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The different roles for the advanced glycation end products axis in heart failure and acute coronary syndrome settings

Beatriz Paradela-Dobarro [a,b], Rosa M. Agra [b,c], Leyre Álvarez [a,c], Alfonso Varela-Román [a,b,c], José M. García-Acuña [a,b,c], José R. González-Juanatey [a,b,c], Ezequiel Álvarez [a,b,*], Francisco J. García-Seara [a,b,c]

[a] *Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complexo Hospitalario Universitario de Santiago de Compostela (CHUS), SERGAS, Travesía da Choupana s/n, Santiago de Compostela, 15706 A Coruña, Spain*
[b] *CIBERCV, Madrid, Spain*
[c] *Servicio de Cardiología y Unidad de Hemodinámica, Complexo Hospitalario Universitario de Santiago de Compostela (CHUS), SERGAS, Travesía da Choupana s/n, Santiago de Compostela, 15706 A Coruña, Spain*

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Chronic heart failure;
Long-term cardiovascular prognosis

Abstract *Aims:* This work aimed to compare the behavior of the advanced glycation end products (AGEs) and their soluble receptor (sRAGE) in two cohorts of patients: those with heart failure (HF) and acute coronary syndrome (ACS).
Methods and results: A unicentric observational clinical study was performed in 102 patients with ACS and 102 patients with chronic HF matched by age and gender. At inclusion, fluorescent AGEs were measured by quantitative fluorescence spectroscopy of plasma, and total sRAGE and endogenous secretory RAGE (esRAGE) levels were determined by enzyme-linked immunosorbent assay kits. A 5-year follow-up period was established for recording cardiac death (primary endpoint) and the incidence of non-fatal myocardial infarction or HF readmission (secondary endpoints). Higher glycation parameters were observed in HF patients, whereas no differences in sRAGE forms were found between HF and ACS cohorts, except for cRAGE, which was higher in HF. Associations between glycation parameters and sRAGE forms were observed in HF, but not in ACS. Differences were also evidenced in the long-term prognosis of each cohort: esRAGE showed an independent prognostic value for cardiac death or non-fatal cardiovascular events in HF, but none of the AGE–RAGE variables were predictors in ACS.
Conclusions: A different role for the AGE–RAGE axis was observed in HF and ACS. All the sRAGE forms were directly related with glycation parameters in HF, but not in ACS. The independent value of the sRAGE forms on each cardiovascular disease was supported by esRAGE being an independent predictor of bad long-term prognosis only for HF.

* Corresponding author. Laboratorio no. 6, Edif. Consultas externas (planta-2), Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complexo Hospitalario Universitario de Santiago de Compostela (CHUS), SERGAS, Travesía da Choupana s/n, Santiago de Compostela, 15706 A Coruña, Spain.
E-mail address: ezequiel.alvarez.castro@gmail.com (E. Álvarez).

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Introduction

Advanced glycation end products (AGEs) and their receptor (RAGE), the so-called AGE–RAGE axis, have gained attention in recent years in cardiovascular diseases. The role of AGEs in the pathogenesis of atherosclerosis [1] and coronary artery disease [2], their prognostic value after an acute myocardial infarction [3,4] and in chronic heart failure (HF) [5,6], and its relationship with heart rhythm [7] have been evidenced. AGEs are chronically produced and accumulated in plasma and vascular tissues, where they can directly interact with the extracellular matrix leading to arterial stiffness and decreased elasticity [8]. Moreover, AGEs can also exert their deleterious effects through their interaction with their multi-ligand receptor (RAGE) at the surface of endothelial cells, vascular smooth muscle cells, and monocytes [9]. Therefore, AGEs could participate in the cardiovascular disease *continuum*, which allows us to hypothesize that they could be new therapeutic targets against cardiovascular disease.

Besides the membrane form, there is also a soluble form of RAGE (sRAGE). These two forms are the main contributors to sRAGE levels: endogenous secretory RAGE (esRAGE) formed by a splicing variant of RAGE gene, and cleaved RAGE (cRAGE), which comes from the degradation of membrane RAGE [10]. It is unclear what pathophysiological processes are linked to an increase of each of these forms of RAGE in plasma. As a consequence, the behavior of both forms could be different, and the levels of each form might vary independently in different pathological situations. In short, the role of each sRAGE variant in cardiovascular disease is unknown, although its therapeutic potential is indisputable [11]. It has been proposed that raising the levels of sRAGE might be a new therapeutic approach to prevent vascular damage and other inflammatory diseases [12]. However, there is also evidence for the opposite idea: the hypothesis that sRAGE is an indicator of coronary heart disease [13] and might even be an independent predictor of HF or serve to stratify the cardiovascular risk [14], as also suggested by our previous results [4]. Therefore, in this work, we perform a comparative analysis of the levels of the AGE–RAGE axis and their relationship with clinical outcomes in two cohorts of age- and gender-matched patients with HF or acute coronary syndrome (ACS). Since it is not clear what is the best parameter to characterize the AGE–RAGE axis activity, circulating AGEs, glycated albumin (as a possible precursor of AGEs) and all the soluble forms of RAGE were measured. From these parameters integrative indexes as AGE/RAGE ratios were also calculated and explored.

Methods

Subjects

This was a prospective and observational study of two cohorts of patients with the following characteristics. The first cohort was composed by consecutive outpatients attending to the HF Unit of our hospital between July 2008 and April 2009 [6]. After that, patients admitted to our coronary care unit (CCU) with ACS and fitting our inclusion criteria were included between October 2009 and January 2011 [15]. Patients from both cohorts were matched by age and gender, resulting in a final population of 204 patients (102 on each cohort). The consort flow diagram of the study is summarized in Fig. 1.

Inclusion criteria for patients were to have a confirmed diagnosis of HF or an ACS according to the diagnostic criteria for HF or ACS proposed by the guidelines of the European Society of Cardiology [16]. The exclusion criteria for all patients were those known to likely modify AGE–RAGE axis levels transiently by acute inflammatory processes or clinical conditions previously associated with changes on these levels. So, exclusion criteria were pregnancy, chronic inflammatory or malignant diseases, severe kidney dysfunction [glomerular filtration rate (GFR) $<$ 30 mL/min/1.73 m^2, liver dysfunction, active or recent infections (last month) or hematological disorders, or had previous major trauma or surgery (within 3 months).

In the cohort of HF, patients with acute coronary syndrome and/or who had undergone myocardial revascularization in the previous 3 months were also excluded, to avoid the influence of concomitant coronary artery disease at the moment of inclusion. In the cohort of ACS, patients with previous myocardial infarction, a history of HF, cardiomyopathy or moderate/severe valvular heart disease, prior stroke, arterial or venous thromboembolic disease or peripheral artery disease were excluded, to avoid simultaneity of HF and previously established symptomatic ischemic disease. Written informed consent was obtained from each included subject according to the protocol approved by the Ethics Committee for Human Studies at Galicia (our Spanish region), in accordance to the 1975 Declaration of Helsinki and its following updates.

