Controlled-Level EVERolimus in Acute Coronary Syndrome (CLEVER-ACS) - A phase II, randomized, double-blind, multi-center, placebo-controlled trial

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Trial Design

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Short title: CLEVER-ACS trial design

Roland Klingenberg[1,2*], Barbara E. Stähli[1*] , Dik Heg[3] , Andrea Denegri[1], Robert Manka[1], Ioannis Kapos[1], Arnold von Eckardstein[4], David Carballo[5], Christian W. Hamm[2], Julia Vietheer[2], Andreas Rolf[2], Ulf Landmesser[1,6], François Mach[5], Tiziano Moccetti[7], Christian Jung[8], Malte Kelm[8] , Thomas Münzel[9], Giovanni Pedrazzini[7], Lorenz Räber[10], Stephan Windecker[10], Christian M. Matter[1,11], Frank Ruschitzka[1§], Thomas F. Lüscher[10,12§]

[1] Department of Cardiology, University Heart Center, University Hospital Zurich, Switzerland

[2] Department of Cardiology, Kerckhoff Heart and Thorax Center, and Campus of the Justus Liebig University of Giessen, Germany; DZHK (German Center for Cardiovascular Research), partner site Rhine-Main, Bad Nauheim, Germany

[3] Clinical Trial Unit, Social and Preventive Medicine, University of Bern, Switzerland

[4] Department of Clinical Chemistry, University Hospital Zurich, Switzerland

[5] Department of Cardiology, Hopitaux Universitaires de Geneve, Geneva, Switzerland

[6] Department of Cardiology, Charité – University Medicine, Campus Benjamin-Franklin, Berlin, Germany

[7] Department of Cardiology, Cardiocentro Ticino, Lugano, Switzerland

[8] Division of Cardiology, Pulmonary Diseases and Vascular Medicine, University Hospital of Duesseldorf, Duesseldorf, Germany

[9] Department of Cardiology, University Hospital Mainz, Mainz, Germany

[10] Department of Cardiology, Bern University Hospital, Inselspital, Bern, Switzerland

[11] Center for Molecular Cardiology, University of Zurich, Schlieren, Switzerland

[12] Imperial College, National Heart and Lung Institute and Royal Brompton and Harefield Hospitals, Heart Division London, U.K.

* contributed equally as first authors

§ contributed equally as last authors

Corresponding Author:

Thomas F. Lüscher, MD, FRCP, FESC, FACC,
Professor and Chairman
Center for Molecular Cardiology
University of Zurich
CH-8952 Schlieren, Switzerland,
Email: cardio@tomluescher.ch

Word count without references or tables: 5419 **Abstract:** 220

Highlights

- Inflammation impacts infarct size and healing
- Mammalian target of rapamycin inhibitor everolimus targets several inflammatory pathways involved in the acute infarct setting
- Cardiac MRI is a recommended method to assess infarct size
- We here describe the design of CLEVER-ACS – an investigator-initiated clinical trial – to evaluate whether a short course of everolimus compared with placebo can reduce infarct size

ABSTRACT

Background: Activation of inflammatory pathways during acute myocardial infarction contributes to infarct size and left ventricular (LV) remodeling. The present prospective randomized clinical trial was designed to test the efficacy and safety of broad-spectrum anti-inflammatory therapy with a mammalian target of rapamycin (mTOR) inhibitor to reduce infarct size.

Design: Controlled-Level EVERolimus in Acute Coronary Syndrome (CLEVER-ACS, clinicaltrials.gov NCT01529554) is a phase II randomized, double-blind, multi-center, placebo-controlled trial on the effects of a 5-day course of oral everolimus on infarct size, LV remodeling, and inflammation in patients with acute ST-elevation myocardial infarction (STEMI). Within 5 days of successful primary percutaneous coronary intervention (pPCI), patients are randomly assigned to everolimus (first 3 days: 7.5 mg qd; days 4 and 5: 5.0 mg qd) or placebo, respectively. The primary efficacy outcome is the change from baseline (defined as 12 h to 5 days after pPCI) to 30-day follow-up in myocardial infarct size as measured by cardiac magnetic resonance imaging (CMRI). Secondary endpoints comprise corresponding changes in cardiac and inflammatory biomarkers as well as microvascular obstruction and LV volumes assessed by CMRI. Clinical events, laboratory parameters, and blood cell counts are reported as safety endpoints at 30 days.

Conclusion: The CLEVER-ACS trial tests the hypothesis whether mTOR inhibition using everolimus at the time of an acute STEMI affects LV infarct size following successful pPCI.

