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ORIGINAL RESEARCH

Association of Systemic Vascular Resistance Analog and Cardiovascular Outcomes: The Heart and Soul Study

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BACKGROUND: Systemic vascular resistance (SVR) is an integral component of the hemodynamic profile. Previous studies have demonstrated a close correlation between an estimated SVR analog (eSVR) based on echocardiographic methods and SVR by direct hemodynamic measurement. However, the prognostic impact of eSVR remains unestablished.

METHODS AND RESULTS: Study participants with established coronary artery disease from the Heart and Soul Study formed this study cohort. We defined Doppler-derived eSVR as the ratio of systolic blood pressure to left ventricular outflow tract velocity time integral. Study participants were separated based on baseline eSVR tertile: <5.6, 5.6 to <6.9, and ≥6.9. An elevated eSVR was defined as an eSVR in the third tertile (≥6.9). Follow-up eSVR was calculated at the fifth year of checkup. Cardiovascular outcomes included heart failure, major cardiovascular events, and all-cause death. Among the 984 participants (67±11 years old, 82% men), subjects with the highest baseline eSVR tertile were the oldest, with the highest systolic blood pressure and lowest left ventricular outflow tract velocity time integral. A higher eSVR was associated with increased risk of heart failure, major cardiovascular events, and death. The hazard ratio for major cardiovascular events was 1.38 (95% CI, 1.02–1.86, *P*=0.03) for subjects with the highest eSVR tertile compared with the lowest. In addition, those with a persistently elevated eSVR during follow-up had the most adverse outcomes.

CONCLUSIONS: An elevated eSVR, derived by the ratio of systolic blood pressure and left ventricular outflow tract velocity time integral, was more closely correlated with cardiovascular events than systolic blood pressure alone. Repeatedly elevated eSVR was associated with more adverse outcomes.

Key Words: blood pressure ■ child ■ CIs ■ coronary artery disease ■ follow-up studies ■ humans ■ male sex ■ prognosis

Coronary heart disease (CHD) is a primary target for therapeutic intervention and secondary prevention.[1] Identifying those at higher risk for cardiovascular events focuses treatments and preventive measures. It is known that systemic vascular resistance (SVR) mediated by vascular reactivity affects left ventricular (LV) function through the imposition of elevated afterload.[2] Studies have shown SVR as a modulator in the management of patients with type 2 diabetes[3] and congestive heart failure.[4] As such, measurement of SVR is important in defining the workload of the heart and guiding therapeutics.

Obtaining SVR requires an invasive procedure, limiting its clinical utility. Studies have proposed noninvasive measurements of SVR using LV chamber quantification[5] or Doppler echocardiography.[6] However, the prognostic impact of a noninvasively estimated SVR analog (eSVR) is unknown. In this study, we investigated the association of eSVR with adverse cardiovascular events in an ambulatory population

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CLINICAL PERSPECTIVE

What Is New?

- A noninvasively estimated systemic vascular resistance analog (eSVR) can be obtained by Doppler echocardiography from the ratio of systemic blood pressure to left ventricular outflow tract velocity-time interval.
- Elevated eSVR is associated with adverse cardiovascular outcomes, even among those with normal blood pressure; persistently elevated eSVR is associated with worse outcomes.

What Are the Clinical Implications?

- Elevated eSVR, derived by the ratio of systemic blood pressure and left ventricular outflow tract velocity-time interval, was associated with adverse cardiovascular outcomes. eSVR is a rapidly obtained bedside parameter using point-of-care ultrasound.
- Elevated eSVR may be a clinically useful marker of future adverse cardiovascular events in coronary artery disease and guide categorization and management of hypertension.

Nonstandard Abbreviations and Acronyms

eSVR	estimated systemic vascular resistance
LVOT-VTI	left ventricular outflow tract velocity time integral
MACE	major cardiovascular events

with CHD and measured the impact of serial improvement of eSVR on outcomes.