For all included patients, detailed information was gathered from medical history and appropriate physical examination and recorded in a database. Also, blood samples were obtained for local laboratory analysis (hemogram, basic biochemistry and coagulation rate, lipid profiles, as well as specialized parameters such as levels of AGE, soluble RAGE of all forms). Peripheral venous blood was collected in EDTA-anticoagulated tubes between 8 and 10 AM after an overnight fast in HF patients and during the 24 h post-infarction in the ACS cohort. Plasma was separated by centrifugation (10 min. 1800×*g*, room temperature) and stored at −40 °C until analysis. An electrocardiogram and echocardiogram were also performed on each patient.

Definitions and laboratory data

Diagnosis of type-2 diabetes was determined according to the criteria of the American Diabetes Association (ADA) [17]. Hypertension was defined as systolic/diastolic blood pressure $>$ 140/90 mmHg or current use of any antihypertensive medication. Similarly, dyslipidemia was defined by total cholesterol $\geq$ 5.69 mmol/L,

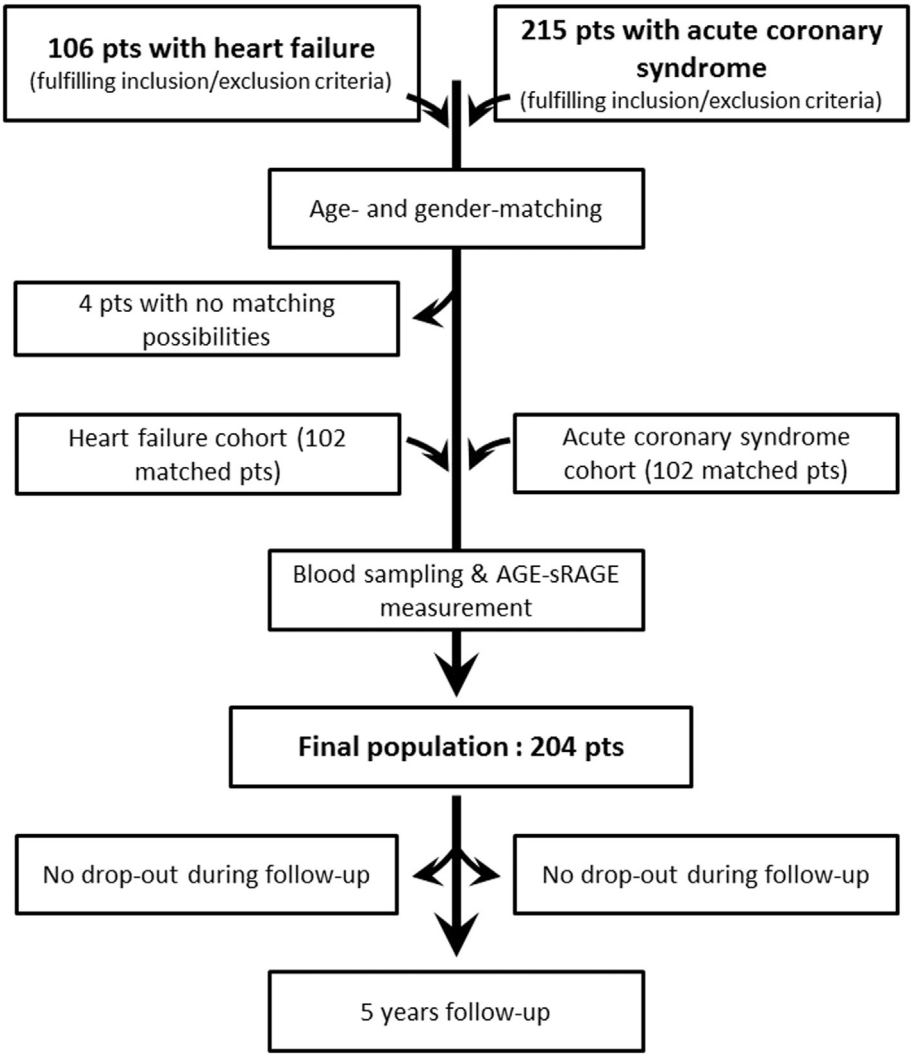

Figure 1 Consort flow diagram of the study.

triglyceride $\geq$ 1.69 mmol/L, high-density lipoprotein cholesterol (HDL-C) $<$ 1.04 mmol/L, or current use of anti-hyperlipidemic drugs. Left ventricular ejection fraction (LVEF) was estimated using Simpson's method according to current international recommendations [18]. LVEF was considered depressed when $<$40%, according to the 2016 ESC HF guidelines [16].

Estimated GFR was calculated by the MDRD-4 formula [19]. Serum lipid levels were measured by enzymatic colorimetric test (Boehringer Ingelheim, Mannheim, Germany) and low-density lipoprotein cholesterol was calculated from the Friedewald formula. Hemoglobin A1c was measured by a latex-enhanced turbidimetric immunoassay (Cobas Integra System, Roche Diagnostics, Mannheim, Germany). Fructosamine determination was done by colorimetric assays in a global analyzer (Cobas Integra System). Glycated albumin was measured in plasma using a commercially available colorimetric assay, according to manufacturer's instructions (SpinReact, Japan). Briefly, endogenous glycated amino acids were eliminated in a previous reaction of the sample with ketoamine oxidase. Then, albumin was specifically decomposed on its amino acids to further react with ketoamine oxidase and produce hydrogen peroxide that will be quantitatively detected colorimetrically.

Fluorescent AGEs (fAGE) were measured by quantitative fluorescence spectroscopy analysis of plasma [in arbitrary units (a.u.) at 360/40:460/40 nm (excitation: emission)] following the protocol previously described [15]. By this method, we could measure multiple AGE modifications simultaneously (e.g., crossline, fluorolink, pyrropyridine, and vesperlysine), for which there are currently no immunological-based methods available. Briefly, plasma was aliquoted into black 96-well plates in duplicate, and fluorescence (360/40:460/40 nm; excitation:emission) was measured in a multi-mode microplate reader (Synergy 2, Biotek, Potton, United Kingdom) at room temperature to estimate the levels of fAGE. Readings were subtracted from those of plasma-free wells to obtain measurements in arbitrary units (a.u.) and the mean of duplicated readings calculated. The intra-assay and inter-assay coefficients of variation were $<$4 and $<$10%, respectively.

Plasma sRAGE levels were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Quantikine; R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocol. Measurements were performed in duplicate, and the results were averaged. This intra-assay and inter-assay coefficients of variation values were <5% and <8%, respectively. Plasma esRAGE levels were measured by ELISA kit (B-Bridge International, Inc. CA, USA) following the manufacturer's instructions. This intra-assay and inter-assay coefficients of variation values were <8% and <10%, respectively. Plasma cRAGE levels were indirectly calculated from the difference between sRAGE and esRAGE levels. The ratios fAGE/sRAGE, fAGE/esRAGE, and fAGE/cRAGE, were calculated from the above parameters in order to explore their possible value as integrative variables of the AGE–RAGE axis.

Follow-up and endpoints

Follow-up data were based on patients' records available at our outpatient clinic. The primary endpoint was cardiac death, as noted and confirmed by review of the death certificate, hospital chart, and physician's records. Secondary endpoints were the incidence non-fatal myocardial infarction, evidenced by the appropriate combination of symptoms, electrocardiogram, and enzyme changes, or HF readmission. The combined endpoint was the incidence of major adverse cardiovascular events (MACE; cardiac death, reinfarction or HF readmission).

