Journal of Clinical Lipidology (2016) ■, ■–■

Journal of Clinical Lipidology

Original Contribution

# Clusterin/apolipoprotein J is independently associated with survival in patients with chronic heart failure

**Lorenz Koller, MD[1], Bernhard Richter, MD[1], Max-Paul Winter, MD, Patrick Sulzgruber, MD, Christos Potolidis, MD, Florian Liebhart, MD, Deddo Mörtl, MD, Rudolf Berger, MD, Georg Goliasch, MD, PhD, Irene Lang, MD, Johann Wojta, PhD, Martin Hülsmann, MD, Alexander Niessner, MD***

*Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Austria (Drs Koller, Richter, Winter, Sulzgruber, Goliasch, Lang, Wojta, Hülsmann, Niessner); Cardiovascular Center, Oberallgäu–Kempten, Kempten, Germany (Dr Potolidis); Department of Internal Medicine, University Hospital Tulln, Karl Landsteiner University of Health Sciences, Tulln, Austria (Dr Liebhart); Department of Internal Medicine III (Cardiology and Emergency Medicine), Landesklinikum St. Poelten, St. Poelten, Austria (Dr Mörtl); and Department of Internal Medicine I, Cardiology and Nephrology, Hospital of St. John of God, Eisenstadt, Austria (Dr Berger)*

**KEYWORDS:**
Clusterin;
Apolipoprotein J;
Prognosis;
Heart failure;
Biomarker

**BACKGROUND:** Clusterin/apolipoprotein J (CLU) is a ubiquitous expressed glycoprotein with cytoprotective properties capable to prevent myocardial injury in experimental studies. We hypothesized that decreasing levels of CLU might be involved in progression of chronic heart failure (HF) and therefore represent a potential biomarker for prognosis in this vulnerable group of patient.

**OBJECTIVE:** We aimed to determine the prognostic value of plasma CLU in patients with HF.

**METHODS:** Plasma CLU levels were determined in a prospectively recruited cohort comprising 318 patients with chronic HF and validated in a second cohort comprising 346 patients with advanced HF.

**RESULTS:** During a median follow-up time of 3.2 years (interquartile range 2.0–4.9), 119 patients (37.3%) deceased including 83 patients (26.1%), who died from cardiovascular events. CLU was an inverse predictor of mortality with a crude hazard ratio (HR) per increase of 1 standard deviation (1 SD) of 0.75 (95% confidence interval [CI]: 0.62 to 0.9, $P = .002$) and specifically cardiovascular mortality with an HR per 1 SD of 0.67 (95% CI: 0.53–0.84, $P < .001$). CLU remained significantly associated with cardiovascular mortality after comprehensive adjustment for established HF-related risk factors and potential confounders with an adjusted HR per 1 SD of 0.79 (95% CI: 0.63–0.99, $P = .042$). Validation in the second cohort yielded similar results and confirmed CLU as independent prognosticator in patients with chronic HF.

**CONCLUSION:** Our results point toward an ongoing consumption of CLU involved in the complex pathophysiology of HF and suggest CLU as novel and promising biomarker for prognosis in patients with chronic HF.



Funding: This work was supported by the Association for the Promotion of Research on Arteriosclerosis, Thrombosis, and Vascular Biology (ATVB).

[1] Contributed equally.

* Corresponding author. Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.

E-mail address: alexander.niessner@meduniwien.ac.at

Submitted November 2, 2016. Accepted for publication November 26, 2016.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2016.11.009

## Introduction

Heart failure (HF) represents a major public health issue in industrial nations with rising incidences mainly due to progressing demographic aging, a high load of predisposing risk factors, and rising proportions of cardiovascular events in tandem with improved survival rates.[1] Thus, continuous efforts in research are warranted to increase our knowledge of the disease and to improve standards of care in this high risk group of patients.

