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CLINICAL RESEARCH

Combined Free Light Chains Are Novel Predictors of Prognosis in Heart Failure

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ABSTRACT

OBJECTIVES This study investigated the prevalence and potential incremental prognostic value of combined free light chains (cFLCs) in patients recently hospitalized with decompensated heart failure (HF).

BACKGROUND Inflammatory pathways are recognized in the pathogenesis and progression of HF. Free light chain (FLC) elevation is conventionally associated with monoclonal gammopathies, including multiple myeloma. Polyclonal increases in both kappa and lambda FLCs occur in autoimmune and other chronic inflammatory conditions. Recently, a novel assay for measuring kappa and lambda immunoglobulin FLCs together, known as combined free light chain (cFLC) has been developed.

METHODS Six hundred twenty-eight patients recently hospitalized with decompensated HF were studied. cFLCs were measured by turbidimetry using an immunoassay. The incremental prognostic value of cFLCs for mortality was evaluated using Cox proportional hazard models including 22 established predictors of outcome in HF.

RESULTS Of 628 patients, 290 (46%) died during a follow-up of 3.2 ± 1.5 years. Two hundred seventy patients (43%) had elevated cFLCs. There was a clear gradient in the risk of death according to cFLC quartile, with those in the top quartile having an unadjusted risk of mortality more than twice that of those in the lowest quartile (hazard ratio: 2.38; $p < 0.0001$). After multivariable analysis, cFLC remained an independent predictor of mortality, with an almost 50% higher adjusted risk for those in the top compared with bottom quartile. Older age, lower body mass index, New York Heart Association classification III/IV, previous myocardial infarction, current smoking and B-type natriuretic peptide, bilirubin, high-sensitivity C-reactive protein, glycated hemoglobin, and lymphocyte concentrations were also independent predictors of mortality.

CONCLUSIONS cFLCs are an independent predictor of mortality in patients recently hospitalized with decompensated HF. Further work is required to assess the effects of HF therapies on cFLC concentrations and whether or not directly targeting this marker of inflammation improves prognosis for patients with HF. (J Am Coll Cardiol HF 2015;3:618–25)

Inflammation is believed to play a role in the pathophysiology of heart failure (HF) and an association between levels of several inflammatory biomarkers, particularly cytokines, and fatal and non-fatal outcomes have been demonstrated in patients with HF (1). B cell–derived plasma cells are central to humoral immune defense, producing immunoglobulins (antibodies) against pathogens and

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pathogen-related toxins. When aberrant, this antibody response may lead to autoimmune disease. Immunoglobulins (antibodies) consist of heavy and light chains with the latter comprising either kappa or lambda variants. B cells, plasma blasts, and plasma cells produce surplus light chains; those not bound to heavy chains can be detected as soluble free light chains (FLCs) in plasma/serum. FLC elevation is conventionally associated with monoclonal gammopathies (2–5), including multiple myeloma. Polyclonal increases in both kappa and lambda FLCs occur in autoimmune and other chronic inflammatory conditions, characterized by chronic B cell maturation, activation, and consequent increased immunoglobulin production such as rheumatoid arthritis, systemic lupus erythematosus, and chronic obstructive pulmonary disease (6–8). Conditions impairing FLC clearance, such as renal or reticuloendothelial system diseases, may also result in elevation of polyclonal FLC concentrations (9–12).

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Traditional methods of measuring excess immunoglobulins, such as serum protein electrophoresis or immunofixation, may not detect minor increases in serum light chains. More sensitive nephelometric assays measuring individual kappa and lambda FLC concentrations have been available for approximately a decade (13). Recently, a sensitive and novel assay measuring both kappa and lambda FLCs, referred to as combined free light chains (cFLCs), has been developed (14). Using this new assay, we have studied the prevalence and prognostic value of elevated cFLC concentrations in HF.

METHODS

Our study complied with the Declaration of Helsinki and was approved by the Local Ethics Committee. All patients provided written informed consent.

STUDY DESIGN. The study design is described elsewhere (15). Briefly, we enrolled 1,003 near-consecutive patients with decompensated HF from 3 hospitals. HF was defined according to the criteria of the European Society of Cardiology (16). Eligible patients were also required to be 18 years of age or older and to have an elevated B-type natriuretic peptide (BNP >100 pg/ml). The main exclusion criteria were primary presentation with myocardial infarction (MI) and significant cognitive impairment or concurrent systemic disease likely to result in reduced life expectancy. Attendance for the study visit was planned 1 month post-discharge. Of 1,003 patients originally enrolled, 648 patients (65%) returned for the study visit. Failure to attend was due to death (n = 115, 11%), deterioration in health (n = 73, 7%), or withdrawal of consent (n = 167, 17%).

LABORATORY MEASUREMENTS. Whole blood was drawn from venipuncture into serum and plasma vacutainers. Samples were processed immediately by centrifugation at 3,000 g for 15 min and serum and plasma fractions were aliquoted for storage at -80°C until assay. cFLCs were measured by turbidimetry using the Combylite immunoassay on a SPAplus automated analyzer (The Binding Site Group Ltd., Birmingham, United Kingdom). Elevated concentrations of cFLCs were defined as >45.7 mg/l, above the 95% reference range for the combined kappa and lambda FLC assays (17). Combylite immunoassay has a limit of quantification of 0.63 mg/l on neat samples, and assay precision (coefficient of variation) of 5.5% around the upper reference interval (54 mg/l) (14). High-sensitivity C-reactive protein (hsCRP) was assayed using a Siemens immunoassay on a Siemens BN II nephelometer (Siemens Healthcare Diagnostics GmbH, Marburg, Germany). Plasma BNP was measured using an Abbott Architect assay (Abbott Diagnostics, Maidenhead, United Kingdom). cFLCs were measured by The Binding Site Group Ltd., who supplied the assay results to the study statistician (CH) but did not have access to any other data and were not involved in the data analysis. All other biomarker assays were performed in local laboratories in Glasgow, United Kingdom.

LEFT VENTRICULAR EJECTION FRACTION. Left ventricular ejection fraction (LVEF) was measured by 2-dimensional echocardiography. Analysis was performed offline, using the biplane method of discs (modified Simpson's rule) by a single operator blinded to patient information. Twenty-six patients had an incalculable LVEF by this method. Reduced systolic function was defined as LVEF <50% (18).

FOLLOW-UP. All enrolled patients consented to be "flagged" with the Information Services Division of the Scottish Health Service for data on in-hospital and out-of-hospital deaths, held by the General Register Office for Scotland. The primary outcome measure of this study was death from any cause.

STATISTICAL ANALYSIS. Differences in clinical characteristics according to quartiles of cFLC concentration were compared using 1-way analysis of variance for continuous variables and Fisher's test for categorical variables. All continuous variables were transformed as appropriate to normalize their distributions.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BNP = B-type natriuretic peptide

cFLC = combined free light chains

HF = heart failure

hsCRP = high-sensitivity C-reactive protein

LVEF = left ventricular ejection fraction

MI = myocardial infarction

NYHA = New York Heart Association

RDW = red cell distribution width