METHODS

Study Participants

The Heart and Soul Study is a prospective cohort study of psychosocial factors and health outcomes in subjects with CHD, and the data from the Heart and Soul Study that support the findings of this current study are available from the corresponding author on reasonable request. Subjects were invited to participate from 2000 to 2002 if they had known CHD documented by history, noninvasive stress imaging, or invasive coronary angiography, and were recruited from 2 Veterans Affairs Medical Centers (San Francisco VA Medical Center and the VA Palo Alto Health Care System, California), 1 university medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network of San Francisco. All study activities were conducted at the San Francisco VA. Detailed study design has been described previously.[7] In brief, participants were enrolled if they met at least 1 of the following criteria: (1) history of myocardial infarction, (2) the presence of at least 50% stenosis in ≥1 coronary artery on angiography, (3) evidence of inducible ischemia by stress testing, or (4) history of coronary revascularization. Subjects were excluded if they were unable to walk 1 block, were within 6 months of an acute coronary syndrome, or were planning to move out of the local area within 2 years. A self-reported questionnaire was used to determine age, sex, race, and medical history.[8] Height and weight were measured, leading to the calculation of body mass index (kg/m^2) and body surface area (m^2). Study participants provided written informed consent for baseline echocardiography and review of their medical records. The study protocol was approved by the institutional review board at each enrolling center. At least 10 years of cardiovascular event outcomes were adjudicated for 90% of study participants, and mortality data are still being updated annually. We vouch for the comprehensiveness and completeness of these well-maintained outcome data.

Between September 2000 and December 2002, a total of 1024 subjects were enrolled. Of these subjects, 40 were excluded because systolic blood pressure (SBP) or LV outflow tract velocity time integral (LVOT-VTI) measurement was unavailable. The remaining 984 participants were included in this analysis.

Echocardiography

Standard 2-dimensional and Doppler transthoracic echocardiography were performed using a commercially available ultrasound system (Acuson Sequoia; Siemens Medical Solutions, Mountain View, CA). Left atrial volumes, LV volumes, and LV ejection fraction were measured using the biplane method of disks from standard apical 2- and 4-chamber views.[9] Doppler measurements included peak mitral regurgitation velocity (mitral regurgitation [MR] Vmax), LVOT-VTI, and early diastolic (E) and late diastolic (A) wave of mitral inflow. LVOT-VTI was obtained from the apical 3- or 5-chamber view using pulsed wave Doppler, with the cursor placed 0.5 cm apical the aortic valve. In participants with atrial fibrillation, 5 consecutive beats were recorded and used to calculate an average. All images were interpreted and verified by the principal investigator (NBS) who was blinded to clinical information.

Definition of eSVR

We defined eSVR as the ratio of SBP to LVOT-VTI (Figure 1). A baseline eSVR was obtained at the first echocardiographic examination, and a follow-up eSVR