Data analysis

The statistical analyses were performed with SPSS (Statistical Package for the Social Sciences), version 17.0. The categorical or dichotomous variables were expressed as absolute values and percentages and were compared with the Pearson χ^2 test. In the case of continuous variables, normality was checked with the Kolmogorov–Smirnov test. When normally distributed, variables were described as the mean ± standard deviation (SD), and when not, as the median and inter-quartile range. The student *t*-test was used for the comparisons of continuous variables between groups of patients (two tail distribution and equal variances between samples) when variables fulfilled the condition of normality, whereas Mann–Whitney U test was used when not. Continuous data from more than two groups were compared with ANOVA followed by Tukey's test. Non-normal distributed variables were compared with Wilcoxon text for two groups or Kruskal–Wallis test (unrelated data) or Friedman test (related data) for comparisons of more than two groups. Correlations between variables were calculated by Pearson's or Spearman's tests according to the normality or not of the variable, respectively. Predictive value of individual variables for new cardiovascular events was analyzed by receiver operating characteristic (ROC) curves. Different Cox proportional hazard analyses were carried out to assess the independence of AGEs or sRAGE levels to predict MACE and data were presented as hazard ratios (HR) with 95% confidence intervals. Kaplan–Meier curves (analyzed with the log-rank test) were performed to evaluate the prognostic value of AGEs or sRAGE during follow-up. A *p*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics and laboratory data

A total of 204 consecutive patients fulfilling the inclusion criteria and distributed in two cohorts of 102 age- and gender-matched HF or ACS patients were included in the study. Basal characteristics in the moment of the inclusion are presented in Table 1. The mean age for the total population was 69.4 ± 11.7 years, and 32% were female. Statistical differences between cohorts were observed for the percentage of patients with reduced LVEF, highly increased in the HF cohort, as expected, and for dyslipidemia and body mass index, which was also higher in HF cohort. Although no differences in the number of patients with diabetes mellitus were observed, percentages of glycated hemoglobin and glycated albumin were significantly higher in the HF cohort, whereas glycemia was higher in the ACS cohort. On the other hand, the proportion of smokers and estimated GFR were significantly higher in the ACS cohort, and HDL-cholesterol was lower (Table 1). Particularly, fAGE and cRAGE levels were higher in the HF cohort, whereas no significant differences were observed for the other soluble forms of RAGE.

Classical glycation parameters were positively related, as expected: glucose levels were positively related with fructosamine and glycated hemoglobin in both HF and ACS cohorts, and fructosamine and glycated hemoglobin also correlated (Supplementary Table S1). However, glycation parameters related with AGE–RAGE axis showed different associations. Levels of fAGE and fructosamine were directly related in both cohorts, whereas glycated albumin was directly related with fructosamine in the ACS cohort, but did not associate in the HF cohort (Supplementary Table S1). Moreover, glycated albumin was positively related with glycated hemoglobin and fAGE levels in HF cohort, but it was not in the ACS cohort (Supplementary Table S1). Interestingly, the levels of the three forms of sRAGE (total sRAGE, esRAGE and cRAGE) were positively related with fructosamine levels in the HF cohort, but no relation was observed in the ACS cohort (Supplementary Table S1). On the other hand, fAGE levels were positively and significantly related to esRAGE levels (Supplementary Table S1) only in the HF cohort.

A marked positive association was observed for sRAGE and esRAGE levels, both in the HF ($r_s = 0.912$, $p < 0.001$) and ACS ($r_s = 0.885$, $p < 0.001$) cohorts. These associations were slightly more pronounced than those observed between esRAGE and cRAGE ($r_s = 0.656$, $p < 0.001$ and $r_s = 0.600$, $p < 0.001$, for HF and ACS cohorts, respectively).

Table 1 Baseline characteristics of the patients stratified by cohorts.

Variable	HF cohort (n = 102)	ACS cohort (n = 102)	p Value[a]
Anthropometry			
Age, years	69.5 ± 11.8	69.3 ± 11.6	0.919
Female, % (n)	33.3 (34)	30.4 (31)	0.652
BMI, kg/m^2	28.2 ± 4.2	26.4 ± 3.4	**0.006**
Vascular risk			
HT, % (n)	64.7 (66)	58.8 (60)	0.387
DLP, % (n)	60.4 (61)	46.1 (47)	**0.041**
DM, % (n)	36.3 (37)	33.3 (34)	0.659
Smokers, % (n)	7.8 (8)	21.6 (22)	**0.006**
Cardiac function			
Heart rate, bpm	74.0 [63.0–85.0]	71.5 [60.0–87.2]	0.618
rLVEF, % (n)	75.8 (75)	18.6 (19)	**<0.001**
Kidney function			
eGFR, mL/min/1.73 m^2	67.5 ± 21.4	79.1 ± 16.1	**<0.001**
Glycemic control			
Glycemia, mmol/L	6.16 [5.49–7.44]	7.44 [6.23–10.94]	**<0.001**
Fructosamine, mmol/L	236.0 [201.0–310.5]	182.0 [156.5–253.0]	**<0.001**
HbA1C, %	6.0 [5.7–7.3]	5.7 [5.5–6.7]	**0.028**
Glycated albumin, %	22.9 [17.9–28.2]	18.8 [15.2–22.7]	**<0.001**
Blood lipids			
TC, mmol/L	4.66 [4.06–5.48]	4.74 [3.96–5.59]	0.962
LDL, mmol/L	2.84 [2.16–3.43]	2.92 [2.11–3.42]	0.798
HDL, mmol/L	1.06 [0.83–1.29	0.92 [0.72–1.20]	**0.032**
TG, mmol/L	1.16 [0.78–1.56]	1.34 [0.93–1.79]	0.074
AGE–RAGE axis			
fAGE, a.u.	62.0 [50.4–78.4]	42.7 [34.4–52.0]	**<0.001**
sRAGE, pg/mL	941.1 [635.2–1472.6]	822.5 [536.0–1178.3]	0.120
esRAGE, pg/mL	384.5 [266.5–765.2]	377.0 [255.0–606.7]	0.443
cRAGE, pg/mL	494.1 [343.7–735.8]	393.8 [276.4–683.0]	**0.031**

BMI: body mass index; DLP: dyslipidaemia; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; fAGE: fluorescent advanced glycation end-products; HbA1C: glycated hemoglobin; HDL: high density lipoprotein cholesterol; HT: hypertension; LDL: low density lipoprotein cholesterol; RAGE: receptor for advanced glycation end products (cRAGE, esRAGE and sRAGE for cleaved, endogenously secreted and soluble RAGE, respectively); rLVEF: reduced left ventricular ejection fraction; TC: total cholesterol; TG: triglycerides.

[a] Statistically difference between cohorts: p value for Student's t test or Mann–Whitney U test for normal and non-normal, respectively when continuous variables; Pearson χ^2 test for categorical variables.

