Inflammation and acute coronary syndromes (ACS) – a clinical research network funded by the Swiss National Science Foundation

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Summary

In February 2009, the Universities of Bern, Geneva, Lausanne and Zurich joined forces for the project *"Inflammation and acute coronary syndromes (ACS) – Novel strategies for prevention and clinical management"*. This clinical research program underwent peer review and was accepted as part of the Special Program University Medicine (SPUM) funded by the Swiss National Science Foundation for three years (2009–2011). The goals of this research program will be pursued within five cooperative subprojects: (1.) PREVENTION/ELIPS will focus on prevention after ACS by improving patient education and counseling health care providers, (2.) BIOMARKERS will discover novel genomic biomarkers of ACS, (3.) PROGNOSIS will evaluate novel diagnostic and prognostic biomarkers in a large cohort, (4.) IMAGING will visualise the vulnerable plaque and total plaque burden using optical coherence tomography (OCT) and intravascular ultrasound (IVUS), and (5.) REPAIR will characterise the role of inflammation for progenitor/stem cell-mediated repair after ACS. We anticipate that fulfilling the aims within these subprojects will provide novel strategies for prevention and clinical management of ACS. "SPUM-ACS" is listed on www.clinicaltrials.gov, NCT01000701 and present on the internet www.spum-acs.ch.

Background

Acute coronary syndromes (ACS) are the most frequent cause leading to myocardial infarction, heart failure, and death. The underlying problem is plaque rupture or erosion, with partial or complete occlusion of a major epicardial coronary artery. Activation of inflammatory pathways may trigger these events. Although progress has been made in recent years, the rate of ACS-related complications remains high owing to incomplete implementation of prevention, insufficient understanding of triggers of the disease, and delayed diagnosis only once myocardial necrosis has occurred. Importantly, inflammatory mechanisms are not yet incorporated into the clinical management. Multidimensional interventions, patient education, novel and early diagnostic markers and implementation of anti-inflammatory strategies may further improve the outcome of ACS patients.

Research aims

Five subprojects (SP) comprise of the following research aims that address these issues (fig. 1):

Aim 1 PREVENTION – improve patient education after ACS

PF. Keller, F. Mach, D. Carballo, Geneva; N. Rodondi, R. Auer, Lausanne:

This subproject aims to prevent recurrent ACS and its complications by increasing awareness and adherence of patients to lifestyle changes and their medications through patient education, and to increase prescription rates of evidence-based medications and counseling practice of health care providers. This will be implemented by a MULTI-DIMENSIONAL PREVENTION

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PROGRAM AFTER ACUTE CORONARY SYNDROME (**ELIPS**) (http://elips.hug-ge.ch/eng/index_eng2.htm).

Aim 2 BIOMARKERS – identify novel ACS biomarkers

C.M. Matter, R. Klingenberg, Zurich:
This subproject will identify novel soluble and cellular biomarkers involved in coronary plaque rupture, using gene expression analyses of systemic and local coronary blood samples and coronary thrombi. Moreover, temporal changes in genomic/soluble biomarkers will be correlated with clinical outcomes, progression of total plaque burden and neointimal thickness post PCI assessed by intravascular ultrasound (IVUS)/ optical coherence tomography (OCT) imaging in STEMI patients.

Aim 3 PROGNOSIS – test candidate markers suitable for ACS prognosis

W. Maier, L. Altwegg, Zurich:
Candidate inflammatory biomarkers, such as MRP 8/14, will be evaluated in a large ACS cohort followed for twelve months to examine their prognostic impact and value for earlier diagnosis compared with routine cardiac biomarkers.

Aim 4 IMAGING – assess the prevalence and evolution of vulnerable plaques

L. Räber, P. Jüni, S. Windecker, Bern:
This subproject will utilise high-resolution imaging consisting of OCT and virtual histology intravascular ultrasound (IVUS-VH) to visualise time-dependent changes of culprit and non-culprit lesions, and to assess vessel remodeling in response to coronary artery stents implanted into ruptured plaques. The imaging study is supplemented by a large scale, multicenter clinical trial comparing a new generation drug-eluting stent with abluminal biodegradable polymer with a bare metal stent (COMFORTABLE-AMI).

