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ORIGINAL RESEARCH

Novel Biomarkers of Cardiac Stress, Cardiovascular Dysfunction, and Outcomes in HIV-Infected Individuals

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ABSTRACT

OBJECTIVES This study sought to determine whether biomarkers ST2, growth differentiation factor (GDF)-15, N-terminal pro–B-type natriuretic peptide (NT-proBNP), and high-sensitivity troponin I are elevated in patients infected with human immunodeficiency virus (HIV) and are associated with cardiovascular dysfunction and all-cause mortality.

BACKGROUND HIV-infected patients have high rates of cardiovascular disease. Markers of myocardial stress may identify at-risk patients and provide additional prognostic information.

METHODS Biomarkers and echocardiograms were assessed in 332 HIV-infected patients and 50 age- and sex-matched control subjects. Left ventricular systolic dysfunction was defined as ejection fraction <50%, diastolic dysfunction (DD) as stage 1 or higher, and pulmonary hypertension as pulmonary artery systolic pressure ≥35 mm Hg. Mortality data were obtained from the National Death Index.

RESULTS Patients with HIV had a median age of 49 years, and 80% were male. Compared with control subjects, HIV-infected patients had higher adjusted percent estimates of all biomarkers except ST2 and interleukin-6. Among HIV-infected patients, 45% had DD; only ST2 was associated with DD (relative risk [RR]: 1.36; $p = 0.047$). Left ventricular systolic dysfunction was rare in this cohort (5%). Pulmonary hypertension was present in 27% of HIV-infected patients and was associated with GDF-15 (RR: 1.18; $p = 0.04$), NT-proBNP (RR: 1.18; $p = 0.007$), and cystatin C (RR: 1.54; $p = 0.03$). Thirty-eight deaths occurred among HIV-infected patients over a median of 6.1 years. In adjusted analysis, all-cause mortality was independently predicted by ST2 (hazard ratio [HR]: 2.04; $p = 0.010$), GDF-15 (HR: 1.42; $p = 0.0054$), high-sensitivity C-reactive protein (HR: 1.25; $p = 0.023$), and D-dimer (HR: 1.49; $p = 0.029$). Relationships were unchanged when analyses were restricted to virally suppressed HIV-infected patients receiving antiretroviral therapy.

CONCLUSIONS Among HIV-infected patients, ST2 and GDF-15 were associated with both cardiovascular dysfunction and all-cause mortality, and these variables may be useful at identifying those at risk for developing cardiovascular events and death. (J Am Coll Cardiol HF 2015;3:591–9) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ART = antiretroviral therapy

CVD = cardiovascular disease

DD = diastolic dysfunction

GDF = growth differentiation factor

HIV = human immunodeficiency virus

hsCRP = high-sensitivity C-reactive protein

hsTnI = high-sensitivity troponin I

ICD-9 = International Classification of Diseases-Ninth Revision

IL = interleukin

IQR = interquartile range

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PHTN = pulmonary hypertension

Through the evolution of the human immunodeficiency virus (HIV) epidemic, cardiovascular disease (CVD) has emerged as a major cause of morbidity and mortality among HIV-infected patients. In contemporary observational studies of patients with HIV, the proportion of total deaths caused by CVD ranges from 6.5% to 15%, with HIV infection alone conferring a 61% increased risk compared with uninfected subjects (1,2).

Previously, this elevated risk of CVD, present even among treated and virally suppressed subjects, was largely attributed to the consequences of antiretroviral therapy (ART) use and the increased burden of traditional risk factors. However, in the SMART (Strategies for Management of Antiretroviral Therapy) trial, chronic inflammation and viral replication were identified as causative factors, which prompted further investigation into the role of HIV-induced inflammation and immune activation as possible mediators of cardiovascular risk (1,3).

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An important step in establishing a relationship between HIV-associated immunologic perturbations and CVD is demonstrating that specific markers of these pathways predict subsequent events. However, most studied biomarkers, including high-sensitivity C-reactive protein (hsCRP), D-dimer, interleukin (IL)-6, and cystatin C, are predominantly released outside of the myocardium and may not represent a direct relationship between HIV infection and CVD.

Among subjects without HIV, novel biomarkers primarily expressed or secreted by cardiovascular tissue in response to pathological stress have been predictive of cardiovascular events and mortality. These include soluble ST2, growth differentiation factor (GDF)-15, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity troponin I (hsTnI) (4). However, only NT-proBNP has been evaluated in the HIV population (5).

The purpose of the present study was to determine whether ST2, GDF-15, NT-proBNP, and hsTnI are elevated in HIV-infected patients compared with uninfected control subjects and if these factors are associated with cardiovascular dysfunction and mortality. We also sought to establish whether these cardiac biomarkers provide independent assessment of risk compared with the previously studied biomarkers hsCRP, IL-6, D-dimer, and cystatin C.

METHODS

PARTICIPANTS. Subjects with HIV infection were consecutively enrolled between September 2004 and March 2011 from SCOPE (Study of the Consequences of the Protease Inhibitor Era), a large clinic-based cohort at San Francisco General Hospital. All participants of SCOPE were documented to be HIV infected. The cohort included: 1) untreated patients, defined as no ART in the preceding 6 months; 2) treated patients with detectable viremia, defined as >24 weeks of ART with the most recent 2 HIV ribonucleic acid levels >75 copies/ml; and 3) treated patients who achieved full viral suppression, defined as >24 weeks of ART with 2 most recent HIV ribonucleic acid levels <75 copies/ml. The only inclusion criterion was HIV infection, and there were no exclusion criteria. Enrollment of the uninfected control group was targeted toward subjects with similar age, sex, and smoking status as the SCOPE population. Control subjects were not known to have CVD at the time of enrollment and tested negative for HIV. Written informed consent was provided by all study participants, and the study was approved by the University of California-San Francisco Committee on Human Research.

MEASUREMENTS. Clinical and sociodemographic characteristics. At enrollment, all participants completed a detailed interview, and information on traditional risk factors, medication use, and sociodemographic factors were collected. HIV-related disease characteristics collected included ART, duration of infection, history of opportunistic infections, and nadir CD4 count.

Echocardiography. As described previously (6), a 2-dimensional transthoracic echocardiogram was

from Merck for participating in an HIV Renal Expert Input Forum; the honorarium was donated to the Northern California Institute for Research and Education to support kidney research. Dr. Wu has a patent with and receives speaker fees from Singulex. Dr. Hsue has received honoraria from Gilead and Pfizer; and grant support from the National Heart, Lung, and Blood Institute (RO1 HL095130 and RO1 HL091526). Dr. Snider is an employee of Critical Care Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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