Soluble Angiotensin-Converting Enzyme 2, Cardiac Biomarkers, Structure, and Function, and Cardiovascular Events (from the Atherosclerosis Risk in Communities Study)

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Membrane-bound angiotensin-converting enzyme 2 is important in regulation of the renin−angiotensin−aldosterone system, but the association of cleaved soluble ACE2 (sACE2) with cardiovascular disease (CVD) is unclear. We evaluated the association of sACE2 with cardiac biomarkers, structure, and function and cardiovascular events in the Atherosclerosis Risk in Communities Study. sACE2 was measured in a subset of 497 participants (mean age 78±5.4 years, 53% men, 27% black); Cox regression analyses assessed prospective associations of sACE2 with time to first CVD event at median 6.1-year follow-up. sACE2 was higher in men, blacks, and participants with prevalent CVD, diabetes, or hypertension. Higher sACE2 levels were associated with significantly higher biomarkers of cardiac injury (high-sensitivity cardiac troponin I and T, N-terminal pro−B-type natriuretic peptide), greater left ventricular mass index, and impaired diastolic function in linear regression analyses, and with increased risk for heart failure hospitalization (adjusted hazard ratio per natural log unit increase [HR] 1.32, 95% confidence interval [CI] 1.10 to 1.58), CVD events (HR 1.34, 95% CI 1.13 to 1.60), and all-cause death (HR 1.26, 95% CI 1.01 to 1.57). In an elderly biracial cohort, sACE2 was positively associated with biomarkers reflecting myocardial injury and neurohormonal activation, left ventricular mass index, impaired diastolic function, CVD, events and all-cause death. **(Am J Cardiol 2021;146:15−21)**

The renin−angiotensin−aldosterone system (RAAS) is an important regulator of blood pressure, but excess activation contributes to development of cardiovascular disease (CVD).[1] In pathological RAAS activation, active tissue-bound, or membrane-bound, angiotensin-converting enzyme 2 (mbACE2) expression is increased, and increased shedding of plasma, or soluble, ACE2 (sACE2) into circulation results in increased sACE2 and relative deficiency of mbACE2.[2] mbACE2 is cardioprotective,[3-5] whereas increased sACE2 levels predict poor outcomes in patients with CHD, HF, or atrial fibrillation.[6-8] Data on the relation of sACE2 levels and cardiovascular events are limited to

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The Atherosclerosis Risk in Communities study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (contract numbers HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). This work was supported by NIH grants F30-DK120160 (O.T.), K24-DK106414 (E.S.), R01-DK089174 (E.S.), R01-HL134320 (E.S. and C.M.B.), R01-HL141824 (B.Y.), R01-HL142003 (B.Y.), T32-HL094301 (J.W.C.), R01-HL135008 (A.M.S.), R01-HL143224 (A.M.S.), R01-HL150342 (A.M.S.), and K24-HL152008 (A.M.S.)]; US Department of Veterans Affairs grants 1I01CX001112-01 (V.N.), IIR 16-072 (S.V.), and IIR 19-069 (S.V.); European Union 7th Framework Programme for Research and Technological Development grant HEALTH-F7-305507 (F.Z., as part of Heart OMics in AGEing); World Heart Federation (S.V.); and American Heart Association grant 17SDG33661228 (B.Y.).

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0002-9149/
https://doi.org/10.1016/j.amjcard.2021.01.017

relatively small cohorts of hospitalized patients with established CVD, with few data on the relation of sACE2 with cardiac biomarkers, structure, and function. We investigated the relations between levels of sACE2 and cardiac biomarkers, echocardiographic measurements of cardiac structure and function, and risk for CVD events in the Atherosclerosis Risk in Communities (ARIC) study, a biracial cohort of older adults with a high prevalence of CVD risk factors, to test the hypothesis that patients with pathological RAAS activation have altered expression of sACE2, higher prevalence of CVD, elevated biomarkers of subclinical cardiac injury, abnormal cardiac structure and function, and increased risk for incident CVD.