Levels of fAGE and sRAGE were inversely related with the estimated GFR in HF (r_s = −0.714, p < 0.001 and r_s = −0.227, p = 0.023, for fAGE and sRAGE, respectively) and ACS (r_s = −0.205, p = 0.040 and r_s = −0.240, p = 0.016, for fAGE and sRAGE, respectively) cohorts, as expected by the known relation between AGE–RAGE axis and kidney disease, but cRAGE levels were related with estimated GFR only in the HF cohort (r_s = −0.253, p = 0.011), whereas no association was observed in the ACS cohort. Surprisingly, esRAGE levels were not associated with estimated GFR in any cohort. Associations with age were also found for fAGE (r_s = 0.453, p < 0.001) and sRAGE (r_s = 0.227, p = 0.025) in the HF cohort and for sRAGE (r_s = 0.222, p = 0.025) and esRAGE (r_s = 0.263, p = 0.010) in the ACS cohort.

Follow-up and prognosis

The median follow-up of event-free patients was 5.0 years for both cohorts under study. None of the 204 patients were lost to follow-up. During this period, 54 cardiac deaths (39 in HF and 15 in ACS cohort) and 88 events (56 in HF and 32 in ACS cohort) were registered in the whole population. The clinical parameters for the events- and event-free groups of patients on each cohort are presented in Table 2 and Supplementary Table S2. Patients with events (MACE, including cardiac death) were significantly older in HF, but not in the ACS. Reduced LVEF was more prevalent in the event groups of both cohorts. Patients with events in the HF cohort showed reduced GFR and a higher percentage of glycated albumin and esRAGE levels. In the ACS cohort, more patients were diabetic, and they presented higher glycated hemoglobin levels. No differences in any of the index ratios calculated between fAGE and the different forms of soluble RAGE were observed. Only the data for the fAGE/sRAGE index is showed in Table 2. The clinical parameters stratified by the type of event (death or secondary events) in the event-group of each cohort are presented in Supplementary Table S2. Some variables that were unrelated with prognosis considering the combined endpoint, showed an association only with death. These were the cases of smoking habit, fAGE and sRAGE in HF cohort, and LDL and HbA1C levels in ACS cohort (Supplementary Table S2).

The value of the AGE–RAGE axis to predict new events during the follow-up period was analyzed by receiver

Table 2 Baseline characteristics of patients stratified by event- and event-free-group in the two cohorts.

Variable	HF cohort			ACS cohort		
	Event-free (n = 45)	Event (MACE) (n = 57)	p Value[a]	Event-free (n = 69)	Event (MACE) (n = 33)	p Value[a]
Age, years	66.2 ± 11.8	72.1 ± 11.3	**0.011**	68.0 ± 11.8	72.0 ± 10.6	0.098
Female, % (n)	31.1 (14)	35.1 (20)	0.672	31.9 (22)	27.3 (9)	0.636
HT, % (n)	71.1 (32)	59.6 (34)	0.229	53.6 (37)	69.7 (23)	0.123
DLP, % (n)	57.8 (26)	62.5 (35)	0.630	44.9 (31)	48.5 (16)	0.736
DM, % (n)	28.9 (13)	42.1 (24)	0.168	26.1 (18)	48.5 (16)	**0.025**
Smokers, % (n)	13.3 (6)	3.5 (2)	0.067	21.7 (15)	21.2 (7)	0.952
Heart rate, bpm	73.5 [64.0–86.5]	75.0 [62.0–85.0]	0.827	70.0 [60.0–85.0]	77.0 [60.5–89.5]	0.629
rLVEF, % (n)	65.9 (29)	83.6 (46)	**0.041**	13.0 (9)	30.3 (10)	**0.036**
BMI, kg/m^2	28.5 ± 4.6	27.9 ± 4.0	0.584	26.9 ± 3.4	25.4 ± 10.6	**0.046**
eGFR, mL/min/1.73 m^2	73.2 ± 20.4	63.2 ± 21.3	**0.020**	80.7 ± 16.0	75.8 ± 16.2	0.161
TC, mmol/L	4.71 [4.08–5.48]	4.64 [3.72–5.47]	0.619	4.68 [4.10–5.57]	4.43 [3.42–5.67]	0.147
LDL, mmol/L	2.84 [2.30–3.52]	2.84 [2.02–3.40]	0.502	2.93 [2.33–3.39]	2.51 [1.74–3.54]	0.399
HDL, mmol/L	0.98 [0.83–1.25]	1.14 [0.83–1.32]	0.397	0.92 [0.72–1.30]	0.90 [0.74–1.16]	0.735
TG, mmol/L	1.24 [0.89–1.65]	1.08 [0.78–1.43]	0.243	1.42 [0.95–1.73]	1.15 [0.86–1.92]	0.396
HbA1C, %	6.0 [5.7–6.7]	6.0 [5.7–7.9]	0.529	5.7 [5.4–6.3]	6.1 [5.5–7.6]	**0.043**
Glycated albumin, %	20.0 [17.1–24.3]	25.6 [18.6–30.9]	**0.005**	19.2 [15.7–22.7]	16.9 [13.4–22.2]	0.270
fAGE, a.u.	60.0 [44.0–71.0]	64.5[52.5–79.5]	0.099	42.0 [33.0–51.0]	43.0 [36.7–58.2]	0.350
sRAGE, pg/mL	815.1 [615.8–1185.0]	1022.2 [632.8–1622.0]	0.080	812.0 [532.0–1092.0]	989.0 [533.7–1433.9]	0.192
esRAGE, pg/mL	352.5 [205.0–525.7]	456.5 [293.6–854.0]	**0.035**	331.0 [255.0–519.0]	494.0 [222.0–787.0]	0.133
cRAGE, pg/mL	459.4 [330.9–710.4]	528.6 [371.0–815.1]	0.543	391.0 [295.7–586.9]	413.0 [226.8–891.1]	0.829
fAGE/sRAGE	0.064 [0.046–0.110]	0.065 [0.038–0.097]	0.564	0.052 [0.035–0.074]	0.047 [0.026–0.086]	0.619

BMI: body mass index; DLP: dyslipidaemia; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; fAGE: fluorescent advanced glycation end-products; HbA1C: glycated hemoglobin; HDL: high density lipoprotein cholesterol; HT: hypertension; LDL: low density lipoprotein cholesterol; RAGE: receptor for advanced glycation end products (cRAGE, esRAGE and sRAGE for cleaved, endogenously secreted and soluble RAGE, respectively); rLVEF: reduced left ventricular ejection fraction; TC: total cholesterol; TG: triglycerides.

[a] Statistically difference between cohorts: p value for Student's t test or Mann–Whitney U test for normal and non-normal, respectively when continuous variables; Pearson χ^2 test for categorical variables.

operating characteristic (ROC) curves in each cohort. So, fAGE [0.703, 95% CI (0.597–0.809), p = 0.001], sRAGE [0.623, 95% CI (0.512–0.734), p = 0.038], and esRAGE [0.621, 95% CI (0.510–0.7132), p = 0.042], but not cRAGE (p = 0.178), presented statistical significant areas under the ROC curves for cardiac death in the HF cohort. None of these variables showed significant areas under the ROC curve in the ACS cohort.