The concept of biomarker in diagnosis, therapy monitoring, and prognosis has successfully been established in HF by the implementation of natriuretic peptides.[2] Apart from that, current HF guidelines recommend also other emerging biomarkers for risk stratification such as troponins as marker of myocardial injury and soluble ST2 and galectin-3 as markers of myocardial fibrosis.[3,4] Beyond their clinical applicability, exploration of novel biomarkers help to improve our understanding of the underlying pathophysiological pathways and the multifaceted processes involved in HF or even may provide future targets for therapeutic interventions.[5]

The heterodimeric secreted glycoprotein clusterin/apolipoprotein J (CLU) represents a heat shock protein-like chaperone, which is ubiquitous expressed in human tissues and with the ability to bind to a wide variety of molecules.[6] CLU is involved in versatile physiological processes ranging from sperm maturation and cell differentiation over lipid transportation to DNA repair and cell-cycle regulation and is upregulated under diverse conditions of cell stress and tissue injury, including myocardial infarction, ischemia, inflammation, apoptosis, and oxidative stress.[7–9] In the extracellular space, CLU is involved in the maintenance of proteostasis by building complexes with misfolded or damaged proteins, which facilitates receptor-mediated endocytosis and lysosomal degradation.[10] With respect to myocardial diseases, CLU protects from inflammatory tissue destruction and disease progression in autoimmune myocarditis.[11,12] Furthermore, CLU alleviates angiotensin II-mediated damage of cardiomyocytes, a key mechanism in the pathogenesis and progression of HF.[13,14] Given the protective role of CLU against myocardial injury, we aimed to determine whether decreased plasma levels of CLU are associated with an unfavorable prognosis in patients with HF. To accomplish the objectives of the study, CLU was measured in a prospectively recruited cohort of 318 patients with chronic HF. In addition, results were validated in a second cohort comprising 346 with advanced stages of HF.

## Methods

### Study population

Informed consent was provided by all patients participating in the study protocols, which were both approved by the ethics committee of the Medical University of Vienna, and both studies comply with the Declaration of Helsinki.

#### Derivation cohort

We prospectively included 318 consecutive patients diagnosed with chronic HF in our observational study referred to the outpatient department for HF at the Medical University of Vienna between January 2008 and July 2013. Patients with clinical signs of chronic HF (New York Heart Association functional classification [NYHA] ≥2) and either levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) >500 pg/mL or a left ventricular ejection fraction (LVEF) < 40% were eligible for enrollment. Patients with noncardiovascular comorbidities reducing life expectancy to <2 years, chronic inflammatory diseases, age <18 years and those who refused informed consent were excluded. Baseline characteristics were assessed using a standardized patient questionnaire, administered, and reviewed by a physician.

#### Validation cohort

For validation of results, CLU levels were measured in a second study cohort comprising 346 patients with advanced HF enrolled between July 2003 and September 2004 at the Medical University of Vienna. Inclusion criteria were defined as: (1) hospitalization due to cardiac decompensation, (2) NYHA class III or IV at the time of admission, and (3) an LVEF <40%.

### Study endpoints and follow-up

Primary study endpoints were defined as all-cause mortality and cardiovascular mortality. Mortality was obtained by systematic screening of the Austrian Death Registry (Statistik Austria). This query provided date of death and cause of death encoded according to the International Code of Diseases, version 10. Results were cross-checked by browsing of the centralized patient management system of the Vienna General Hospital (AKIM-AKH-Informationsmanagement).

### Laboratory measurements

Venous blood samples were obtained at time of study inclusion. Routine laboratory measurements were determined on fresh samples according to the study sites laboratory standard procedure. NT-proBNP levels were assessed by electrochemiluminescence on an Elecsys 2010 (Roche Diagnostics). EDTA plasma samples were centrifuged at 3000 rpm for 20 minutes, stored at −80 C and analyzed immediately after thawing. Plasma concentrations of CLU were measured using the Human Clusterin Quantikine ELISA Kit (R&D Systems, Minneapolis, MN) according to the manufacturer's manual. Intraassay and interassay CVs were 3.7% and 8.4%, respectively.