Methods

Detailed methods are provided in the Supplementary Data. The ARIC Study is a population-based study that recruited residents aged 45 to 65 years in 1987 to 1989 from 4 communities in North Carolina, Mississippi, Minnesota, and Maryland. A detailed description of the ARIC Study has been published.[9] The study protocol was approved by each field center's institutional review board and complies with the Declaration of Helsinki; all participants provided written informed consent. This analysis used data from participants in ARIC visit 5 (2011 to 2013; aged 66 to 90 years).

Of the 6538 participants in visit 5, we excluded those with self-reported race neither black nor white (N=14) and black participants at the Minnesota and Washington County field centers (N=17) because of small enrollment numbers and those with missing information on cardiac biomarkers (high-sensitivity cardiac troponin I [hs-cTnI] or T [hs-cTnT], N-terminal pro−B-type natriuretic peptide [NT-proBNP]; N=1,227) to include 5280 for cardiac biomarker analysis. sACE2 measurements were available from a case-control study of incident HF for a subset of 497 patients, 152 with prevalent CVD and 345 without (Supplementary Figure 1S).

The selection of the sACE2 subset from ARIC visit 5 was based on a case−control study design. Both cases and controls had to be free of HF at visit 5. For each case (incident HF between visit 5 and December 31, 2016), a matched control was selected, matched on age, sex, and being free of HF after the same follow-up time since visit 5 (incidence density sampling).

hs-cTnI was measured using a highly sensitive chemiluminescent immunoassay (Architect Stat Troponin-I; Abbott) on an automated chemistry analyzer (Architect i 2000sr; Abbott).[10] hs-cTnT was measured using a highly sensitive assay (Elecsys Troponin T Gen 5 STAT; Roche).[10] NT-proBNP was measured using a electrochemiluminescent immunoassay on an automated analyzer (Cobas e411; Roche).[11] Participants with hs-cTnI, hs-cTnT, or NT-proBNP levels below the lower limits of detection were assigned values equal to half the lower limits of detection.

sACE2 protein levels were measured using the cardiovascular panel II of the Olink Multiplex platform (Olink Proteomics, Uppsala, Sweden) in a subset of 497 participants from ARIC visit 5. Cardiovascular panel II is validated with respect to sensitivity, dynamic range, specificity, precision (repeatability and reproducibility), and scalability.[12]

Echocardiography was performed according to a study-specific protocol and using uniform equipment by dedicated sonographers as described.[13] Quantitative measures of cardiac structure and function were determined by a central reading center according to American Society of Echocardiography recommendations[14]; reproducibility metrics are published.[13]

Clinical end points assessed included first CHD, ischemic stroke, and HF hospitalization events and all-cause mortality as described.[15-17] All outcomes were assessed after ARIC visit 5, with follow-up through December 31, 2018. Global CVD was a composite of CHD, stroke, and HF hospitalization events; ASCVD was a composite of CHD and stroke events. Median (25th, 75th percentile) follow-up periods were 6.1 (4.6, 6.8) years for global CVD, 6.2 (5.1, 6.8) years for ASCVD, and 6.2 (5.2, 6.8) years for HF hospitalizations.

sACE2 was modeled as a continuous variable or classified by tertiles of its distribution for categorical analysis. Baseline characteristics of participants were tabulated by sACE2 tertile. Categorical variables were expressed as count (percentage); continuous variables were reported as mean ± standard deviation or median (25th, 75th percentile) depending on normality of the data.