The same analysis was done for the secondary endpoint (reinfarction and HF readmission), with different results: glycated albumin [0.680, 95% CI (0.574–0.786), p = 0.002] and esRAGE [0.631, 95% CI (0.521–0.741), p = 0.024], showed statistically significant areas under the ROC curves for events in the HF cohort, but none of them, nor AGE or other forms of sRAGE, presented this association in the ACS cohort. The integration of the AGE–RAGE axis on an index ratio such as AGE/sRAGE did not show any relationship with events (death or MACE) in any cohort (data not shown).

Finally, only glycated albumin [0.668, 95% CI (0.561–0.775), p = 0.005] and esRAGE [0.622, 95% CI (0.512–0.733), p = 0.035] maintained their prognosis value in the HF cohort for the combined endpoint (MACE). No relationships were observed in the ACS cohort for these variables with long-time prognosis.

From these analyses, cut-off values for predicting death or MACE were selected as follows: 58 a.u. for fAGE, 1100 and 435 pg/mL for sRAGE and esRAGE, respectively. These cut-off values were used in the following statistical analysis of prognosis. Cumulative survival curves for esRAGE are shown in Fig. 2.

All relevant variables for prognosis were analyzed by univariate Cox regression tests for cardiac death, secondary events (reinfarction or HF readmission), and the combined endpoint (MACE). Hazard ratios for these analyses are presented in Supplementary Tables S3-S5. From this analysis, age, diabetes mellitus, reduced LVEF, estimated GFR, plasma proteins or albumin, glycated albumin, fAGE, and esRAGE were found to be significantly related to cardiovascular events. Those variables with statistical significance in the univariate analysis and others considered important, such as gender or plasma lipids, were further adjusted in a multivariate regression model for long-term prognosis to achieve the best prediction models for the different endpoints.

Final regression models were adjusted by age, gender, diabetes mellitus, reduced GFR and reduced LVEF. It was found that the AGE–RAGE axis was independently associated with long-term cardiovascular prognosis in the HF cohort, and the best prognostic parameter of this axis was esRAGE > 435 pg/mL, whatever the endpoint considered (Table 3). However, in the ACS cohort, the AGE–RAGE axis did not show such value for long-time prognosis. Age, reduced LVEF or diabetes mellitus were the best markers for long-time prediction of cardiovascular events in this cohort. The best regression models are presented in Table 3.

Discussion

Here, for the first time (to the best of our knowledge) the components of the AGE–RAGE axis were compared in two

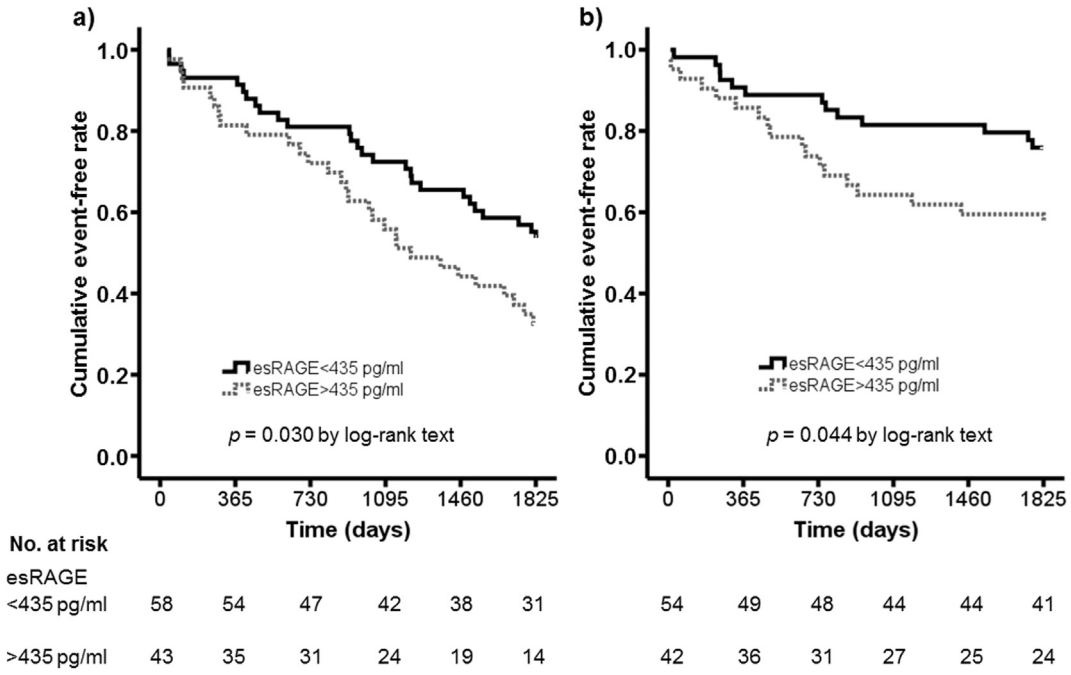

Figure 2 Kaplan–Meier curves and the results of the log-rank test for the stratification by 435 pg/mL esRAGE level in HF (a) and ACS cohort (b). Number of patients at risk for each time and group are indicated in the bottom rows of the figure.

age- and gender-matched cohorts of HF and ACS. The levels of each specific sRAGE form (esRAGE or cRAGE) were also compared on these settings. Higher glycation parameters were observed in HF patients. On the contrary, no differences in soluble RAGE forms were found between HF and ACS cohorts, except for cRAGE, which was also higher in HF. The relationships between glycation parameters and soluble forms of RAGE were not the same in HF as in ACS, suggesting a different role for the receptor on each cardiovascular disease. This was also evidenced in the relationship between the AGE–RAGE axis with long-term prognosis on each cohort. Whereas esRAGE showed an independent prognostic value for cardiac death or non-fatal cardiovascular events in the HF cohort, the AGE–RAGE axis variables were not independent predictors for long-term prognosis in the ACS cohort.

Table 3 Multivariate analysis for AGE–RAGE axis (esRAGE) to predict follow-up cardiac mortality, secondary events (reinfarction or HF readmission) and the combined endpoint (MACE), adjusted by age, gender, GFR, rLVEF and DM.

Variable	HF (death)		ACS (death)	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age	1.061 (1.021–1.103)	**0.002**	1.112 (1.032–1.198)	**0.005**
$esRAGE_{435}$	2.141 (1.111–4.125)	**0.023**		
	HF (secondary events)		ACS (secondary events)	
$esRAGE_{435}$	1.883 (1.097–3.233)	**0.022**		
	HF (MACE)		ACS (MACE)	
rLVEF	1.893 (0.912–3.933)	0.087	2.243 (1.057–4.759)	**0.035**
$esRAGE_{435}$	1.756 (1.019–3.026)	**0.043**		

ACS: acute coronary syndrome; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; esRAGE435: endogenously secreted receptor for advanced glycation end products > 435 pg/mL; HF: heart failure; MACE: major adverse cardiovascular events; N.A.: non-adjusted; rLVEF: reduced left ventricular ejection fraction.