Aim 5 REPAIR – investigate the role of progenitor cells after ACS

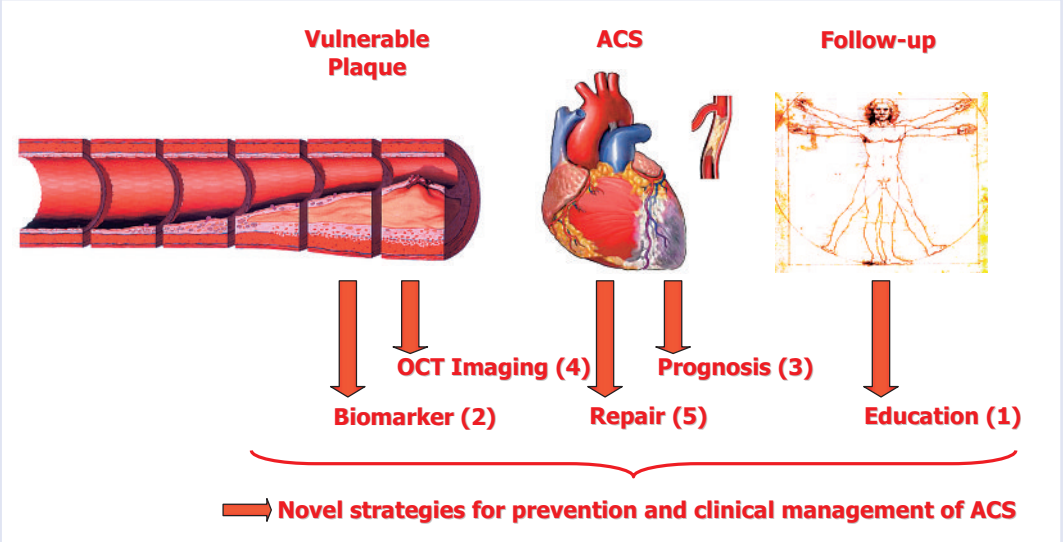
U. Landmesser, C. Templin, Zurich:
These researchers will identify the relationship between inflammatory pathways and stem/progenitor cell function in patients with ACS *ex vivo* and *in vivo*. Furthermore, the effects of stem/progenitor cell-mediated cardiac repair will be analysed.

Outcome measures

Primary outcome measures are Major Adverse Cardiovascular Events (MACE) in the overall population defined as composite of cardiac death, target vessel-related myocardial infarction or ischemia-driven target lesion revascularisation as well as stroke and documented unstable angina requiring rehospitalisation (SP1).

Secondary outcome measures for SP2/SP3/SP4 are changes in biomarkers over time (12 months) and correlation with plaque burden and neointimal thickness assessed by IVUS-VH/OCT imaging in the STEMI patient subgroup (13 months).

Figure 1
Scheme of the research aims of the Swiss research network.
Five major research areas (subproject #) are investigated in a joint effort designed to improve diagnosis, prognosis, therapy, and prevention of patients with ACS in Switzerland.

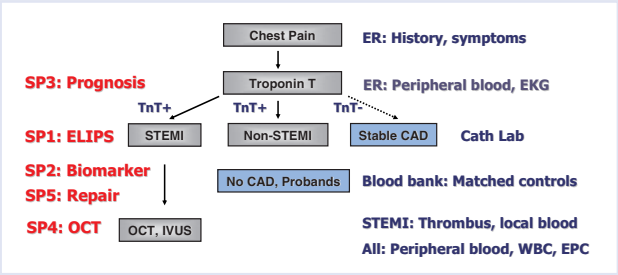


Experimental Protocols

We will include a total of 2400 patients at all four Swiss University Hospitals (fig. 2). Patients with chest pain will be recruited in the emergency rooms or catheterization laboratories for the SPs 1 (PREVENTION), 2 (BIOMARKERS) and 3 (PROGNOSIS). In this context, we will test the prognostic impact of biomarkers using peripheral blood samples and the effects of better education of patients and counseling of caregivers using questionnaires (fig. 3). The SPs 2 (BIOMARKERS), 3 (PROGNOSIS), 4 (OCT IMAGING) and 5 (REPAIR) will include patients with STEMI, non-STEMI and stable coronary artery disease in the catheterisation laboratories. In STEMI patients, we will investigate vulnerable plaques and total plaque burden via imaging (OCT and IVUS-VH), coronary thrombus aspiration and blood samples (local and systemic). Controls will consist of matched patients with stable CAD and matched individuals recruited from the local blood bank (blood donors).