We modeled hs-cTnT, hs-cTnI, and NT-proBNP at visit 5 as both categorical and continuous variables. For the hs-cTnT categorical analysis, patients were classified by prespecified cutpoints: <6 ng/L ("low"; the limit of quantification for the assay), 6 to <14 ng/L ("intermediate"), and ≥14 ng/L ("high"; 90th percentile in ARIC[18] and 99th percentile upper reference in multisociety guidelines for defining myocardial infarction[19]). Respective categories for hs-cTnI were <2 ng/L ("low"; lowest integer above limit of detection), 2 to <10 ng/L ("intermediate"), and ≥10 ng/L ("high"; as published[10]). For NT-proBNP, patients were classified by prespecified reference cutpoints of <100 pg/mL (low), ≥100 to <300 pg/mL (intermediate), and ≥300 pg/mL (high).[11] For the continuous analyses, hs-cTnI, hs-cTnT, and NT-proBNP values were natural log (ln) transformed. We examined cross-sectional correlations among sACE2, hs-cTnI, hs-cTnT, and NT-proBNP levels using Spearman rank correlation. We further assessed cross-sectional association of sACE2 with hs-cTnI, hs-cTnT, and NT-proBNP as categorical and continuous variables using multivariable logistic or linear regression models, respectively. Model 1 was adjusted for age, sex, and race. Model 2 was adjusted for all variables in model 1 plus total cholesterol, high-density lipoprotein cholesterol, smoking status, systolic blood pressure, antihypertensive medication use, diabetes status, lipid-lowering medication use, prevalent CVD (composite of CHD, stroke, and HF hospitalization), and estimated glomerular filtration rate (eGFR).

Linear regression models were used to assess cross-sectional association of sACE2 with echocardiographic measures of systolic function (left ventricular [LV] ejection fraction, global longitudinal strain [GLS]), cardiac structure (LV mass index [LVMi]), and diastolic function (left atrial volume index [LAVi], tissue doppler imaging [TDI] septal e′ and septal E/e′ ratio). Adjustments were made with model 1 and model 2 as above; model 3 included all variables in model 2 plus log hs-cTnI, log hs-cTnT, and log NT-proBNP.

Table 1
Characteristics across sACE2 tertiles at ARIC visit 5, 2011-2013

Variable	sACE2 tertile*			p-value
	18.54-55.01 (n=166)	55.09-88.84 (n=166)	90.62-1491.37 (n=165)	
Age (years)	77.1±5.4	78.4±4.9	77.9±5.8	**0.13**
Male	38.6%	63.3%	60.0%	**<0.001**
Black	19.9%	31.3%	30.3%	**0.03**
Prevalent CHD	16.6%	23.8%	30.9%	**0.002**
Prevalent stroke	3.0%	4.2%	6.1%	0.17
Prevalent HF	7.3%	9.8%	9.3%	0.54
Hypertension	79.1%	74.6%	87.7%	**0.05**
Diabetes mellitus	32.9%	29.6%	45.3%	**0.02**
Obesity	34.0%	34.6%	36.1%	0.69
Current smoker	7.7%	6.5%	6.9%	0.79
SBP (mm Hg)	130.9±19.1	132.3±19.6	136.7±20.7	**0.009**
DBP (mm Hg)	64.7±12.1	66.0±11.4	67.3±13.4	**0.04**
Pulse pressure (mm Hg)	66.2±17.0	66.2±15.6	69.4±15.3	0.06
BMI (kg/m^2)	28.9±6.0	28.6±5.6	29.0±5.6	0.79
Use of antihypertension medications	76.5%	78.3%	87.8%	**0.009**
Use of ACEi or ARB	36.4%	41.6%	43.9%	0.16
Fasting glucose (mg/dL)	112.4±31.3	110.8±24.7	121.4±43.2	**0.05**
Total cholesterol (mg/dL)	178.5±43.1	170.3±39.3	172.8±45.2	0.17
Triglycerides (mg/dL)	103 (76, 141)	103 (80, 136)	112 (84, 168)	0.07
HDL-C (mg/dL)	52.4±13.7	49.5±12.0	50.5±15.4	0.06
LDL-C (mg/dL)	103.0±35.4	97.3±32.6	95.4±36.9	**0.03**
Lipid-lowering medications	60.0%	56.6%	64.6%	0.39
eGFR (mL/min/1.73m^2)	69.3±18.1	63.8±18.2	67.0±19.7	0.19
hs-CRP (mg/L)	1.8 (0.8, 4.3)	2.2 (1.1, 4.6)	3.0 (1.4, 7.4)	**0.001**
Cardiac biomarkers				
hs-cTnI (ng/L)	3.7 (2.5, 5.4)	4.5 (3.1, 8.7)	6.9 (3.5, 12.8)	**<0.001**
hs-cTnT (ng/L)	12 (8, 16)	15 (10, 24)	18 (12, 27)	**<0.001**
NT-proBNP (pg/mL)	176.4 (86.2, 343.3)	231.2 (108.1, 536.3)	330.6 (121.4, 1002.0)	**<0.001**
LVEF (%)	65.3 (60.8, 69.3)	63.6 (59.4, 67.0)	64.3 (58.1, 68.8)	0.08
LVMi (g/m^2)	81.0 (68.8, 93.0)	83.0 (71.0, 99.1)	89.8 (74.2, 105.7)	**0.001**
LAVi (mL/m^2)	26.5 (21.5, 32.6)	27.7 (22.5, 34.0)	30.0 (23.9, 37.9)	**<0.001**
Septal e′ (cm/sec)	5.3 (4.5, 6.4)	5.3 (4.5, 6.2)	5.1 (4.3, 5.8)	**0.02**
Septal E/e′	12.4 (9.5, 15.5)	11.9 (9.4, 14.9)	13.5 (10.9, 17.8)	**0.004**
GLS (%)	−17.53 (−19.1, −16.0)	−17.1 (−18.9, −15.2)	−16.5 (−18.7, −14.8)	**0.001**