Keywords: Acute coronary syndromes – Everolimus – Inflammation - Intervention trial - Biomarkers

Abbreviations:

ACS = Acute coronary syndromes
AE = Adverse events
AMI = Acute myocardial infarction
CAD = Coronary artery disease
CLEVER-ACS = Controlled Level EVERolimus in Acute Coronary Syndromes Trial
CMRI = Cardiac magnetic resonance imaging

HDL-C = High-density-lipoprotein cholesterol
LAD = Left anterior descending coronary artery
LCX = Left circumflex coronary artery
LDL-C = Low-density-lipoprotein cholesterol
LVEF = Left ventricular ejection fraction
MACE = Major adverse cardiovascular events
MVO = Microvascular obstruction
mTOR = Mammalian target of rapamycin
NT-proBNP = N-terminal pro brain natriuretic peptide
PCI = Percutaneous coronary intervention
pPCI = Primary percutaneous coronary intervention
RCA = Right coronary artery
SAE = Serious adverse event
STEMI = ST-Segment Elevation Myocardial Infarction
hs-TnT = High-sensitivity Troponin T

INTRODUCTION

Inflammation in Atherothrombosis and Left Ventricular Remodeling

Inflammation is a characteristic feature throughout the distinct stages of atherosclerotic lesion formation preceding acute myocardial infarction (AMI), at the time of plaque rupture or erosion and during the post-infarction repair phase, involving components of both innate and adaptive immunity [1-3]. As such, acute inflammation acts as a trigger initiating thrombus formation and coronary artery occlusion and infarct size. The cardiac immune cellular response to AMI comprises an initial, pro-inflammatory phase followed by a healing phase that impacts infarct size. Of note, infarct size, the primary endpoint in this study, constitutes a critical determinant of outcomes after AMI [4]. A persistent and severe pro-inflammatory reaction within the myocardium in patients with AMI may lead to adverse left ventricular (LV) remodeling and subsequent heart failure [1, 3].

Microvascular obstruction (MVO), characterized by the so-called “no-reflow” phenomenon after restoration of patency of the epicardial artery following primary percutaneous coronary intervention (pPCI), is a typical sequela of ischemia-reperfusion injury [5]. Among immune cells involved in orchestrating this complex and dynamic inflammatory post-infarct response, neutrophils play a pivotal role in the initial stages by migrating into ischemic myocardium and contributing to MVO [1, 3, 5].

Recent trials using inhibitors of innate immunity, such as the interleukin-1ß antibody canakinumab in CANTOS [6] and colchicine in COLCOT [7], in patients with increased baseline inflammation demonstrated a reduction of major adverse cardiovascular events (MACE) in patients with recent AMI. These findings support the concept that targeting excessive inflammation in the acute setting of AMI provides cardioprotection. Conversely, oral administration of high-dose colchicine in

patients with ST-segment elevation myocardial infarction (STEMI) at the time of reperfusion and for 5 days did not reduce infarct size assessed by cardiac magnetic resonance imaging [8], warranting further studies with respect to timing, pharmacokinetics, and dose response of colchicine and other anti-inflammatory agents.

Targeting multiple cell types involved in post-infarct inflammation appears to be a promising therapeutic approach to modulating inflammatory responses following AMI [3]. The interplay between different immune cells and inflammatory pathways is amenable to various drugs such as everolimus, shown to modulate cell proliferation, cell migration, and osteogenic/fibrous turnover of extracellular matrix (**Figure 1 A** and **B**).

mTOR Inhibitor Everolimus to Attenuate Inflammation in Myocardial Infarction

Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), is an immunosuppressive drug widely used both systemically in transplantation medicine and locally on drug-eluting stents. Everolimus binds to the intracellular FK506-binding protein, thereby inhibiting intracellular signal transduction initiated by interleukin-2 and cell cycle-progression at the G1/S transition stage by inhibition of the serine/threonine protein kinase mTOR. Through this mechanism, everolimus modulates both innate and adaptive immunity as well as cell proliferation. In addition to its influence on antigen-presenting and T cells, mTOR inhibition exerts a broad spectrum of inhibitory effects on immune effector cells including neutrophils, monocytes, B cells, mast cells, and natural killer cells, while promoting tolerance-inducing regulatory T cells [9-12]. These inflammatory cells are involved in the natural history of atherosclerosis and in particular, in inflammation-induced remodeling

following AMI [1, 2]. Consistently, in a rat model of myocardial infarction, inhibition of mTOR reduced infarct size and improved LV remodeling [13].

Based on these findings, the Controlled Level EVERolimus in Acute Coronary Syndromes (CLEVER-ACS) trial was designed to investigate the efficacy and safety of everolimus in reducing infarct size following successful pPCI in STEMI (NCT01529554).