The molecular mechanisms underlying the role of the AGE–RAGE axis in HF [20] and cardiovascular ischemic diseases [2] are far from clear, so comparing the effects of this axis on different clinical settings is crucial to gain knowledge about the possibility of common molecular mechanisms and to take advantage of the possible therapeutic opportunities. In our comparison, the possible effects from age or gender were eliminated by the matching, and no differences were observed in the incidence of conventional risk factors, such as diabetes mellitus or hypertension between cohorts, although renal function was worse in the HF cohort. Body mass index was higher in HF. A negative association has been found previously between sRAGE levels and accumulation of visceral fat in healthy women [21] and also in HF patients between sRAGE or AGE and body mass index or percentage of body fat [22]. However, no differences on total sRAGE between cohorts were observed in the present study. Only cRAGE was higher in HF, but no association was found with body mass index.

Elevated fasting glucose plasma levels have been associated with an increased risk of myocardial infarction [23], which might explain the highest levels of glucose found in ACS compared to HF cohort. In contrast, the glycation parameters (fructosamine, fAGE, glycated albumin and glycated hemoglobin) were significantly higher in the HF cohort suggesting that glucose-independent glycation might be related to an increased risk of developing HF.

Moreover, all the forms of sRAGE were shown to be related with fructosamine levels in the HF, but not in the ACS cohort, and esRAGE levels were positively associated with fAGE and glycated albumin in the HF cohort. The absence of an association between sRAGE forms and glycation parameters in the ACS cohort suggest an AGE-independent mechanism involved in the regulation of soluble RAGE forms in ACS or that glycated proteins have a greater impact on sRAGE forms in HF. The association between esRAGE and fAGE in HF might indicate a positive feedback between sRAGE, specially esRAGE, and fAGEs levels in this cohort, and would support the data from Colhoun et al. [24], which point to the increase in esRAGE as being responsible for the increase in sRAGE. AGE-induced changes might result in the development and progression of diastolic and systolic dysfunction, and subsequent HF [25,26], but also vascular dysfunction [20]. Higher levels of AGEs in the HF cohort could reflect the progression of HF since a direct association has recently been reported between fAGE and HF evolution after an acute HF decompensation [22].

Regarding sRAGE, only cRAGE levels showed significant differences between cohorts, which suggests a possible difference in the contribution of each soluble form of RAGE to each cardiovascular pathology. It has been previously shown that cRAGE levels are increased in HF patients with respect to control subjects, and also related with the severity of the disease, independently of diabetes [27]. An association between total sRAGE and the severity of HF was also observed by us in our HF cohort [6].

The hypothesis of the AGE–RAGE axis being more important in HF is supported by the fact that esRAGE remained as an independent prognostic factor of long-term mortality and cardiovascular events in HF after adjustment by other variables. Nevertheless, neither fAGE nor any soluble form of RAGE were predictors of cardiac death in the univariate Cox regression analysis in the ACS cohort. It seems that the possible value of this axis on ACS progression is reduced to a shorter period. In our previous studies, elevated levels of sRAGE were associated with worse in-hospital (few days) prognosis, whereas high fAGE levels were associated with cardiovascular events during a follow-up period of 366 [273–519] days [15]. As suggested in that time, the prognostic meaning of the different parameters of the AGE–RAGE axis change over the time: total sRAGE levels are predictive of events in the very short time (several days), whereas fAGE concentration is on the medium-long period (up to 3 years) [3], but not so much as five years after the ACS. However, in the HF cohort, sRAGE levels have been predictive of cardiac death in the medium-long period (1–2 years) [5], but they retain their predictive value, at least in the form of esRAGE, after a prolonged period (up to 5 years), as demonstrated in the present work (Fig. 3).

Attending to our results, we propose a single value of 435 pg/mL esRAGE as the cut-off value for stratification of patients with cardiovascular disease already developed. Total sRAGE levels in healthy volunteers have been reported to be 1300–1600 pg/mL, from which, esRAGE represents only the 20% (~350–400 pg/mL), leaving the remaining 80% for cRAGE (~1000 pg/mL) [10,28–31]. These levels allow sRAGE to function as a decoy for AGEs, limiting their interaction with RAGE and conferring vascular protection [32]. Supporting this, in a cohort from the ARIC study without a history of coronary artery disease, stroke or HF, lower circulating levels of sRAGE were independently associated with the development of HF over a median of 20 years of follow-up [33]. However, under several pathological conditions, such as hypertension [29], hypercholesterolemia [34], inflammation [35] or coronary artery disease [28,31], levels of sRAGE become reduced, limiting its ability to work as a decoy. This could explain why the average levels of sRAGE and its forms in our cohorts are lower than those presented above since the subjects of this study are all patients with established cardiovascular problems.

During the pre-symptomatic stage of the disease, low levels of sRAGE would be predictors of bad prognosis [36]. Once the disease has been already initiated, a change of trend seems to happen: higher levels of sRAGE would be predictors of various cardiovascular outcomes [5,14,24]. For this reason, we think that sRAGE level dynamics (and also esRAGE) during a cardiovascular process is the key factor to understand its possible role in the disease. In the case of HF, the point of change of trend for sRAGE might be an acute decompensation [22] or another type of complication. Preliminary reports suggest sRAGE to be a potential clinical indicator of HF prognosis and mortality [37]. However, none of these works analyzed esRAGE and cRAGE separately. In the populations of this study, the levels of esRAGE represented almost half of the total sRAGE in both cohorts (with a mean value of 46.2% for ACS and 45,3% for HF). This important finding differs from healthy subjects [10,28–31], and might suggest that variations in this ratio can be involved in the development of cardiovascular disease or be a consequence of this pathological condition. This hypothesis is supported by the similar percentage of esRAGE found in ACS patients (47.5%) by Park et al. [38].

Regarding cRAGE levels, a significant decrease (by half) is observed in both cohorts of our population with respect to normal values from healthy volunteers previously reported [10,28–31]. The low levels of cRAGE in HF patients might play an important role in the early development of the disease, as suggested by the results of the ARIC study [33]. Altogether, the reduction in cRAGE and the increase in esRAGE levels, suggest that the increase in total sRAGE levels found in ACS patients just after the acute event [39] would be more related to an increase in esRAGE production, than an increase in proteolytic cleavage of membrane RAGE. As a consequence, esRAGE could be a better marker than total sRAGE for cardiovascular outcomes. Nevertheless, due to the differences found at this point in the prognostic role of the different soluble forms of RAGE for each disease, the evolution of each pathological condition might be different. Thus, the implication of both soluble forms in the progression of these cardiovascular conditions might also be different. In fact, esRAGE was a predictor of long-term prognosis in HF, but not in ACS cohort.