Significant values in bold.

Data presented as mean±SD, median (25th, 75th percentiles), or percentage. p-values for linear trend were calculated by using trend test across ordered groups.

Obesity defined as BMI ≥30 kg/m^2.

Abbreviations: ACEi = ACE inhibitors; ARB = angiotensin receptor blockers; BMI = body mass index; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LVEF = LV ejection fraction; SBP = systolic blood pressure; TR = tricuspid regurgitation.

* ACE2 measured in normalized protein expression (NPX).

Finally, we used Cox proportional hazards models to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the prospective associations of sACE2 at visit 5 with time to first ASCVD, HF hospitalization, or global CVD event, adjusted by models 1−3 as above. P-trend was calculated for linear increase in log relative hazard with increasing categories. Sensitivity analyses were performed by stratifying the cohort into those with or without prevalent CVD and into NT-proBNP categories (<100, 100 to <300, ≥300 pg/mL), to determine if findings were consistent among patients with or without prevalent CVD and across low, intermediate, and high NT-proBNP categories.

Results

Patients in the higher sACE2 tertiles were more likely to be black men and have prevalent CHD, hypertension, or diabetes mellitus and higher fasting glucose, high-sensitivity C-reactive protein (hs-CRP), hs-cTnI, hs-cTnT, and NT-proBNP (Table 1) sACE2 levels were positively correlated with hs-cTnI (R=0.27), hs-cTnT (R=0.27), and NT-proBNP (R=0.18) (Supplementary Table 1S).

Use of ACE inhibitors/angiotensin receptor blockers or mineralocorticoid receptor antagonists was not associated with statistically significant differences in median sACE2 levels. On the other hand, patients using loop diuretics or

Table 2
Association of sACE2 with hs-cTnI, hs-cTnT, and NT-proBNP as continuous variables (ln transformed) at ARIC visit 5

Biomarker	Model	Beta-coefficient*	95% CI	p-value
ln−hs-cTnI	1	0.27	0.16-0.39	<0.001
	2	0.25	0.13-0.36	<0.001
ln−hs-cTnT	1	0.15	0.08-0.23	<0.001
	2	0.15	0.08-0.22	<0.001
ln−NT-proBNP	1	0.33	0.18-0.48	<0.001
	2	0.29	0.14-0.44	<0.001

* Increment in hs-cTnI, hs-cTnT, or NT-proBNP (log unit) per log unit increase of sACE2, where sACE2 is independent and hs-cTnI, hs-cTnT, or NT-proBNP the dependent variables.

