays (Tina-quant hsCRP latex assay (validated to measure CRP concentrations between 0.3 – 20 mg) (Roche/Hitachi)). SuPAR and hsCRP have both proven stable in frozen samples (Riisbro et al. 2001, Nilsson et al. 2005).

SAFETY CONSIDERATIONS

There are no health-related risks for patients in relation to the blood analyses and outcome results. Due to the retrospective nature of the project it will not impose any burden on patients.

FOLLOW-UP

No physical follow-up of the study participant will be performed beyond the all-ready existing cardiac rehabilitation program which is being offered to all patients undergoing cardiac surgery at our site.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

This study will be registered with the Danish Data Protection Agency. The law on patients' data protection will be followed. Data will be handled according to the Danish Data Protection Agency and stored within the PERSIMUNE Data Warehouse. The study database, data analyses and reporting of data will be anonymized. All investigators have confidentiality. The data are only available to inspection from relevant authorities.

Sample size and statistical analyses

Previous studies with <500 patients have found a significant difference in mortality between suPAR quartiles in populations with similar mortality rates as ours (Lyngbæk et al. 2012). In a prospective observational study of 66 patients undergoing on-pump CABG, Balciunas et al. found that a value of hsCRP greater or equal to 3.3 mg/L was an independent predictor of postoperative cardiovascular events in a multivariate logistic regression model. Approximately 1000 patients will be included in this study.

A table 1 with patient characteristics for the entire study population will be generated presenting frequencies (percent), mean ± standard deviation (SD), and median (25–75% quartile), where appropriate. This table will include the following variables: age (continuous (years)), sex (male), body-mass-index/BMI (continuous (kg/m^2), diabetes mellitus (NIDDM/IDDM), arterial hypertension (yes), EuroSCORE II value (continuous (%)), smoking status (never/previous/active), precious PCI (yes), NYHA (I-IV), CCS class 4 (yes), left ventricle ejection fraction/LVEF (continuous (%)), Previous cardiac surgery (yes), chronic lung disease (yes), acute myocardial infarction (AMI) within 90 days of surgery (yes), pulmonary hypertension (no, moderate, severe), weight on the intervention (isolated CABG, single non CABG, 2 procedures, 3 procedures), surgery on thoracic aorta (yes), baseline creatinine (continuous (µmol/L)), hsCRP (continuous (mg/L)), suPAR (continuous (ng/mL)),
In addition, the following peri- and postoperative variables will be used for analysis: cardiopulmonary by-pass/CPB time (continuous (min)), aorta clamp time (continuous (min)), length of stay – ICU (continuous (hours)), length of stay – Hospitalisation (continuous (days)).
A table 2 will be generated including relevant tests for association between the individual variables mentioned above and continuous values of suPAR and hsCRP, respectively.

We will fit Cox proportional hazards models to assess the association between preoperative suPAR and hsCRP-values and death from any cause. The goodness-of-fit of the Cox model will be investigated and the model will be adapted as required to fulfil the model assumptions. The model will be adjusted for sex, age, current smoker, AMI within 90 days, diabetes mellitus, creatinine, CPB time and aorta clamp time. 30-days survival

will be modelled using logistic regression. If we cannot find Cox and/or logistic models that fit the data, alternative models will be considered.

Receiver operating characteristics (ROC) curve and area under the curve (AUC) analysis will be performed comparing EuroSCORE II, suPAR, hsCRP, suPAR+hsCRP, EuroSCOREII+suPAR, EuroSCOREII+hsCRP and EuroSCOREII+suPAR+hsCRP. Sensitivity and specificity values will be included.

Regression analysis between suPAR and hsCRP measurement will be performed.

Kaplan-Meier survival plots will be generated for the 4 quartiles of suPAR and hsCRP, respectively.

Two supplementary tables will be generated presenting the pre-, peri- and postoperative variables divided into the 4 quartiles of suPAR and hsCRP, respectively.

A two-sided *p* value <0.05 will be considered significant.

QUALITY ASSURANCE

An internal quality control of the reliability of the biochemical analyses of the study biomarkers will be performed at the department of clinical biochemistry. Since the remaining clinical data is extracted from well-established electronical databases, no internal validation on the data will be performed.

An experienced statistician from the project group will handle the statistical analysis, to ensure quality of the statistical methodology and processing of data.

EXPECTED OUTCOMES OF THE STUDY

The results of this study are expected to provide further knowledge on the applicability of the biomarkers suPAR and hsCRP - specific in the setting of cardiovascular surgery. These inflammatory biomarkers might be able to reveal a pro-inflammatory disease state that represents a risk in patients undergoing cardiovascular surgery. We expect that preoperative high levels of suPAR and hsCRP are associated with death after cardiac surgery.