METHODS

Study Population

Patients with acute STEMI undergoing pPCI for proximal occlusion of a coronary artery were recruited at tertiary centers in Switzerland and Germany (four in each country) after providing written informed consent. Inclusion and exclusion criteria are listed in **Table I**. The four centers in Switzerland comprised University Hospital Geneva, University Hospital Berne, CardioCentro Lugano, and University Hospital Zurich and recruitment of additional centers during the course of the study in Germany to enhance recruitment including Kerckhoff Heart and Thorax Center Bad Nauheim, University Hospital Mainz, and Charité – University Medicine Berlin, Campus Benjamin Franklin and University Hospital Duesseldorf. Exclusive use of drug-eluting stents and high-dose statins along with standard guideline-recommended medications after STEMI was advised to all study investigators. The first patient was included on 11/26/2014 and enrolment was completed on 10/29/2021. The study was approved by the local ethics committees at all recruiting centers.

Study Design

This is a randomized, multi-center, placebo-controlled, double-blind study that enrolled a total of 150 STEMI patients with a follow-up of 30 days (30±3 days after randomization). Screening, baseline assessment, and randomization was performed after coronary angiography as detailed in **Figure 2** and **Table II**. Treatment consists of oral everolimus (first 3 days 7.5 mg qd, days 4 and 5: 5.0 mg qd) or matching placebo after the index STEMI. According to the local ethics committees, written informed consent had to obtained after coronary angiography, outside of the emergency situation. Thus, everolimus, which is not available in a soluble format, was scheduled to be administered orally within the next 5 days after reperfusion. Unlike in the acute post-MI phase, edema appears to be more stable in the time window between days 3 and 7 post-MI, providing the rationale for assessing infarct size (primary endpoint) within this timeframe complemented by an additional CMRI at 30 days when edema has abated [14]. The primary endpoint is the change from baseline (defined as 12 h to 5 days after pPCI) to the 30-day follow-up in infarct size measured by standard 2D protocols on 1.5/3.0 Tesla cardiac magnetic resonance imaging (CMRI) [15]. The secondary endpoint is MVO assessed as the change from baseline (12 h to 5 days after pPCI) to 30-day follow-up measured by CMRI. Tertiary endpoints comprise the change in LV volumes from baseline (12 h – 5 days after PCI) to 30 days follow-up measured by CMRI.

Core Lab measurements will be performed to reflect potential changes in biomarkers levels from baseline to the 30-day follow-up, including a time course with area under the curve (AUC) analysis. This may provide cues to pathophysiological changes in the heart and help identify potential surrogate markers. Cardiac and inflammatory biomarkers comprise hs-TnT, NT-proBNP, hs-CRP, IL-1ß, IL-6, IL-18,

OPG, sRANKL, OPN, galectin 3, ST2 and CCN1 [16]. Routine blood samples are collected at all centers after coronary catheterization (12-24 hours later), upon hospital discharge, and at 30 days. Core Lab blood is drawn for a dedicated biobank with sampling and analyses in a uniform manner at all centers in Switzerland. For this purpose, a total of 30-40 ml blood at each timepoint (plus 8 ml of urine at 12-24h) are drawn. Samples are processed immediately (centrifugation, aliquoting, and freezing at -80°C) at the local clinical chemistry laboratories. Four vials of 1 ml each of EDTA and heparinized plasma and serum, respectively, are aliquoted. Urine is also frozen at -80°C. Additional biomarker analysis will be performed centrally at the Department of Clinical Chemistry, University Hospital Zurich, Zurich, Switzerland (Core Lab).

Cardiac magnetic resonance imaging

CMRI protocols include functional and morphological sequences for volumetric measurements, T1- and T2-weighted sequences for tissue characterization, and late gadolinium enhancement (LGE) for scar and fibrosis visualization. T1-weighted (T1W) LGE is considered the best in vivo surrogate for infarct size and is expressed both in absolute (grams) and relative (percentage of LV mass) terms. T1W LGE is the recommended methodology for MVO imaging (areas of hypoenhancement within LGE, in grams or as % of LV) [14].

Functional imaging of the LV will be performed using standard ECG-triggered, steady state-free precession acquisitions (in-plane resolution: typically 1.5 mm x 1.5 mm; slice thickness**:** 8 mm) during repetitive breath holds in contiguous short-axis orientation, covering the entire LV and 3 long-axis orientations (4-, 3-, and 2-chamber orientation). A bolus of conventional extracellular gadolinium-chelates contrast medium at a dose of 0.20 mmol/kg of body weight is administered to assess the myocardial scar, using an inversion recovery fast-gradient echo imaging sequence

(in-plane resolution: typically 1.5 mm x 1.5 mm; slice thickness**:** 8 mm). Scar imaging is performed 15 min after administration of contrast medium in the same slice position as the functional data are acquired.