Model 1: adjusted by visit 5 age, sex, and race; model 2: model 1 plus visit 5 total cholesterol, HDL-C, SBP; use of antihypertension medication, current smoking, diabetes status, use of lipid-lowering medication, prevalent CVD, and eGFR.

beta-blockers had significantly higher sACE2 levels compared with patients not using these medications (Supplementary Table 2S).

sACE2 (ln transformed) was significantly and positively associated with (ln-transformed) hs-cTnI (β 0.25, 95% CI 0.13 to 0.36), hs-cTnT (β 0.15, 95% CI 0.08 to 0.22), and NT-proBNP (β 0.29, 0.14 to 0.44) per log unit of sACE2, after adjusting for clinical variables (traditional risk factors + prevalent CVD and eGFR; model 2) (Table 2). Patients with higher sACE2 levels had significantly higher odds of having "elevated" hs-cTnI, hs-cTnT, and NT-proBNP levels after adjusting for variables in model 2 (Supplementary Table 3S).

After adjustment for demographic and clinical covariates (model 2), higher sACE2 levels were associated with significantly greater LVMi, larger LAVi, and higher TDI E/e′ and less-negative GLS. Although septal e′ was associated with sACE2 levels in model 1, the association was not significant after adjustment for model 2. Associations of sACE2 with all echocardiographic measures of systolic and diastolic function and cardiac structure were attenuated and no longer significant after further adjusting for cardiac biomarkers in model 3 (Table 3). The results remained unchanged when patients with prevalent CVD were excluded (Supplementary Table 4S).

sACE2 (ln transformed) was significantly associated with global CVD events (HR 1.34 per ln unit increase, 95% CI 1.13 to 1.60), HF hospitalization (HR 1.32 per ln unit increase, 95% CI 1.10 to 1.58), and all-cause death (HR 1.26, 95% CI 1.01 to 1.57) after adjusting for variables in model 2. Further adjusting with (ln-transformed) hs-cTnT, hs-cTnT, and NT-proBNP attenuated the associations, which were no longer significant. sACE2 was borderline-significantly associated with ASCVD events when adjusted for model 1, but not after adjusting for model 2 (Table 4). Sensitivity analyses indicated that associations of sACE2 with incident global CVD and HF hospitalization were unchanged and the association with all-cause death was attenuated when patients with prevalent CVD were excluded (Supplementary Table 5S).

Table 3
Association of sACE2 as continuous variable (ln transformed) and echocardiographic parameters at ARIC visit 5

Echocardiographic parameter	Model	Beta-coefficient	95% CI	p-value
Ln-LVEF	1	−0.02	−0.04, 0.002	0.08
	2	−0.02	−0.04, 0.002	0.07
	3	−0.004	−0.03, 0.02	0.68
Ln-LVMi	1	**0.06**	**0.02, 0.09**	**0.001**
	2	**0.05**	**0.01, 0.08**	**0.009**
	3	0.002	−0.03, 0.03	0.91
Ln-LAVi	1	**0.08**	**0.03, 0.13**	**0.001**
	2	**0.06**	**0.01, 0.11**	**0.011**
	3	0.01	−0.03, 0.05	0.73
Ln-septal e′	1	**−0.04**	**−0.08, -0.01**	**0.02**
	2	−0.03	−0.07, 0.01	0.10
	3	−0.01	−0.04, 0.03	0.76
Ln-septal E/e′	1	**0.10**	**0.05, 0.15**	**<0.001**
	2	**0.07**	**0.02, 0.12**	**0.01**
	3	0.02	−0.03, 0.07	0.47
GLS	1	**0.61**	**0.21, 1.00**	**0.003**
	2	**0.53**	**0.14, 0.93**	**0.009**
	3	0.16	−0.21, 0.54	0.39

Significant values in bold.

Increment in LVEF, LVMi, septal e′, septal E/e′ (log unit) and GLS (%) per log unit increase of sACE2, where sACE2 is the independent and hs-cTnI, hs-cTnT, or NT-proBNP dependent variable.

Model 1 is adjusted by age, sex, and race; model 2 is model 1 plus total cholesterol, HDL-C, current smoking, SBP, antihypertension medication use, diabetes status, lipid-lowering medication use, history of CVD (stroke, total CHD, and HF), and eGFR; model 3 is model 2 plus log hs-cTnI, log hs-cTnT, and log NT-proBNP.