As part of this nationwide study, patients will be followed 30 days after inclusion by a telephone interview and 1 year thereafter in the outpatient clinic. Prognosis will be determined within this period by assessing MACE. Medical care of patients will be continued by the practicing physicians. During the one year study period, adherence to the study medications is crucial. We ask the treating physicians to inform the corresponding study center about events that may affect study participation or changes in cardiovascular medication.

Figure 2
Organisation of the consortium.
We plan to include 2400 patients from the Emergency Rooms of all 4 University Hospitals for the subprojects 1 (Prevention, ELIPS) and 3 (Markers of Prognosis) with clinical checks and peripheral blood samples. Subprojects 2 (Novel Biomarkers), 4 (OCT Imaging) and 5 (Repair – progenitor cells) will recruit patients in the catheterisation laboratory for analyses of plaques via imaging, thrombus aspiration, and local blood samples focusing on white blood cells (WBC) and endothelial progenitor cells (EPC).



Interdisciplinary and translational aspects of the subprojects

Our consortium investigates a broad spectrum of novel diagnostic, prognostic, and preventive aspects of ACS in a collaborative effort. For this purpose, it combines experts with backgrounds in various fields of cardiovascular disease (fig. 4): Coronary interventions, epi-

Figure 3
Time course of analyses.
Patients with STEMI and non-STEMI will be recruited in the emergency rooms (ER) and catheterisation laboratories (Cath Lab) at 4 University Hospitals: A clinical exam, EKG and peripheral blood samples will be obtained. In patients with STEMI, a coronary blood sample will be obtained and the thrombus aspirate will be analysed; in selected patients of this group, a substudy with plaque imaging using high-speed OCT and IVUS-VH will be performed. The status of the patient will be checked again by a telephone interview 30 days after inclusion. Patients will be seen again for the study on the basis of an outpatient visit or with a coronary angiography for the OCT substudy in STEMI patients.