CMRI data analysis will be performed in a core laboratory (University Hospital Zurich/CH, Switzerland) using dedicated cardiac analysis software (GTVolume, Gyrotools Ltd, Zurich/CH). LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes, LV ejection fraction (LVEF), and LV mass will be assessed. The extent of MVO, delineated as dark areas in the core of the necrotic zone in the late gadolinium images, will be quantified by contouring the dark core areas manually. Scar mass and tissue with MVO will be expressed in grams and as a percentage of LV mass and of scar mass, respectively.

Changes over time (baseline to 30 days) of volumetric, functional, and scar parameters will be compared between the groups to assess the influence of treatment on global systolic function and scar mass.

Safety Measures

Safety endpoints comprise any clinical events within 30 days. These events are further documented by extensive laboratory tests at 30 days, including red blood cell count, hematocrit, hemoglobin, WBC, lymphocyte count and subtypes, platelet count, APTT, PT, NT-proBNP, hs-TnT, BUN, creatinine, uric acid, phosphorus, sodium, chloride, potassium, calcium, total protein, albumin, AST (SGOT), ALT (SGPT), total bilirubin, alkaline phosphatase, gamma-GT, lactate dehydrogenase (LDH), creatine phosphokinase, total cholesterol, low-density-lipoprotein cholesterol (LDL-C), high-density-lipoprotein cholesterol (HDL-C), and triglycerides.

These data are complemented by sub-analyses assessing everolimus-induced immunosuppression and host defense such as analyses of inflammatory cell subsets

in the peripheral blood (such as $CD4^+$ T helper cell subsets and monocyte subsets) in individual centers. In addition, structural and functional data are available at baseline (Visit 1) and 30 days (Visit 3) by means of CMRI performed as part of the trial. Serial CMRI data will allow additional detection of potential subclinical adverse effects of everolimus on myocardial structure or function (i.e. LV thrombus). Everolimus levels are monitored and AUCs will be determined to enable correlation analyses with endpoints.

Randomization Procedure

Patient allocation is based on computer-generated, stratified randomization lists. Treatment assignment includes selection of a sequentially numbered drug pack based on the randomization number. The access to the codes will be controlled and documented locally and centrally by the Institute of Social and Preventive Medicine, University of Bern, and the Institute for Hospital Pharmacy, University Hospital Bern, both Bern, Switzerland. This implies monitoring of under- or over-recruitment of single centers that would lead to an adaptation of recruitment at individual centers. Patients who fulfill all inclusion criteria and none of the exclusion criteria and who signed the informed consent form are eligible for the trial and are included. After patient registration in the web-based data entry system and confirmation of all inclusion and exclusion criteria, patients are randomized based on the sequential drug pack number, thus ensuring concealment of allocation. Patients are randomized in a 1:1 ratio to one of the two intervention groups. The allocation sequence is generated by an independent statistician at the Clinical Trial Unit, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland, who is not involved in the final analysis of the trial. It is based on computer-generated random numbers in randomly varying blocks of 2, 4, and 6 using the statistical software package Stata

(StataCorp LP, College Station, TX, USA). Randomization is stratified by trial center. Blinding of investigators and patients will be maintained throughout the trial period until the last patient has completed the trial.

An independent Clinical Events Committee (CEC) has been established to assess any adverse events and an independent Data Safety Monitoring Board (DSMB) to ascertain and adjudicate serious adverse events of patients enrolled in the trial.

Statistics

The statistical power analysis was based on the hypothesis that the primary efficacy outcome, the change in infarct size (scar mass at 30 days minus scar mass at baseline), is reduced by everolimus. In an animal model of myocardial infarction, a decrease in infarct size was observed upon mTOR inhibition as compared to placebo (34.7% larger reduction in the treated as compared to the control group) [13]. In humans, based on Goetti et al. [15] and Mather et al. [17], we estimated a 30-day follow-up infarct scar mass of 23 g with a standard deviation (SD) of 14 g for the control group. We assumed an intra-patient correlation between baseline and 30-day follow-up infarct scar mass of 0.55, representing a safe assumption and considering the high reproducibility of the 2D CMRI procedure and the baseline variation in infarct scar mass among patients [15]. Using a two-sided, two-sample repeated measures test on the change in infarct scar mass with 14 g SD in both arms, with an alpha level of 5%, and a sample size of n=75 per treatment arm, yields 90% power to detect a difference in the change in infarct scar mass of half a standard deviation (7 g). This appears a safe group size to determine the efficacy of the treatment arm.