Discussion

Despite many animal studies demonstrating the protective role of ACE2 in cardiovascular physiology through ameliorating cardiac fibrosis, remodeling, and hypertrophy,[3-5]

Table 4
Risk for CVD events, HF hospitalization, ASCVD events, and all-cause death by sACE2 levels as a continuous variable (natural log)

Outcome	n/N	Model	HR	95% CI	p-value
Global CVD	282/497 (56.7%)	1	**1.41**	**1.20-1.65**	**<0.001**
		2	**1.34**	**1.13-1.60**	**0.001**
		3	1.11	0.93-1.34	0.25
HF	260/497 (52.3%)	1	**1.40**	**1.19-1.66**	**<0.001**
		2	**1.32**	**1.10-1.58**	**0.003**
		3	1.07	0.88-1.30	0.48
ASCVD	150/497 (30.2%)	1	1.24	0.99-1.55	0.06
		2	1.09	0.85-1.39	0.49
		3	0.95	0.73-1.24	0.71
All-cause death	190/497 (38.2%)	1	**1.26**	**1.03-1.54**	**0.02**
		2	**1.26**	**1.01-1.57**	**0.04**
		3	1.01	0.80-1.28	0.91

Significant values in bold.

Data are presented as number of events [n] / number at risk [N] (percent) and HR per natural log unit increase for sACE2 with 95% CI.

Model 1 is adjusted by age, sex, and race; model 2 is model 1 plus total cholesterol, HDL-C, current smoking, SBP, antihypertension medication use, diabetes status, lipid-lowering medication use, history of CVD (stroke, total CHD, and HF), and eGFR; model 3 is model 2 plus log hs-cTnI, log hs-cTnT, and log NT-proBNP.

relatively little information is available on the relation of sACE2 with CVD in humans. Our study has important implications in this regard. In a large elderly population-based cohort with a high prevalence of cardiovascular risk factors, increased sACE2 levels were associated with significantly higher cardiac biomarkers (hs-cTnI, hs-cTnT, and NT-proBNP), reflecting neurohormonal activation and cardiac inflammation and injury; echocardiographic measures of myocardial hypertrophy and impaired diastolic function; and increased risk for cardiovascular events, driven primarily by an increased risk for HF hospitalizations.

The specific relations between mbACE2 and sACE2 protein (or circulating ACE2 activity) as measured in other studies are not completely understood. Active mbACE2 is shed into circulation as sACE2 by enzymatic cleavage by tumor necrosis factor alpha−converting enzyme (TACE). In states of pathological RAAS activation, mbACE2 expression is increased (as counter-regulatory response), and shedding into circulation is increased through upregulation of TACE by angiotensin II[2] resulting in increased sACE2 and relative deficiency of active mbACE2. Therefore, circulating sACE2 protein or activity, perhaps similarly to BNP, serve protective biological functions but increase in counter-regulatory response to disease stimuli.

To our knowledge, this is the first study to investigate relations between sACE2 and biomarkers of cardiac injury and the largest study evaluating echocardiographic parameters. A recent case−cohort study in 10,753 participants in 14 countries (Prospective Urban Rural Epidemiology study) showed similar results as our study; increased concentrations of plasma ACE2 were associated with increased risk for CVD and non-CVD death, HF, and myocardial infarction independent of age, sex, ancestry, and traditional cardiac risk factors.[20] However, the association with echocardiographic parameters or biomarkers was not explored. [20]

Plasma ACE2 activity is usually low in healthy patients,[21] higher in patients with CVD[22,23] or diabetes,[24] and correlated with extent of tissue damage or CVD progression.[21] Higher plasma ACE2 activity has been associated with adverse CVD outcomes in patients with CHD,[6] HF,[7] or atrial fibrillation,[8] with higher activity seen with greater infarct size, ventricular systolic dysfunction,[7] and adverse cardiac remodeling.[8]