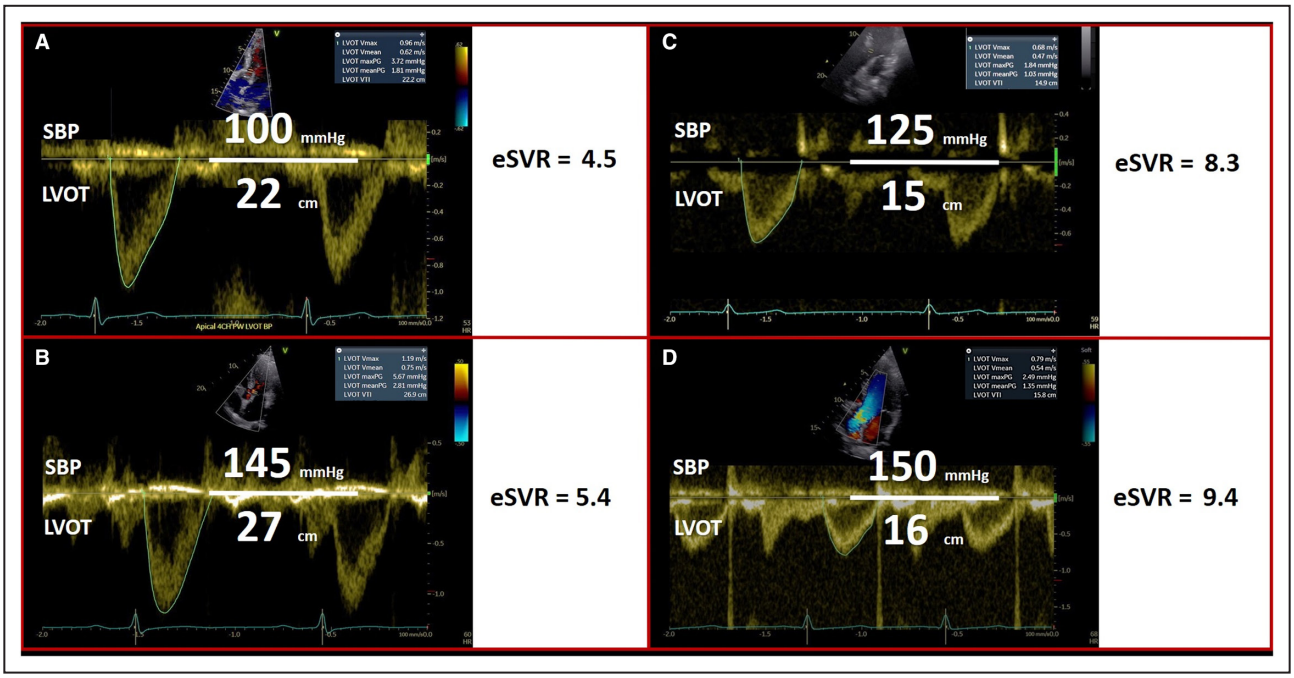

Figure 1. Representative images of noninvasive systemic vascular resistance (eSVR) calculation from patients with various combinations of systolic blood pressure (SBP) and left ventricular outflow tract velocity time integral (LVOT-VTI).
(A) Subjects with a normal SBP, a normal LVOT-VTI, and a nonelevated eSVR. (B) subjects with an elevated BP, an elevated LVOT-VTI, and an nonelevated eSVR. (C) subjects with a normal BP, a reduced LVOT-VTI, and an elevated eSVR. (D) subjects with an elevated BP, a reduced LVOT-VTI, and an elevated eSVR.

was obtained at the end of the fifth year after enrollment. Subjects were divided into tertiles based on the baseline eSVR. An elevated eSVR was defined as an eSVR in the third tertile (≧6.9).

Blood pressure parameters were carefully measured in close temporal proximity with echocardiographic exam using an automated sphygmomanometer. Study participants rested in the supine position for at least 5 minutes before the 2 determinations were obtained and the lowest recorded.[10]

Outcomes

We defined 3 outcomes in this study: (1) heart failure (HF) including HF hospitalizations; (2) major adverse cardiovascular events (MACE) consisting of HF hospitalizations, myocardial infarction, stroke, and death from cardiovascular diseases; and (3) all-cause death.[11] Hospitalization for HF was defined as a clinical syndrome requiring a minimum 1-night hospital stay with the presence of 2 of the following: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, a third heart sound, cardiomegaly on chest radiograph, or pulmonary edema on chest radiograph.[12] Cardiovascular death was defined as death due to myocardial infarction, ventricular failure with progressive symptomatic deterioration, stroke, vascular causes, or cardiovascular procedure related. Annual telephone follow-up interviews with subjects or their proxies regarding recent emergency department visits, hospitalizations, or death were conducted. For any reported event, medical records, death certificates, and coroner's reports were retrieved. Participants were considered as having MACE outcome upon the first occurrence of any event of HF hospitalizations, myocardial infarction, stroke, and death from cardiovascular diseases. Mortality adjudications were based on hospital records, death certificates, and autopsy results. Time to event was defined as the time span from enrollment until any of the defining events. Patients were censored if they dropped out or if they remained event free for 10 years at the administrative close date, February 1, 2012.

Laboratory

We measured serum N-terminal pro-B-type natriuretic peptide, C-reactive protein, high-density lipoprotein, low-density lipoprotein, and creatinine from fasting blood samples drawn at the initial visit. Estimated glomerular filtration rate was determined by the combined creatinine-cystatin C equation.[13]