Blinding of investigators and patients will be maintained throughout the trial period until the last patient has completed the trial.

SARS-CoV-2 Pandemic

With the onset of the SARS-CoV-2 pandemic, prior testing for the presence of the virus RNA (RT-PCR), along with questions regarding symptoms compatible with COVID-19 or contact with a COVID-19 positive person, is mandatory for all patients. Questions include whether the patient has experienced fever in the week before, headache, muscle pain, cough, loss of taste or smell, or has been in contact with COVID-19 positive persons. Patients can be enrolled in the trial only in the case of a negative PCR test and negative answers to the above-mentioned questions regarding COVID-19. These measures are taken to exclude patients with or at risk of COVID-19 infection and to prevent that they are randomized into the everolimus arm. Patients will be informed about the COVID-19 pandemic and asked to report immediately to the local study team during the 30-day follow-up in case of symptoms and/or positive swab tests. Great care will be taken to inform patients about their risk status, to respect distance rules, to wear a mask in public, and to avoid contact with COVID-19-positive persons. Patients that develop COVID-19 will be treated according to local policy based on the current recommendations (in Germany, the Robert Koch Institute https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Corona-virus/nCoV.html). Cases of COVID-19 will be adjudicated as adverse events (AE) or severe adverse events (SAE).

DISCUSSION

Current concepts of post-infarct LV remodeling assume that innate immune pathways play a major role, complemented by adaptive immune reactions [1, 3]. In support of this

concept, the amount of circulating “classical” monocytes ($CD14^{+}CD16^{-}$) after AMI is inversely related to the amount of myocardium at risk and recovery of the left ventricular ejection fraction at 6 months as assessed by CMRI [18]. As the deleterious effects of acute inflammation occur in the early phase after an AMI (i.e. week 1), any broad-spectrum anti-inflammatory approaches should focus on this early stage of AMI, with a rapid tapering regimen to avoid potential interference with putative protective inflammation in the ensuing healing phase. As everolimus is not available as an intravenous formulation, an oral dosing regimen is administered in CLEVER-ACS.

In patients with chronic coronary syndromes undergoing PCI with bare-metal stent implantation, oral sirolimus (rapamycin) was shown to prevent recurrence of in-stent restenosis at both 6 and 9 months, respectively (OSIRIS trial) [19], and to prevent in-stent restenosis in *de novo* stented coronary lesions (ORAR II) [20]. Long-term follow-up of the OSIRIS trial documented a similar incidence of the composite of death, myocardial infarction, and target vessel revascularization at 4 years. In both trials, administration of sirolimus was safe with low drop-out rates of only 2.7% and 4.0%, respectively. Clinically relevant side effects ranged from allergic reactions, infections, and diarrhea (4%) to mouth ulcerations (16%). There was a trend towards an increased incidence of newly diagnosed malignancies in the high-dose, but not in the normal-dose rapamycin-treated group [21]. Direct comparison of oral rapamycin in conjunction with bare metal stents versus drug-eluting stents showed similar efficacy and safety in 200 randomized patients during a mean follow-up of 18 months (ORAR III) [22]. Finally, everolimus has increasingly been evaluated in the non-transplant setting. In particular, everolimus administered for >18 months reduced the cystic kidney volumes in patients with autosomal dominant polycystic kidney disease [23, 24].

Hence, with the short-term administration of everolimus using standard dosages as used in the OSIRIS and ORAR trials, few side effects are to be expected in CLEVER-ACS [23, 24]. Based on the efficacy and safety profile of patients with chronic coronary syndromes in the OSIRIS trial [19], using a dose tapering scheme starting with 6 mg at day 2, followed by 2 mg from day 3 to 10 in the “usual dose” sirolimus group, a similar dose-tapering regimen for everolimus: (first 3 days 7.5 mg qd, days 4 and 5: 5.0 mg qd) or placebo was chosen for CLEVER-ACS.

Randomized controlled trials in the transplantation setting have compared everolimus and cyclosporine regimens, including two target everolimus blood trough level ranges of 3-8 ng/mL and 6-12 ng/mL. With superior safety in the lower dosage range without significant loss of efficacy, the target therapeutic range for everolimus blood trough level is defined as 3-8 ng/mL in combination with reduced exposure of cyclosporine as recommended. Therefore, we will assess trough level measurements in CLEVER-ACS at baseline (d0), at 12-24 hours, at hospital discharge, and at 30 days follow-up, and will correlate them with efficacy and safety after completion and unblinding of the trial.