Although these smaller studies measured ACE2 activity in patients with established CVD, we measured sACE2 protein levels in a substantially larger elderly population and observed that elevated plasma sACE2 levels were associated with higher odds of elevated hs-cTnI and hs-cTnT, greater LV mass, and worse LV diastolic function, mirroring the cardiac structural and functional correlates that we previously reported with higher hs-cTnT levels.[25] Patients with higher sACE2 had increased risk for global CVD events, driven by HF hospitalization, independent of traditional risk factors, kidney function, or prevalent CVD. Based on these data, we propose that elevated sACE2 may be a marker of pathological activation of RAAS (Figure 1), with concomitant elevation of biomarkers of cardiac injury and abnormalities of cardiac structure and function resulting in increased risk for HF.

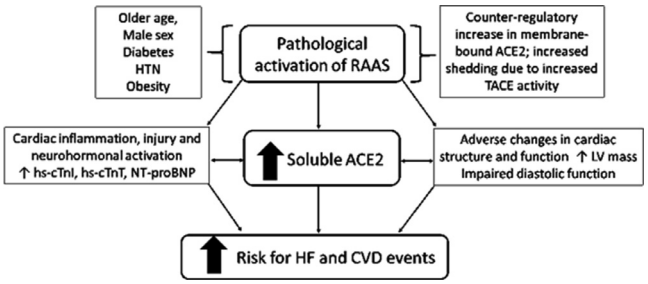

Figure 1. sACE2 and cardiac biomarkers, structure, and function: potential implication for CVD. Pathological activation of RAAS as evidenced by elevated sACE2 levels was associated with elevated cardiac biomarkers and echocardiographic measures of cardiac structural abnormalities and diastolic dysfunction, and independently predicted cardiovascular events including HF hospitalizations.

Although sACE2 levels were significantly associated with echocardiographic abnormalities and increased risk for HF events after adjusting for traditional risk factors, the associations were no longer significant after additional adjustment for cardiac biomarkers. This loss of significance may suggest that both sACE2 and cardiac biomarkers may be in the same biological pathway related to RAAS overactivation. The finding that sACE2 was associated with incident HF only in patients who also had elevation of NT-proBNP may reflect increased cleavage present when there is increased pressure overload and needs confirmation in larger studies and ideally examination of both plasma and tissue levels of ACE2.

Limitations of our study include measurement of soluble plasma (not tissue) ACE2 in only a subset of participants at only one time-point; moreover, the number of black participants was small (n=134, 27%) and may provide insufficient power to study this subpopulation. The correlations of sACE2 with some biomarkers was weak, even though statistically significant because of the large number of samples. It is hypothesized that sACE 2 concentrations are associated with tissue concentration. ACE2 cleaves angiotensin-II to angiotensin 1 to 7; although measuring circulating levels of both angiotensins and evaluating their associations with sACE2 would increase our understanding of the RAAS axis, these measurements were not available in ARIC. Our study cohort included an elderly population with mean age 78 (SD 5); therefore, the results of our study may not be applicable to a younger age group. In addition, this study is hypothesis generating, and our proposal that increased levels of sACE2 and cardiac biomarkers may be useful to identify patients with increased susceptibility to adverse cardiac outcomes is intended to encourage future investigation into this area.

In conclusion, elevated sACE2 levels were significantly and positively associated with increased levels of biomarkers of cardiac injury and neurohormonal activation, increased LV mass, impaired diastolic function, and increased risk for prospective CVD events in a large biracial elderly American cohort. sACE2 may therefore serve as an indicator of end-organ damage from pathological imbalance of the RAAS axis, which in turn increases risk for future CVD events.