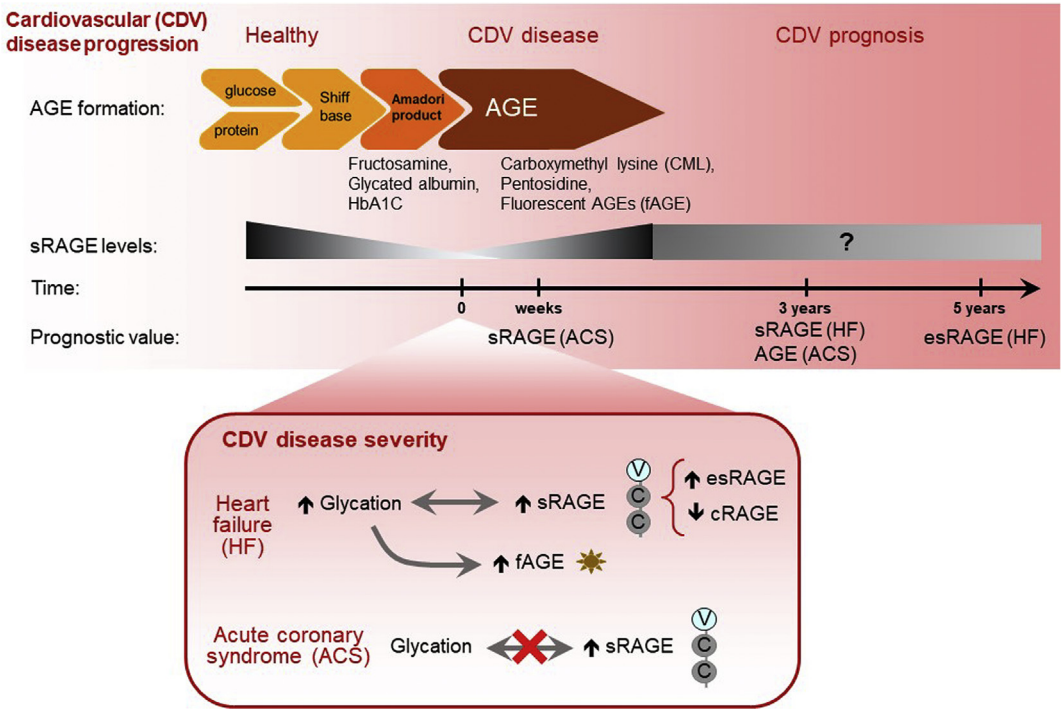

Figure 3 AGE–RAGE axis dynamics on cardiovascular disease progression. Advanced glycation end products (AGEs) are spontaneously formed from the interaction of sugars with proteins in sequential steps until the development of the disease. Soluble receptor for AGE (sRAGE) levels also change from healthy subjects to cardiovascular patients, but little is known about the levels during chronic disease. Several parameters of the axis (sRAGE and fluorescent AGE (fAGE)) are related with the severity of the disease, once developed, but differently related with glycation. They also can serve as prognostic markers of clinical outcomes in heart failure (HF) or after acute coronary syndrome (ACS), at different times.

The different roles of each soluble form of RAGE on each cardiovascular setting could help explain the absence of a significant association between AGE/sRAGE index and prognosis, at least in the conditions of our study. This index has been proposed for the identification of non-ST elevation myocardial infarction [40] or for prediction of endothelial dysfunction [41], previously.

Limitations

This is a unicentric, prospective, and observational study with the limitations inherent to this type of study design. The design of the study does not allow conclusions about the causality of AGE/RAGE axis components in HF and ACS populations. The number of patients included is small but is comparable to other studies that assessed similar objectives and outcomes, and the results are statistically significant, and therefore we believe that this issue will have future clinical relevance. Second, our study was made only in patients with HF or ACS, so the findings might be different in other cardiovascular patients. Also, we did not include the medications of the patients that could influence our results. Finally, our study was performed in ambulatory HF patients, so the extrapolation of our results to patients with acute HF would need to be supported by appropriate data collection.

Conclusions

Our results show a different role of the AGE–RAGE axis in HF and ACS. All forms of sRAGE were directly related with glycation parameters in HF, but not in ACS. The independent value of each sRAGE form on each cardiovascular disease was supported by esRAGE being an independent predictor of bad long-term prognosis only in HF, not in ACS. To properly stratify risk in the population, further studies in larger populations monitoring all the sRAGE forms are needed to correctly establish their roles in disease.

Declarations of interest

None.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.06.014.

References

[1] Lindsey JB, de Lemos JA, Cipollone F, Ayers CR, Rohatgi A, Morrow DA, et al. Association between circulating soluble receptor for advanced glycation end products (sRAGE) and atherosclerosis: observations from the Dallas heart study. Diabetes Care 2009 Jul; 32(7):1218–20.

[2] Hofmann B, Jacobs K, Navarrete Santos A, Wienke A, Silber RE, Simm A. Relationship between cardiac tissue glycation and skin autofluorescence in patients with coronary artery disease. Diabetes Metab 2015 Nov;41(5):410–5.

[3] Raposeiras-Roubin S, Rodino-Janeiro BK, Paradela-Dobarro B, Almansour H, Grigorian-Shamagian L, Reino-Maceiras MV, et al. Advanced glycation end-products as long-term predictors of death and reinfarction after an acute coronary syndrome. Biomark Med 2015 Mar;9(3):209–16.

[4] Raposeiras-Roubin S, Rodino-Janeiro BK, Paradela-Dobarro B, Grigorian-Shamagian L, Garcia-Acuna JM, Aguiar-Souto P, et al. Predictive value of advanced glycation end products for the development of post-infarction heart failure: a preliminary report. Cardiovasc Diabetol 2012 Aug 21;11(1):102.

[5] Raposeiras-Roubin S, Rodino-Janeiro BK, Grigorian-Shamagian L, Moure-Gonzalez M, Seoane-Blanco A, Varela-Roman A, et al. Relation of soluble receptor for advanced glycation end products to predict mortality in patients with chronic heart failure independently of Seattle heart failure score. Am J Cardiol 2011 Mar 15; 107(6):938–44.

[6] Raposeiras-Roubin S, Rodino-Janeiro BK, Grigorian-Shamagian L, Moure-Gonzalez M, Seoane-Blanco A, Varela-Roman A, et al. Soluble receptor of advanced glycation end products levels are related to ischaemic aetiology and extent of coronary disease in chronic heart failure patients, independent of advanced glycation end products levels: new roles for soluble RAGE. Eur J Heart Fail 2010 Oct;12(10):1092–100.

[7] Raposeiras-Roubin S, Rodino-Janeiro BK, Grigorian-Shamagian L, Seoane-Blanco A, Moure-Gonzalez M, Varela-Roman A, et al. Evidence for a role of advanced glycation end products in atrial fibrillation. Int J Cardiol 2012 Jun 6;157(3):397–402.

[8] Yan SF, Ramasamy R, Naka Y, Schmidt AM. Glycation, inflammation, and RAGE: a scaffold for the macrovascular complications of diabetes and beyond. Circ Res 2003 Dec 12;93(12):1159–69.

[9] Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation 2006 Aug 8;114(6):597–605.

[10] Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al. A soluble form of the receptor for advanced glycation endproducts (RAGE) is produced by proteolytic cleavage of the membrane-bound form by the sheddase a disintegrin and metalloprotease 10 (ADAM10). FASEB J 2008 Oct;22(10):3716–27.

[11] Santilli F, Vazzana N, Bucciarelli LG, Davi G. Soluble forms of RAGE in human diseases: clinical and therapeutical implications. Curr Med Chem 2009;16(8):940–52.