Conduct of the trial during the SARS-CoV-2 pandemic mandated special care to avoid inclusion of vulnerable patients into the trial and has hampered the recruitment rate.

Perspective

The results of CLEVER-ACS will provide evidence whether modulating inflammation by oral administration of everolimus early after pPCI in patients with STEMI translates into a reduction in LV infarct size at 30 days and, if positive, will warrant a large outcome trial.

DISCLOSURES

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CRediT author statement

Roland Klingenberg: Conceptualization, Methodology, Investigation, Writing – Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition, **Barbara E. Stähli**: Methodology, Investigation, Writing - Review & Editing, Visualization, Supervision, Project administration, **Dik Heg**: Methodology, Software, Formal analysis, Data Curation, **Andrea Denegri**: Investigation, Writing - Review & Editing, **Robert Manka**: Investigation, Methodology, Formal analysis, Writing - Review & Editing, **Ioannis Kapos**: Investigation,

Methodology, Formal analysis, Writing - Review & Editing, **Arnold von Eckardstein**: Investigation, Resources, Writing - Review & Editing,, **David Carballo**: Investigation, Writing - Review & Editing, **Christian Hamm**: Investigation, Writing - Review & Editing, **Julia Vietheer**: Investigation, Methodology, Formal analysis, Writing - Review & Editing, **Andreas Rolf**: Investigation, Methodology, Formal analysis, Writing - Review & Editing, **Ulf Landmesser**: Investigation, Writing - Review & Editing, **François Mach**: Investigation, Writing - Review & Editing,, **Tiziano Moccetti**: Investigation, Writing - Review & Editing, **Christian Jung**: Investigation, Writing - Review & Editing, **Malte Kelm**: Investigation, Writing - Review & Editing, **Thomas Münzel**: Investigation, Writing - Review & Editing, **Giovanni Pedrazzini**: Investigation, Writing - Review & Editing, **Lorenz Räber**: Investigation, Writing - Review & Editing, Stephan Windecker: Investigation, Writing - Review & Editing, **Christian M. Matter**: Investigation, Project administration, Writing - Review & Editing, **Frank Ruschitzka**: Investigation, Writing - Review & Editing, Visualization, Supervision, Project administration, **Thomas F. Lüscher**: Conceptualization, Methodology, Investigation, Writing – Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition.

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TABLES

Table I: Inclusion and exclusion criteria of the CLEVER-ACS trial.

Inclusion Criteria	Exclusion Criteria
Acute STEMI: • Male and female patients 18 to 90 years of age • First myocardial infarction • ST-elevation > 1 mm in > 2 leads OR • New left bundle-branch block (LBBB) OR • Posterior MI with ST-depression > 1 mm in > 2 leads • Chest pain duration of > 10 min • PCI with drug-eluting stent within 24 h of chest pain onset in the culprit lesion of the coronary artery • Occlusion of one coronary artery in the proximal third of either LAD, LCX, or RCA, mid segment of RCA or mid segment of a LAD, i.e. when the latter reaches the apex. • Signed informed consent form	• Contraindications(e.g. known hypersensitivity or allergy) to mTOR inhibitors), or placebo • Individuals with contraindication(s) to CMRI • Contraindication to CMRI contrast agent containing gadolinium • Concomitant use of immunosuppressants up to 4 weeks prior to index STEMI (i.e. steroids, methotrexate, cyclosporine, TNF-α antagonists or rituximab). • Participation in another trial with an investigational product within 30 days preceding the present trial covering 5 terminal half-lives (30 days or 5 terminal half-lives, whichever is longer) • Previous enrolment in this trial • Mechanical complication of AMI • Scheduled PCI within 30 days • Multivessel coronary artery disease, likely needing revascularization (PCI or CABG) in another coronary artery within the trial period • Pregnant women or nursing mothers • Women of childbearing potential, not using or not willing to use reliable contraception for the trial duration (e.g. oral, injectable, implantable contraceptives, or intrauterine devices, or any other reliable method) • Men who are not willing to use reliable contraception • Major elective surgery during trial

	• Malignancy (unless cured or remission > 5 years) • Documented chronic infection (HIV, Tbc, empyema) • GFR < 30 ml/min • Known or suspected non-compliance, drug or alcohol abuse • Temporary inability to reason (due to AMI or drug influence) • Inability to follow procedures of the trial (e.g. due to language problems, psychological disorders, dementia, etc.) • Positive PCR for SARS-CoV-2 or at least one positive answer to symptoms/contact COVID-19 questionnaire • Enrolment of a CLEVER-ACS investigator, his/her family members, employees, or other dependent persons • Inability to sign informed consent form