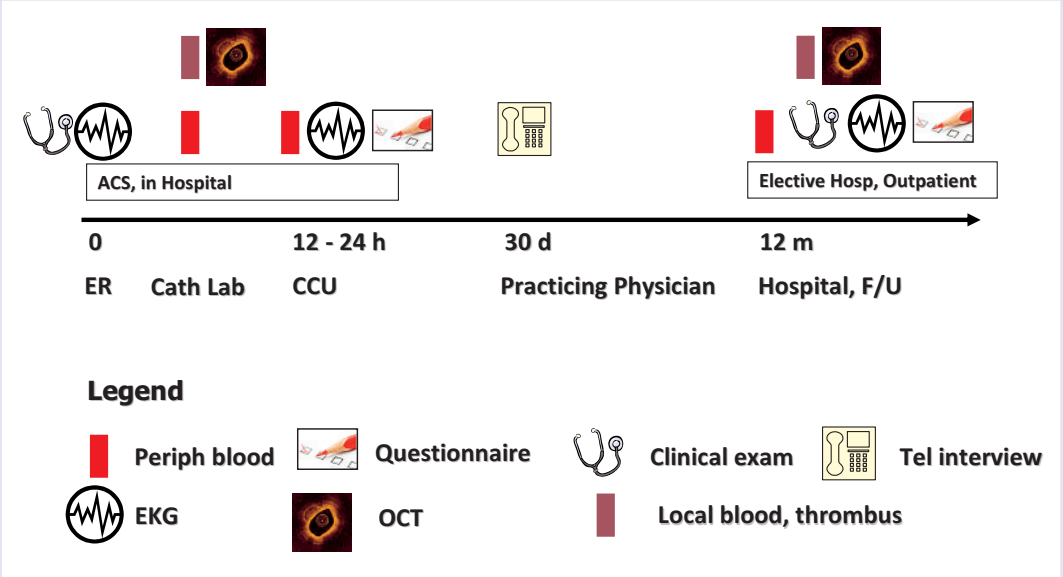
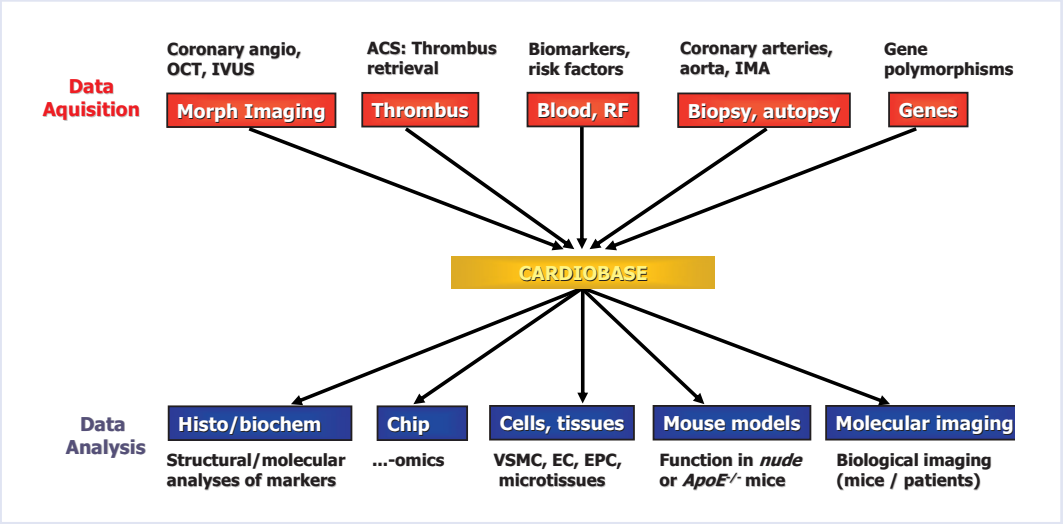


Figure 4
Central data collection.
This project links detailed information and samples of patients with ACS (top, Data Acquisition [red]) to standardised readouts (bottom, Data Analysis [blue]) collected in a web-based Cardiovascular Research Data Bank (CARDIOBASE® [yellow]). This data bank will contain clinical and laboratory patient data, risk factors, genes, cells, biomarkers, and imaging.



demiology, social and preventive medicine, statistics, high-throughput analyses, as well as basic research with foci on pathways of inflammation, stem/progenitor cell biology, and molecular plaque imaging. Moreover, we appreciate support from additional collaborators at all centers that provide complementary expertise in clinical chemistry, rheumatology, genetics, pathology, imaging, regenerative medicine, data management and statistics. These interdisciplinary aspects of our collaborative project provide a unique opportunity to create added value to our research proposal. Thus, we anticipate that our consortium will foster synergies between all SPs that will be valuable for extending our projects to Science and/or Industry. The visible outcome of these joint efforts is the creation of an internet-based cardiovascular database (CARDIOBASE®) for multicenter trials under the leadership of Stephan Windecker, Lorenz Räber and Peter Jüni in Bern.

Teaching and organisation of the research network

Teaching of all participants and study nurses is ensured by Peter Jüni and Sven Trelle in Bern (Institute of Social and Preventive Medicine), as well as by Gabriela Senti and Gregor Zünd at the Clinical Trial Center, Zurich.

The management committee of this cooperative project comprises of Stephan Windecker (Bern), François Mach (Geneva), Nicolas Rodondi (Lausanne) with Thomas F. Lüscher (principal investigator), and Christian M. Matter (Co-principal investigator and coordinator) from Zurich as the leading department.

Relevance

In Switzerland, ACS remains the major cause of death and hospitalisation with more than 20 000 citizens dying every year. The societal and economic impact of ACS is substantial. Therefore, improved prevention, diagnosis, and treatment of patients with ACS should reduce health costs, sick leave, invalidity, and ultimately death. The exchange of expertise and data within this collaboration will facilitate the development of novel approaches in the management of ACS and their clinical evaluation in a large cohort recruited at the four participating centers.

Acknowledgements

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