We also expect suPAR and hsCRP to provide increased predictive accuracy of the clinical risk model EuroSCORE II, which is currently used in in the risk evaluation prior to surgery.

If suPAR and hsCRP are associated with death after cardiac surgery, and if they increase the preoperative risk evaluation, these biomarkers may assist clinicians in selecting compassionate treatment for high risk patients and improve cost utility. The results of this study may lead to prospective studies evaluating the biomarkers and taking the first step towards introducing personalised medicine on the patient level.

DISSEMINATION OF RESULT AND PUBLICATION POLICY

Manuscript submission is expected in primo 2020. Authorship will be based on the Vancouver Authorship Guidelines. Both positive, negative and inconclusive findings will be published.

DURATION OF THE PROJECT

PROBLEMS ANTICIPATED

We are confident that the project group is capable of conducting the study including the planned blood sample analyses and statistical analyses. The project group is experienced in this type of research however unexpected problems and time delay may always occur. Since the study is fully financed, no financial barriers are potentially interrupting the completion of the study.

PROJECT MANAGEMENT

Sebastian Roed Rasmussen, MD, Dept. Cardiothoracic Anaesthesiology
Role: primary investigator, concept and design, data analysis and interpretation

Rikke Vibeke Nielsen, MD, PhD, Post.doc, Dept. Cardiothoracic Anaesthesiology
Role: concept and design, collection and assembly of data, data analysis and interpretation

Hanne Berg Ravn, MD, PhD, DMSc, Professor, Dept. Cardiothoracic Anaesthesiology
Role: concept and design, administrative support, provision of study materials or patients, data analysis and interpretation

Sisse Ostrowski, MD, PhD, DMSc, Associate professor, Dept. Clinical Immunology
Role: concept and design, administrative support, data analysis and interpretation

Frank Eriksson, Ass. Professor, Section of Biostatistics, University of Copenhagen.
Role: concept and design, data analysis and interpretation

Rasmus Møgelvang, MD, PhD, consultant, professor, centre director, the centre for cardiac, vascular, pulmonary and infectious diseases, Dept. Cardiology, Rigshospitalet
Role: concept and design, administrative support

Collaborators:
PERSIMUNE Department Infectious Diseases, Rigshospitalet, University Hospital Copenhagen.

ETHICS

This study will be conducted according to the principles of the Helsinki Declaration. The protocol will be registered in The Regional Committee on Health Research Ethics and the Data Protection Agency for approval. Further the investigator will report back to these institutions if any changes are made to the protocol.

There are no additional health related risks for the patients related to these analyses as the blood samples were obtained during their previous cardiac procedure. Further we do not consider this study to be a burden to the patients. We consider the risk of coincidental findings on patients' health status to be minimal. We will only measure the level of suPAR and hsCRP in relation to their cardiac surgical procedure. The suPAR and hsCRP levels are only of interest in relations to the historical surgical procedure. It has no relation to the present health state of the patient.

The Regional Committee on Health Research Ethics has approved the study (H-18002379).

INFORMED CONSENT FORMS (DANISH)

PERSIMUNE
CENTRE OF EXCELLENCE FOR PERSONALISED MEDICINE OF INFECTIOUS COMPLICATIONS IN IMMUNE DEFICIENCY
REGION H
Rigshospitalet
Danmarks Grundforskningsfond Danish National Research Foundation

Navn og cpr. nr. (label)

Samtykke til opbevaring af biologisk materiale fra patienter på Rigshospitalet.

I forbindelse med din behandling på Rigshospitalet vil vi gerne gemme prøver fra dig i en biobank. Prøverne kan i fremtiden anvendes til laboratorie-undersøgelse inden for din sygdomskategori for at belyse sammenhænge mellem arv, infektioner, miljø, livsstil, andre sygdomme, og så den sygdom du har. Formålet er at forbedre diagnostik og behandling af patienter med samme sygdom.

Alle forskningsprojekter, der udgår fra biobanken, skal godkendes af Den Videnskabsetiske Komité og anmeldes til Datatilsynet, og oplysningerne om din sygdom, som beskrevet i afsnittet herover vil indgå på en måde, som ikke afslører din identitet (i anonymiseret form).

Blod og andet biologisk materiale må gerne gemmes til senere videnskabelig brug indenfor min sygdomskategori /diagnose.