Statistical Analysis

Subjects were divided into tertiles by eSVR for comparative analysis. Continuous variables were presented as mean±SD or median (25th–75th percentile) if nonnormally distributed. Categorical variables were presented

as the total number and percentage. Differences in baseline characteristics among tertiles were determined using ANOVA for continuous variables if normally distributed or Kruskal-Wallis test if nonnormally distributed. Chi-square tests were performed for categorical variables. We used Kaplan–Meier analysis to examine cumulative event-free survival for HF, MACE, and all-cause death stratified by baseline eSVR, and significance was based on results of the log-rank test. Cox proportional-hazard models were developed to evaluate the independent association of eSVR with each outcome. To further examine the risk profile of serial changes of eSVR between the baseline and at the fifth year, eSVR and other covariates were treated as time-dependent variables in the extended Kaplan–Meier analysis and Cox model. Cubic spline regression analysis was used to evaluate the nonlinear relationship. Nonnormally distributed variables, including pro-B-type natriuretic peptide and C-reactive protein level, were log-transformed to fit in the models. Among the variables examined in this study, 8 of them had 1% to 3% missing data. Five percent of data were missing for ratio of early diastolic mitral flow velocity/late diastolic mitral flow velocity, and 19% for pulmonary artery systolic pressure. Missing values were handled with multiple imputation by chained equations with a separate conditional distribution for each imputed variable. A P value <0.05 was considered statistically significant. All analyses were performed using Stata/IC 13 (StataCorp LP, College Station, Texas) and R survival package.

RESULTS

Baseline Characteristics

The mean age of the study cohort was 67±11 years, with 82% men. The average eSVR was 6.4±1.6 for the entire cohort (median 6.2, 25th–75th percentile 5.3–7.3) (Figure S1). The study participants were divided into tertiles by eSVR, and the range of eSVR in each subgroup was <5.6, 5.6 to <6.9, and ≧ 6.9, respectively. Baseline characteristics of the participants were listed in Table 1. Subjects with the highest eSVR tertile had highest SBP and lowest LVOT-VTI. They were older and more likely to have history of hypertension. They also had the largest LV volume, LV mass, but the lowest LV ejection fraction.

Prognostic Impact of Baseline eSVR

The Heart and Soul Study had an attrition rate of 9.6% at the eighth year of follow-up. The cumulative risk of MACE increased with the increase of SBP as well as eSVR (Figure S2). Subjects with the highest eSVR tertile had the highest risk of adverse cardiovascular events, including HF, MACE, and all-cause death. (Figure 2). Conversely, subjects with the lowest eSVR tertile were associated with the best outcomes in HF and MACE.

The event rate of MACE from the first to third tertile was 35, 55, and 84 per 1000 person-years (P<0.001). In multivariate analyses, subjects with the highest tertile had a hazard ratio (HR) of 1.38 for MACE (95% CI, 1.02–1.86, P=0.03) compared with the lowest tertile. When the eSVR was treated as a continuous variable, the HRs for HF and MACE remained significant (Table 2). Additional sensitivity analysis was performed after participants with history of revascularization were excluded. Limited by fewer events in the remaining 407 subjects, an elevated eSVR (tertile III) was predictive of MACE after adjusted for conventional Framingham risk factors (Table S1, Model 1) but was insignificant in the fully adjusted model.

The increment of eSVR was associated with a dose–response increase of MACE, whereas the increment of SBP or LVOT-VTI was not (Figure 3A through C). In the subgroup analysis, subjects with an elevated eSVR were consistently associated with higher risks for MACE compared with those with an eSVR <6.9 among subgroups based on age, sex, race, baseline SBP<or≥140 mm Hg, LV ejection fraction <or≥55%, or presence of LV hypertrophy (Figure 4, P<0.05 for each subgroup comparison).

Changes of eSVR and Clinical Outcomes

The baseline eSVR in combination with the change of eSVR during follow-up provided incremental prognostic information. A repeatedly elevated eSVR ≧6.9 was associated with a higher risk of MACE (Figure 5). The trend remained significant after adjusting for Framingham risk factors (Table S2, Model 2). Subjects who had a persistently elevated eSVR ≧6.9 also had a higher risk of all-cause death after additional adjustment of laboratory parameters, medications, and echocardiographic parameters (Table S2, Model 4).

DISCUSSION

This study demonstrates the prognostic value of noninvasively estimated SVR in subjects with CHD. The ratio of SBP to LVOT-VTI, eSVR, provided more robust risk estimation than SBP alone. An elevated eSVR was associated with higher risk of adverse outcomes, including HF, MACE, and all-cause death. The risk trend of elevated eSVR was consistent, irrespective of age, sex, race, blood pressure, and previous history of HF or diabetes. Furthermore, a persistently elevated eSVR was also associated with a higher risk of adverse events.