Credit Author Statement

Author contributions: AH made substantial contributions to the conception and design of the work, interpretation of data, and drafting of the manuscript. CS made substantial contributions to the analysis and interpretation of data for the manuscript. OT, XJ, ES, VN, AF, GH, FZ, TM, SSV, JC, EB, BY, JWC, AMS, SDS, and JAdL contributed to the interpretation of the data, revising it critically for important intellectual content. RCH and CMB made substantial contributions to the conception and design of the work, interpretation of data and ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Olive Tang, Elizabeth Selvin, Vijay Nambi, Faiez Zannad, Salim S. Virani, Bing Yu, Jonathan W. Cunningham, Amil M. Shah, Christie M. Ballantyne report financial support was provided by National Institutes of Health, US Department of Veterans Affairs, European Union 7th Framework Programme for Research and Technological Development, World Heart Federation, American Heart Association. Dr. Selvin reports a relationship with Novo Nordisk. that includes:. Dr. Nambi reports a relationship with Merck. that includes:. Ballantyne reports a relationship with Abbott Diagnostic, Denka Seiken, Roche Diagnostic. that includes:. Zannad reports a relationship with Janssen, Bayer, Boston Scientific, Amgen, CVRx, Boehringer, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmacuetical, Applied Therapeutics, Merck, and Novartis, CVCT. that includes:. Virani reports a relationship with American College of Cardiology, PALM registry at Duke Clinical Research Institute that includes:. Shah reports a relationship with Novartis, Philips Ultrasound that includes:. De Lemos reports a relationship with Roche Diagnostics, Abbott Diagnostics, Ortho Clinical Diagnostics, Quidel Cardiovascular, Inc. that includes:. Dr. Hoogeveen reports a relationship with Denka Seiken that includes:. Declaration of competing interests: Dr. Selvin: honoraria from Novo Nordisk. Dr. Nambi: site PI study sponsored by Merck. Dr. Zannad: personal fees from Janssen, Bayer, Boston Scientific, Amgen, CVRx, Boehringer, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmacuetical, Applied Therapeutics, Merck, and Novartis; founder of CVCT. Dr. Virani: honorarium: American College of Cardiology (Associate editor for Innovations acc.org); Steering Committee member: PALM registry at Duke Clinical Research Institute (no financial remuneration). Dr Shah: research support (significant; paid to institution, not patient) from Novartis, and consultant (modest) for Philips Ultrasound. Dr. de Lemos: grant support and consulting income from Roche Diagnostics and Abbott Diagnostics, consulting income from Ortho Clinical Diagnostics and Quidel Cardiovascular, Inc. Dr. Hoogeveen: grant support and consulting fees from Denka Seiken outside the submitted work. Dr. Ballantyne: grants/research support (significant; paid to institution, not patient): Abbott Diagnostic, Roche Diagnostic; consultant (modest): Abbott Diagnostic, Denka Seiken, Roche Diagnostic. Dr. Hussain, Ms. Tang, Ms. Sun, Dr. Jia, Dr. Folsom, Dr. Heiss, Dr. Mosley, Dr. Coresh, Dr. Boerwinkle, Dr. Yu, Dr. Cunningham, Dr. Solomon: none.

Grant support: The Atherosclerosis Risk in Communities study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (contract numbers HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN26 8201700005I, HHSN268201700004I). This work was supported by NIH grants F30-DK120160 (O.T.), K24-DK106414 (E.S.), R01-DK089174 (E.S.), R01-HL134320 (E.S. and C.M.B.), R01-HL141824 (B.Y.), R01-HL142003 (B.Y.), T32-HL094301 (J.W.C.), R01-HL135008 (A.M.S.), R01-HL143224 (A.M.S.), R01-HL150342 (A.M.S.), and K24-HL152008 (A.M.S.)]; US Department of Veterans Affairs grants 1I01CX001112-01 (V.N.), IIR 16-072 (S.V.), and IIR 19-069 (S.V.); European Union 7th Framework Programme for Research and Technological Development grant HEALTH-F7-305507 (F.Z., as part of Heart OMics in AGEing); World Heart Federation (S.V.); and American Heart Association grant 17SDG33661228 (B.Y.).

Acknowledgment

The authors thank the staff and participants of the ARIC study for their important contributions. Roche supplied reagents for hs-cTnT and NT-proBNP, Abbott supplied reagents for hs-cTnI, and SomaLogic provided assays without charge. The authors acknowledge Kerrie Jara, MLIS, Baylor College of Medicine, for editorial assistance.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.01.017.

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