Ja ☐ Nej ☐

Hvis jeg fortryder, er jeg klar over, at jeg kan henvende mig til personalet på Rigshospitalet og få udleveret pjecen "Dit væv, dit valg" udgivet af Indenrigs- og Sundhedsministeriet, som giver mig vejledning i at trække mit tilsagn tilbage, *uden at dette vil påvirke min nuværende eller fremtidige behandling.*

Dato: _____ Underskrift: _____

Samtykke indhentet af: _____

Den udfyldte erklæring bedes afleveret til personalet på Rigshospitalet.

5. januar 2016

Forskning til gavn for fremtidens patienter

Vi vil spørge, om du vil tillade at vi opbevarer biologisk materiale fra dig i PERSIMUNE biobank med henblik på fremtidig forskning i immunforsvaret overfor infektioner.

I PERSIMUNE-biobank opbevares forskelligt biologisk materiale fra patienter, som kunne være i risiko for at udvikle infektion, fordi deres immunsystem måske ikke fungerer helt optimalt. Materialet fra biobanken vil senere blive anvendt til forskningsprojekter, der har til formål nærmere at belyse sygdomsforholdene omkring risikoen for at udvikle infektion.

Det præcise fokus for disse forskningsprojekter er ikke afklaret endnu. Generelt set vil det biologiske materiale undergå laboratorie-analyser, som giver oplysning om, hvordan immunsystemet fungerer, om stofskiftet eller om en eventuel pågående infektion. Disse analyser kan påvise sporstoffer. Der kan også være tale om analyser af den genetiske information, som det biologiske materiale indeholder, for der igennem at belyse betydning af arv for menneskets evne til at få sit immunsystem til at fungere og for risikoen for at få infektion. Analyserne vil have fokus på såvel patientens egne prøver og på de mikro-organismer, der eventuelt findes i materialet.

Data fra disse nye analyser vil blive koblet til oplysningerne i din journal for at kunne tolke resultaterne bedst muligt. Det biologiske materiale du donerer til PERSIMUNE-biobanken har derfor stor betydning for forskernes arbejde med udvikling af ny diagnostik og behandling til gavn for fremtidens patienter. Laboratorieanalyser og databehandling af resultater vil blive foretaget på Rigshospitalet eller hos vores samarbejdspartnere på offentlige institutioner i EU-lande.

Blodprøverne til PERSIMUNE-biobank tages samtidig med andre blodprøver, der indhentes som led i behandlingen og vil derfor ikke medføre ekstra stik. Der udtages blod i tre prøvetagningsrør (2 x 9 mL og 1 x 3 mL), og den beskedne mængde er uden helbredsmæssig betydning.

Blodprøven – og eventuelt spyt- og afføringsprøver - tages i forbindelse med at samtykke afgives, efter 3-6 måneder og derefter årligt så længe du følges på Rigshospitalet. Planen for prøvetagning kan ændres, hvis du modtager behandling, der påvirker dit immunsystem eller får symptomer på akut nedsat modstandskraft mod infektioner.

Vi registrerer og opbevarer prøverne ifølge Datatilsynets godkendelse. Vi behandler personlige oplysninger fuldt fortroligt. Før vi bruger prøver fra biobanken til forskningsprojekter, skal hvert projekt godkendes af Videnskabsetisk Komité og Datatilsynet.

Det er frivilligt, om du vil deltage, og dit valg vil ikke på nogen måde påvirke din nuværende eller fremtidige behandling. Hvis du vælger at deltage og senere fortryder, kan du altid med øjeblikkelig virkning trække dit tilsagn tilbage, uden at du behøver at give en begrundelse.

Hvis du senere fortryder din tilladelse, beder vi dig sørge for, at din beslutning registreres i Vævsanvendelsesregisteret. Det kan du gøre ved at udfylde blanketten "Dit væv, dit valg", som du skal sende til Sundhedsstyrelsens Vævsanvendelsesregister. Hvis du har brug for hjælp til dette kan du kontakte personalet i klinikken eller PERSIMUNE-centret.

Tak, fordi du tog dig tid til at læse denne information og tog stilling til spørgsmålet om biobanken.

Vi vil bede dig tage stilling til, om du tillader, at vi gemmer prøver i PERSIMUNE biobank ved at udfylde og underskrive det medfølgende samtykke til videregivelse af helbredsoplysninger og opbevaring af biologisk materiale.

Med venlig hilsen

Personalet i PERSIMUNE

Oplysninger om PERSIMUNE kan fås ved henvendelse til CHIP, Klinik for infektionsmedicin, Afsnit 2100, Rigshospitalet, Blegdamsvej 9, 2100 København Ø. Tlf.: 35455757 (i tidsrummet kl. 9-15). E-mail: persimune.rigshospitalet@regionh.dk

PERSIMUNE
CENTRE OF EXCELLENCE FOR PERSONALISED MEDICINE OF INFECTIOUS COMPLICATIONS IN IMMUNE DEFICIENCY
REGION H
Rigshospitalet
Danmarks Grundforskningsfond
Danish National Research Foundation

Name and CPR no (label)

Consent to the disclosure of health information for research and the retention of biological material from patients at Copenhagen University Hospital.