Vascular resistance is a factor in maintaining organ perfusion, and the regulation of peripheral vascular resistance occurs at the arteriolar level.[14,15] Maintenance

Table 1. Baseline and Echocardiographic Characteristics of Participants Stratified by Tertile of eSVR

	Overall n=984	eSVR tertile I (<5.6) n=330	eSVR tertile II (≥5.6 to <6.9) n=327	eSVR tertile III (≥6.9) n=327	*P* value
Systolic blood pressure, mm Hg	130 (120, 144)	120 (110, 132)	130 (120, 142)	140 (130, 154)	<0.001
Mean arterial pressure, mm Hg	93 (85, 101)	87 (79, 94)	94 (87, 101)	100 (93, 109)	<0.001
Diastolic blood pressure, mm Hg	75 (68, 80)	70 (62, 78)	75 (69, 80)	80 (70, 86)	<0.001
Heart rate, bpm	68±12	65±11	68±11	71±13	<0.001
LV outflow tract velocity-time integral, cm	21 (18, 24)	25 (23, 28)	21 (19, 23)	18 (16, 19)	<0.001
Demographics					
Age, y	67±11	66±10	66±11	68±11	0.04
Male sex	804 (82)	249 (75)	268 (82)	287 (88)	<0.001
Body mass index, kg/m^2	28.4±5.3	28.7±4.8	28.2±5.4	28.2±5.6	0.41
Race					0.22
White	589 (60)	206 (62)	194 (60)	189 (57)	
Black	163 (17)	45 (14)	52 (16)	66 (20)	
Asian	112 (11)	31 (9)	40 (12)	41 (12)	
Others	120 (12)	48 (15)	40 (12)	32 (10)	
Medical history					
Hypertension	694 (71)	221 (67)	225 (69)	248 (76)	0.04
Diabetes	257 (26)	78 (24)	82 (25)	97 (30)	0.19
Heart failure	172 (18)	53 (16)	51 (16)	68 (21)	0.16
Stroke	142 (14)	47 (14)	43 (13)	52 (16)	0.61
Myocardial infarction	531 (54)	165 (51)	190 (58)	176 (54)	0.13
Revascularization*	578 (59)	185 (56)	198 (61)	195 (59)	0.41
Current smoking	194 (20)	64 (19)	61 (19)	69 (21)	0.76
Laboratory					
Estimated glomerular filtration rate, mL/min per 1.73 m^2	71±22	74±21	72±22	66±23	<0.001
Total cholesterol, mg/dL	172 (149–199)	170 (146–199)	169 (151–192)	177 (150–204)	0.10
Low-density lipoprotein, mg/dL	99 (82–122)	97 (80–124)	98 (151–192)	101 (84–128)	0.18
High-density lipoprotein, mg/dL	43 (36–54)	44 (35–53)	43 (37–52)	43 (35–54)	0.96
N-terminal pro-B-type natriuretic peptide, pg/mL	176 (74–454)	134 (69–295)	157 (58–386)	261 (107–714)	<0.001
C-reactive protein, μg/mL	3.4 (1.6–8.8)	2.9 (1.5–7.0)	3.5 (1.7–9.2)	3.9 (1.9–10.0)	0.01
Medication					
ACEI or ARB	504 (52)	154 (48)	167 (51)	183 (57)	0.07
Beta blocker	568 (58)	198 (61)	183 (56)	187 (58)	0.45
Calcium channel blocker	237 (24)	85 (26)	79 (24)	73 (22)	0.58
Diuretics	312 (32)	99 (30)	93 (28)	120 (37)	0.06
Number of blood pressure medications†	1.6±1.1	1.6±1.1	1.6±1.1	1.7±1.1	0.24
Statin	629 (65)	212 (65)	217 (67)	200 (62)	0.41
Aspirin	713 (73)	254 (78)	238 (73)	221 (68)	0.02
Echocardiography					
Left atrial end-systolic volume index, mL/m^2	33±12	33±10	33±11	34±15	0.47
Ratio of early diastolic mitral flow velocity/late diastolic mitral flow velocity	1.1±0.5	1.1±0.4	1.1±0.5	1.0±0.5	0.02
Pulmonary arterial systolic pressure, mm Hg	32±9	32±9	32±10	33±10	0.58
LV end-diastolic volume index, mL/m^2	52±18	50±16	52±18	55±20	<0.001
LV end-systolic volume index, mL/m^2	21±13	18±10	21±13	24±16	<0.001
LV ejection fraction, %	62±10	65±8	62±9	59±11	<0.001
LV mass index, g/m^2	100±34	97±44	97±25	105±30	0.001

Values are shown as mean±SD, median (25th–75th percentile), or n (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eSVR, noninvasive systemic vascular resistance; and LV, left ventricular.