[12] Geroldi D, Falcone C, Emanuele E. Soluble receptor for advanced glycation end products: from disease marker to potential therapeutic target. Curr Med Chem 2006;13(17):1971–8.

[13] Basta G, Del Turco S, Marchi F, Navarra T, Battaglia D, Mercuri A, et al. Elevated soluble receptor for advanced glycation end product levels in patients with acute coronary syndrome and positive cardiac troponin I. Coron Artery Dis 2011 Dec;22(8):590–4.

[14] Koyama Y, Takeishi Y, Niizeki T, Suzuki S, Kitahara T, Sasaki T, et al. Soluble Receptor for advanced glycation end products (RAGE) is a prognostic factor for heart failure. J Card Fail 2008 Mar;14(2): 133–9.

[15] Raposeiras-Roubin S, Rodino-Janeiro BK, Paradela-Dobarro B, Grigorian-Shamagian L, Garcia-Acuna JM, Aguiar-Souto P, et al. Fluorescent advanced glycation end products and their soluble receptor: the birth of new plasmatic biomarkers for risk stratification of acute coronary syndrome. PLoS One 2013;8(9):e74302.

[16] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016 Jul 14;37(27):2129–200.

[17] Diagnosis and classification of diabetes mellitus. Diabetes Care 2010 Jan;33(Suppl. 1):S62–9.

[18] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr 2015 Jan;28(1):1–39.

[19] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006 Aug 15;145(4):247–54.

[20] Hartog JW, Voors AA, Bakker SJ, Smit AJ, van Veldhuisen DJ. Advanced glycation end-products (AGEs) and heart failure: pathophysiology and clinical implications. Eur J Heart Fail 2007 Dec; 9(12):1146–55.

[21] Dozio E, Briganti S, Delnevo A, Vianello E, Ermetici F, Secchi F, et al. Relationship between soluble receptor for advanced glycation end products (sRAGE), body composition and fat distribution in healthy women. Eur J Nutr 2016 Aug 13.

[22] Paradela-Dobarro B, Fernandez-Trasancos A, Bou-Teen D, Eiras S, Gonzalez-Ferreiro R, Agra RM, et al. Evolution and bad prognostic value of advanced glycation end products after acute heart failure: relation with body composition. Cardiovasc Diabetol 2017 Sep 15; 16(1):115.

[23] Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013 Oct;34(39):3035–87.

[24] Colhoun HM, Betteridge DJ, Durrington P, Hitman G, Neil A, Livingstone S, et al. Total soluble and endogenous secretory receptor for advanced glycation endproducts as predictive biomarkers of coronary heart disease risk in patients with type 2 diabetes: an analysis from the CARDS trial. Diabetes 2011 Jul 19.

[25] Zieman S, Kass D. Advanced glycation end product cross-linking: pathophysiologic role and therapeutic target in cardiovascular disease. Congest Heart Fail 2004 May-Jun;10(3):144–9. quiz 50-1.

[26] Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. J Hypertens 2003 Jan;21(1):3–12.

[27] Wang LJ, Lu L, Zhang FR, Chen QJ, De Caterina R, Shen WF. Increased serum high-mobility group box-1 and cleaved receptor for advanced glycation endproducts levels and decreased endogenous secretory receptor for advanced glycation endproducts levels in diabetic and non-diabetic patients with heart failure. Eur J Heart Fail 2011 Apr;13(4):440–9.

[28] Falcone C, Emanuele E, D'Angelo A, Buzzi MP, Belvito C, Cuccia M, et al. Plasma levels of soluble receptor for advanced glycation end products and coronary artery disease in nondiabetic men. Arterioscler Thromb Vasc Biol 2005 May;25(5):1032–7.

[29] Geroldi D, Falcone C, Emanuele E, D'Angelo A, Calcagnino M, Buzzi MP, et al. Decreased plasma levels of soluble receptor for advanced glycation end-products in patients with essential hypertension. J Hypertens 2005 Sep;23(9):1725–9.

[30] McNair ED, Wells CR, Qureshi AM, Pearce C, Caspar-Bell G, Prasad K. Inverse association between cardiac troponin-I and soluble receptor for advanced glycation end products in patients with non-ST-segment elevation myocardial infarction. Int J Angiol 2011 Mar;20(1):49–54.

[31] Mahajan N, Malik N, Bahl A, Dhawan V. Receptor for advanced glycation end products (RAGE) and its inflammatory ligand EN-RAGE in non-diabetic subjects with pre-mature coronary artery disease. Atherosclerosis 2009 Jun 11;207(2):597–602.

[32] Ramasamy R, Schmidt AM. Receptor for advanced glycation end products (RAGE) and implications for the pathophysiology of heart failure. Curr Heart Fail Rep 2012 Jun;9(2):107–16.

[33] Lazo M, Halushka MK, Shen L, Maruthur N, Rebholz CM, Rawlings AM, et al. Soluble receptor for advanced glycation end products and the risk for incident heart failure: the Atherosclerosis Risk in Communities Study. Am Heart J 2015 Nov;170(5):961–7.

[34] Santilli F, Bucciarelli L, Noto D, Cefalu AB, Davi V, Ferrante E, et al. Decreased plasma soluble RAGE in patients with

hypercholesterolemia: effects of statins. Free Radic Biol Med 2007 Nov 1;43(9):1255–62.
[35] Wittkowski H, Hirono K, Ichida F, Vogl T, Ye F, Yanlin X, et al. Acute Kawasaki disease is associated with reverse regulation of soluble receptor for advance glycation end products and its proinflammatory ligand S100A12. Arthritis Rheum 2007 Dec;56(12):4174–81.
[36] Selvin E, Halushka MK, Rawlings AM, Hoogeveen RC, Ballantyne CM, Coresh J, et al. sRAGE and risk of diabetes, cardiovascular disease, and death. Diabetes 2013 Jun;62(6):2116–21.
[37] Marsh AM, Nguyen AH, Parker TM, Agrawal DK. Clinical use of high mobility group box 1 and the receptor for advanced glycation end products in the prognosis and risk stratification of heart failure: a literature review. Can J Physiol Pharmacol 2017 Mar;95(3):253–9.
[38] Park HJ, Baek JY, Shin WS, Kim DB, Jang SW, Shin DI, et al. Soluble receptor of advanced glycated endproducts is associated with plaque vulnerability in patients with acute myocardial infarction. Circ J 2011;75(7):1685–90.
[39] Jensen LJ, Lindberg S, Hoffmann S, Iversen AZ, Pedersen SH, Mogelvang R, et al. Dynamic changes in sRAGE levels and relationship with cardiac function in STEMI patients. Clin Biochem 2015 Mar;48(4–5):297–301.
[40] McNair ED, Wells CR, Qureshi AM, Basran RS, Pearce C, Orvold J, et al. Low levels of soluble receptor for advanced glycation end products in non-ST elevation myocardial infarction patients. Int J Angiol 2009 Winter;18(4):187–92.
[41] Kajikawa M, Nakashima A, Fujimura N, Maruhashi T, Iwamoto Y, Iwamoto A, et al. Ratio of serum levels of AGEs to soluble form of RAGE is a predictor of endothelial function. Diabetes Care 2015 Jan;38(1):119–25.