In connection with your treatment at Copenhagen University Hospital we would like to store samples from you in a biobank. The samples may be used in the future for laboratory tests within your disease category, to reveal relationships between heredity, environment, lifestyle, infections, other diseases and the disease that you have. The aim is to improve the diagnosis and treatment of patients with your disease.

All research projects that make use of the biobank have to be approved by the Committee on Health Research Ethics and registered with the Danish Data Protection Agency.
Information about your disease, as described above, will be included in a way that does not disclose your identity (anonymized).

Blood and other biological material may be stored for later scientific use within my disease category/diagnosis.

Yes ☐ No ☐

If I change my mind, I am aware that I can contact the staff at Copenhagen University Hospital to obtain the booklet "Your tissue, your choice", published by the Ministry of Health, which will tell me how to withdraw my consent *without this affecting my treatment now or in the future.*

Date: _____ Signature: _____

Consent obtained from: _____

Please hand the completed declaration to the staff at Copenhagen University Hospital when you are admitted.

24 November 2015

PERSIMUNE
CENTRE OF EXCELLENCE FOR PERSONALISED MEDICINE OF INFECTIOUS COMPLICATIONS IN IMMUNE DEFICIENCY

REGION H Rigshospitalet Danmarks Grundforskningsfond Danish National Research Foundation

Research to benefit future patients

We would like to ask your permission for us to store biological material from you in the PERSIMUNE biobank for the purposes of future research into immune defences against infections.

The PERSIMUNE biobank is used to store various biological material from patients who could be at risk of infection because their immune systems may not be working properly. The material from the biobank will later be used in research projects aimed at gaining a better understanding of the medical factors behind the risk of developing an infection.

The precise focus of these research projects has not yet been defined. The biological material will generally undergo laboratory analyses to examine how the immune system works, as well as the metabolism and any ongoing infection. These analyses may reveal trace elements. There may also be analyses of the genetic information contained in the biological material, in order to understand the relevance of heredity to the functioning of a person's immune system and the risk of picking up an infection. The analyses will focus both on the patient's own samples and on the micro-organisms that may be present in the material.

Data from these new analyses will be linked to information in your patient record to enable the best possible interpretation of the results. The biological material you donate to the PERSIMUNE biobank are therefore very important to the work of the researchers to develop new diagnoses and treatments to benefit future patients. Laboratory analyses and data processing of the results will be performed at Copenhagen University Hospital or by our project partners in public institutions in EU countries.

The blood samples for the PERSIMUNE biobank will be taken at the same time as other blood samples obtained as part of your treatment, so will not involve any extra needle pricks. Blood will be taken in three sampling tubes (2 x 9 ml and 1 x 3 ml), and this modest quantity has no effect on health.

The blood sample – and possible saliva and stool samples – will be taken when you give your consent, after 3-6 months and then once a year for as long as you are being monitored at Copenhagen University Hospital. The sampling schedule may be changed if you receive treatment that affects your immune system or you show symptoms of acute diminished resistance to infections.

We will record and store the samples with the approval of the Danish Data Protection Agency. We treat personal information with complete confidentiality. Before we use samples from the biobank for research projects, each project has to be approved by the Committee on Health Research Ethics and the Data Protection Agency.

Your participation is voluntary, and your decision will not affect your treatment now or in the future in any way. If you choose to take part and later change your mind, you can withdraw your consent at any time with immediate effect, without having to give any reasons.

If you later change your mind, please ensure that your decision is recorded in the Use of Tissue Register. You can do this by completing the form "Your tissue, your choice", and sending it to the Use of Tissue Register at the Danish Health and Medicines Authority. If you need help with this, you can contact the staff at the clinic or the PERSIMUNE centre.

Thank you for taking the time to read this information and thinking about the biobank.

Please let us know whether you agree to us storing samples in the PERSIMUNE biobank by completing and signing the attached consent to the disclosure of health information and the retention of biological material.

Best regards,

The staff at PERSIMUNE

Information about PERSIMUNE can be requested from CHIP, Department of Infectious Diseases and Rheumatology, Section 2100, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen Ø. Tel.: +45 35455757 (from 09:00 to 15:00). E-mail: persimune.rigshospitalet@regionh.dk 24 November 2015

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