*Surgical or percutaneous revascularization.

†Including ACEI or ARB, beta blocker, calcium channel blocker, and diuretics.

Others indicate participants who were not nonHispanic White, Black, or Asian.

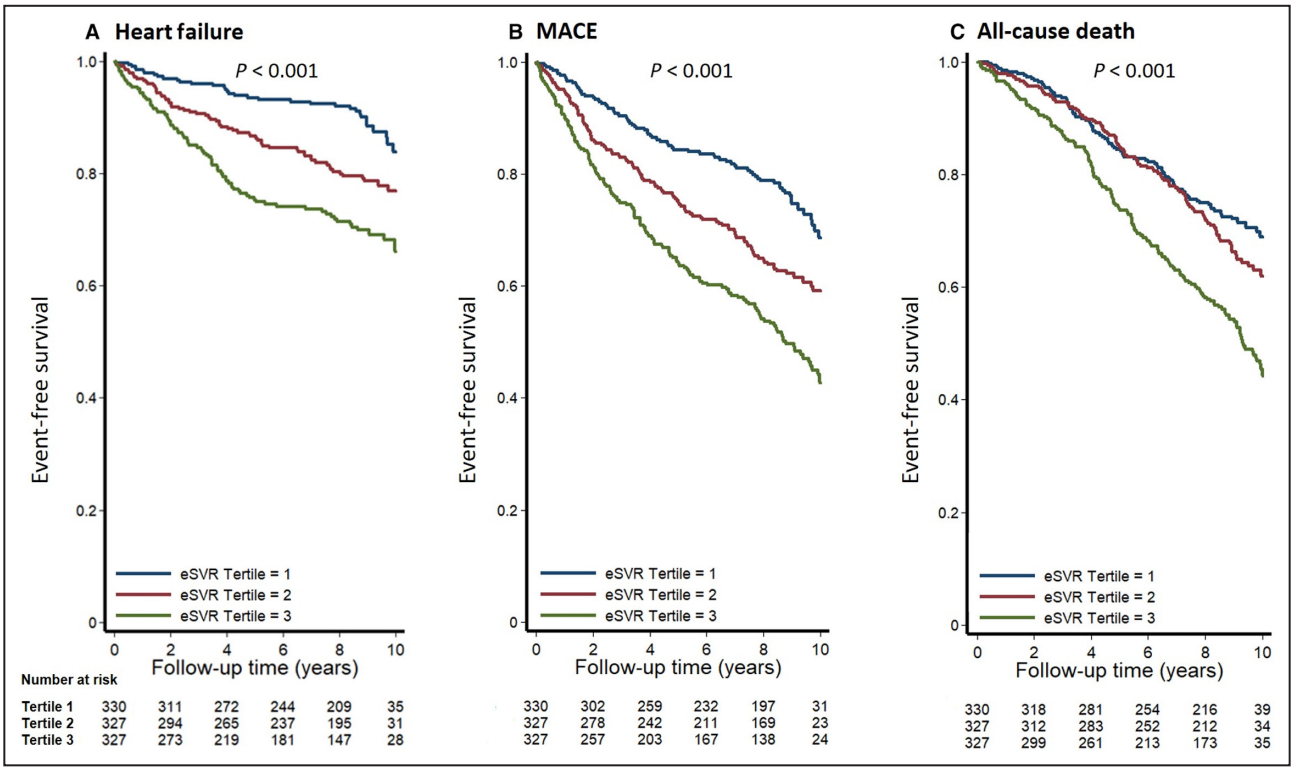

Figure 2. Kaplan–Meier curves of (A) heart failure hospitalization, (B) major cardiovascular events (MACE), and (C) all-cause death, stratified by tertiles of the noninvasive systemic vascular resistance (eSVR).