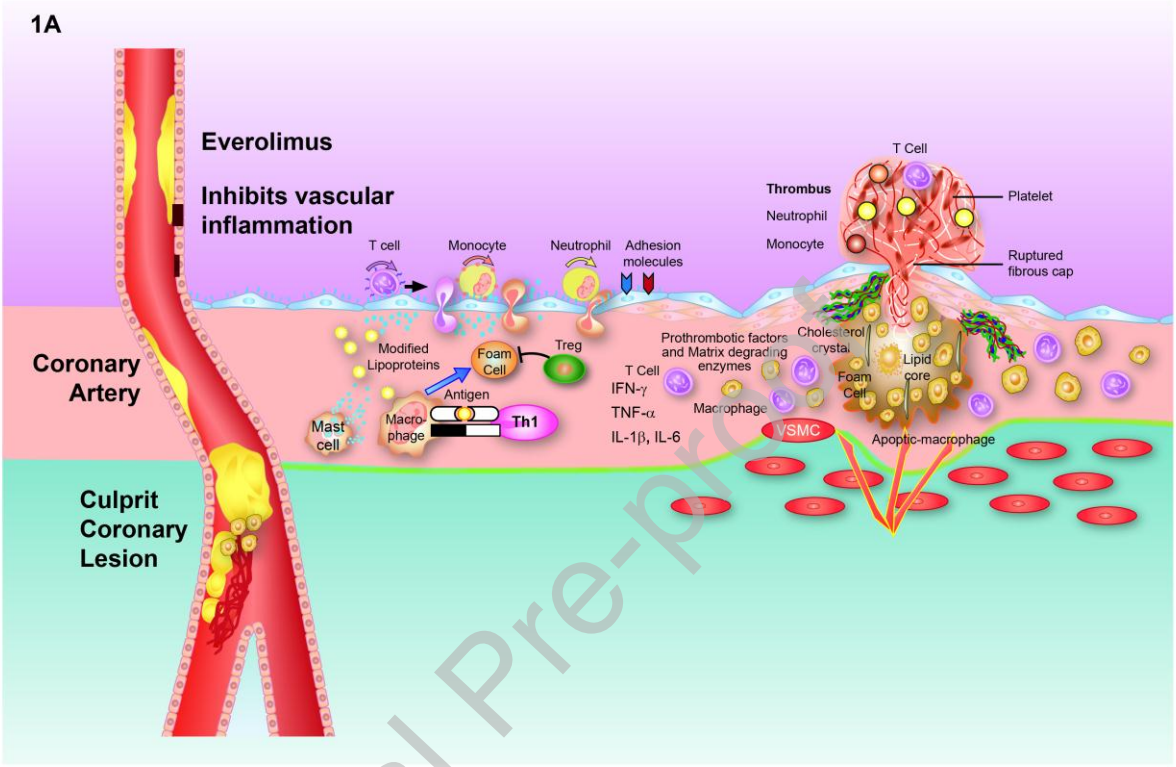
Abbreviations: AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; CMRI: cardiac magnetic resonance imaging; GFR: glomerular filtration rate; LAD: left anterior descending coronary artery; LBBB: left bundle branch block; mTOR: mammalian target of rapamycin; PCI: percutaneous coronary intervention; PCR: polymerase chain reaction; RCA: right coronary artery; RCX: right circumflex coronary artery; STEMI: ST-elevation myocardial infarction; TNF: tissue necrosis factor.

Table II: Outline of the trial design of the CLEVER-ACS trial

	Visit 1 Screening, baseline, and randomization	**Visit 2** Discharge within 5 days	**Visit 3** 30 days (+/- 3 days)
Informed consent: signed	X		
Inclusion/Exclusion criteria	X		
Demographic data	X		
Clinical history	X		
General physical examination and vital signs	X		X
Concomitant medication	X	X	X
Any adverse events	X	X	X
Routine hematology and biochemistry	X	X	X
Pregnancy test (if applicable)	X		X
Core laboratory (centers in Switzerland)	X	X	X
CMRI	X		X
Hand-out of study medication	X		
SARS-CoV-2 PCR test and COVID-19 questionnaire	X		

Abbreviations: CMRI: cardiac magnetic resonance imaging; PCR: polymerase chain reaction

