Soluble receptor for advanced glycation end products and the risk for incident heart failure: The Atherosclerosis Risk in Communities Study

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Abstract Background Experimental studies in animals suggest that circulating soluble receptor for advanced glycation end products (sRAGE) decrease oxidative stress, inflammation, and fibrosis. The association between sRAGE and incident heart failure has not been systematically examined in a prospective study.

Methods We conducted a prospective analysis of a subsample of 1,086 participants from the Atherosclerosis Risk in Communities Study who attended visit 2 (1990-1992) without a history of coronary heart disease, stroke, or heart failure and with measured plasma sRAGE levels. *Incident heart failure* was defined as death from heart failure or hospitalization due to heart failure during a median of 20 years of follow-up.

Results In this sample of a community-based population (mean age 63 years, 60% women, 78% white), there were 126 incident cases of heart failure. Lower levels of sRAGE were significantly associated with an increased risk of heart failure; the adjusted hazard ratios (95% CIs) of heart failure were 1.0 (reference), 1.81 (0.94-3.49), 1.57 (0.80-3.08), and 3.37 (1.75-6.50), for fourth, third, second, and first quartiles, respectively (*P* for trend = .001). We did not observe significant interactions by diabetes status or by race or obesity status.

Conclusions Lower circulating levels of sRAGE are independently associated with the development of heart failure in a community-based population. Our results add to the growing evidence that sRAGE is a valuable predictor of cardiovascular disease. (Am Heart J 2015;170:961-7.)

Advanced glycation end products (AGEs) are a group of compounds generated under hyperglycemic conditions, oxidative stress, and hypoxia. Advanced glycation end products bind to the cellular receptor for AGEs (RAGE) and lead to generation of reactive oxygen species and activation of intracellular second messengers involved in inflammation and fibrosis.[1,2] Non-AGE ligands to the RAGE that also elicit inflammatory responses have been reported and include high-mobility group box 1 and S-100/calgranulins.[3,4]

The soluble receptor for advanced glycation end products (sRAGE) is the isoform of RAGE found in serum and is formed by proteolytic cleavage of RAGE. The relevance of sRAGE is that it competes with cellular RAGE for binding of AGEs and other ligands such as high-mobility group box 1[5] and, therefore, may reduce the activation of the RAGE-mediated proinflammatory and profibrotic signaling pathways.[6,7] In fact, experimental models have demonstrated that administration of sRAGE reduces immune and inflammatory responses.[8]

Given that the pathogenesis of heart failure includes insult to myocardial tissue through oxidative stress, inflammation, and fibrosis, all of which are related to the activity of RAGE pathway[9]; we hypothesized that sRAGE levels are related to future heart failure risk. The goal of the current study was to examine the prospective association between sRAGE and risk of heart failure among individuals without history of cardiovascular disease, heart failure, or stroke.

Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing cohort study of 15,792 initially middle-aged

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Table I. Baseline characteristics of the study population by quartiles of sRAGE (picograms per milliliter) overall and stratified by race groups

RAGE	Overall (n = 1086)			
Quartiles	Q1	Q2	Q3	Q4
Mean (range), pg/mL	550.7 (≤714.1)	840.9 (714.7-966.3)	1116.2 (966.4-1271.8)	1700.8 (≥1272)
Male (%)	47.6	44.1	41.3	29.8*
Mean age (y)	56.5	56.2	56.5	56.3
Black (%)	46.9	20.2	11.4	5.9*
Diabetes (%)	16.9	12.5	10.3	5.2*
Mean BMI (kg/m^2)	30.0	27.9	27.2	26.6*
CRP (%)				
<1 mg/L	17.0	29.0	35.4	39.3*
1-2.99 mg/L	33.9	34.9	34.7	33.8
≥3 mg/L	49.1	36.0	29.9	26.8
Mean glucose (mg/dL)	114.0	111.4	108.9	102.7*
Mean GGT (U/L)	35.6	32.3	23.2	20.6*
Current smoker (%)	15.1	21.7	19.6	15.8
Current drinker (%)	54.6	58.1	63.8	60.3
Hypertension (%)	33.9	24.6	21.8	17.3*

*P for trend across quartiles of sRAGE <.05.

adults recruited from 4 US communities: Forsyth Country, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland.[10] The first examination of participants took place from 1987 to 1989, with 3 follow-up visits, occurring approximately 3 years apart, and a fifth visit in 2011 to 2013. The study population for the present study is composed of a subsample of participants who attended visit 2 (1990-1992). Briefly, a random sample of 1,289 participants with normal kidney function (glomerular filtration rate >60 mL/min per 1.73 m^2) was selected from the 14,348 participants who attended visit 2. For the current study, we excluded participants with race/ethnicity other than black or white, and persons with a history of coronary heart disease, stroke, or heart failure at baseline. The final sample size was 1,086 adults. The characteristics of the participants included in the current analyses and those excluded are presented in the Supplementary Table I.

All participants provided written informed consent, and the institutional review boards at each clinical site approved the study.

Measurements of sRAGE

Soluble receptor for AGEs was measured in stored plasma samples using a commercially available kit (R&D Systems, Minneapolis, MN). The intra-assay and interassay coefficients of variation for the assay were 2.8% and 9.6%, respectively. In addition, measurement of sRAGE levels has been reported to be highly reliable, with an intraclass correlation of 0.76 and Pearson correlation of 0.78 when measurements were compared 3 years apart.[11]

Assessment of incident heart failure

Incident heart failure was defined as death from heart failure in any position on the death certificate or as the first heart failure hospitalization with *International Classification of Diseases, Ninth Revision*, code 428 or *International Statistical Classification of Diseases, 10th Revision*, code I50 in any position of the hospital discharge summary obtained during the ongoing active surveillance for all cardiovascular-related hospitalizations and deaths for all ARIC participants. For the current analyses, follow-up information was available up to December 31, 2011.

Other measurements

Smoking history and alcohol consumption were assessed during interviews with the participants. Participants were asked to bring all medications, which were coded by trained personnel. We defined history of cardiovascular disease as self-reported myocardial infarction or stroke before visit 1 or silent myocardial infarction (diagnosed by electrocardiographic changes) or adjudicated myocardial infarction or revascularization (at or before visit 2). *Prevalent heart failure* was defined as self-reported treatment for heart failure or hospitalization for heart failure at or before visit 2. *Diabetes* was defined as self-reported physician diagnosis or hemoglobin A1c ≥6.5%. Using standardized methods, height, weight, waist circumference, and blood pressure were measured. C-reactive protein (CRP) was measured in stored plasma samples using an immunoturbidimetric assay on the Siemens BNII autoanalyzer (Dade Behring, Deerfield, IL and Glasgow, DE). Frozen whole blood samples collected at ARIC visit 2 (1990-1992) were thawed and assayed for hemoglobin A1c using a high-performance liquid chromatography instruments (Tosoh Corporation, Tokyo, Japan). The coefficient of variation (CV) for quality control replicate samples (n = 259) was 1.4%. γ-Glutamyl-transferase (GGT), as surrogate marker