FIGURE LEGENDS



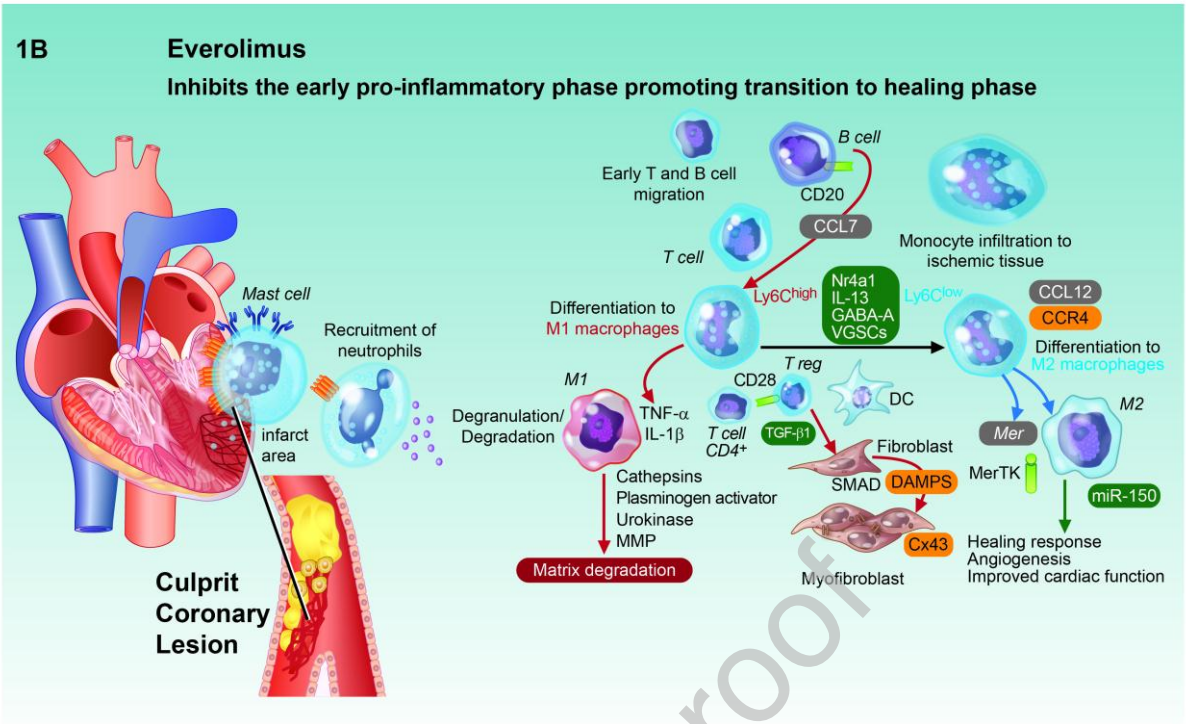


Figure 1: Proposed mechanism of action of the mTOR inhibitor everolimus in response to myocardial injury.

Everolimus inhibits immune effector cells of innate immunity including neutrophils, monocytes, mast cells, and natural killer (NK) cells, along with cells of adaptive immunity (i.e. antigen-presenting (APC), T and B cells), while promoting tolerance-inducing regulatory T cells. These combined effects are anticipated to attenuate the excessive early pro-inflammatory phase and to promote a shift towards the subsequent healing phase. Thus, everolimus exerts a dual effect on the endothelium/coronary vasculature (A) and the myocardium (B) upon reperfusion. (modified from ref. (2))

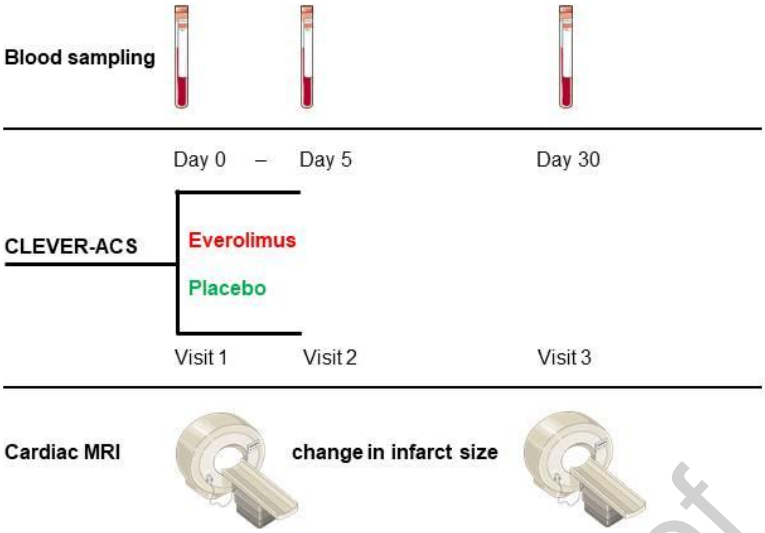


Figure 2: Patient allocation and time schedule.