of normal blood pressure is dependent on the balance between cardiac output and peripheral vascular resistance. Prolonged constriction of arterioles is thought to induce structural thickening of the arteriolar walls possibly mediated by angiotensin, leading to an irreversible rise in peripheral resistance.[16] Studies have shown a detrimental impact of increased SVR on cardiovascular risk. Systemic vascular resistance predicts the eventual onset of hypertension in young adults.[17] Increased peripheral resistance is also a feature of chronic heart failure, where it serves as a compensatory mechanism to maintain organ perfusion as stroke volume declines.[18] Fagard et al. demonstrated that exercise SVR added prognostic information about cardiovascular events and total mortality.[19] In line with previous studies, our study indicates that noninvasively estimated eSVR is associated with cardiovascular end points: heart failure admission, MACE, and all-cause death.

SBP was initially chosen as the basis for arterial resistance analog because our previous study documented the correlation of the ratio of peak mitral regurgitation velocity to LVOT-VTI as an accurate means calculating invasive SVR.[6] Peak MR jets are closely correlated with SBP (r=0.43, P<0.001), but technically adequate peak MR jets are available in only a small percentage of studies. Therefore, we used SBP as a logical substitute for peak MR. Conventionally, SVR is defined as the ratio of mean arterial pressure (MAP) and cardiac output. In comparing eSVR from SBP to eSVR from MAP, we found that SBP-derived eSVR was as predictive of outcome as MAP-derived eSVR (Table S3). SBP-derived eSVR is more advantageous than MAP-derived eSVR in that it is easier to calculate. Clinicians do not need to take an extra step to calculate the MAP beforehand.

Another unique feature of our equation is to substitute LVOT-VTI for cardiac output. We have previously demonstrated that LVOT-VTI is independent of body surface area whereas LVOT diameter is not.[20] This observation is particularly important because stroke volume and cardiac output do vary with body size, and the dependence of stroke volume on body size is mandated by the LVOT diameter/cross-sectional area. The fact that LVOT-VTI is not correlated to body size makes it an independent indicator of LV performance that exists in a narrow range, irrespective of allometric consideration.

Hypertension is conventionally defined as an elevation of blood pressure, however, it is actually characterized by abnormalities of cardiac output, SVR, and arterial compliance.[21] Among the normotensive subjects, those with an elevated eSVR had a higher risk of MACE than their relatively normal eSVR counterparts. Their risk was also higher than those who had high blood pressure but a normal eSVR (Figure 4). This observation suggests that among patients with preserved

Table 2. Association of eSVR Tertile With Clinical Outcomes

	eSVR tertile I	eSVR tertile II		eSVR tertile III		eSVR per unit	
	(Reference)	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Heart failure hospitalization							
Event rate (per 1000 person-y)	15 (11–20)	28 (22–36)		43 (35–53)		28 (25–32)	
Unadjusted HR	Reference	1.91 (1.28–2.85)	0.002	2.88 (1.96–4.23)	<0.001	1.36 (1.26–1.48)	<0.001
Model 1	Reference	1.94 (1.29–2.91)	0.002	2.56 (1.71–3.84)	<0.001	1.33 (1.22–1.44)	<0.001
Model 2	Reference	1.64 (1.08–2.50)	0.02	1.47 (0.96–2.27)	0.08	1.12 (1.02–1.23)	0.02
Model 3	Reference	1.58 (1.03–2.41)	0.03	1.40 (0.91–2.17)	0.13	1.11 (1.01–1.23)	0.03
Model 4	Reference	1.48 (0.97–2.25)	0.07	1.31 (0.85–2.04)	0.22	1.11 (1.00–1.22)	0.05
Major cardiovascular event (including heart failure hospitalization, myocardial infarction, stroke, and death from cardiovascular diseases)							
Event rate (per 1000 person-y)	35 (28–43)	55 (46–66)		84 (72–98)		57 (52–63)	
Unadjusted HR	Reference	1.58 (1.20–2.09)	0.001	2.39 (1.83–3.11)	<0.001	1.28 (1.20–1.36)	<0.001
Model 1	Reference	1.53 (1.15–2.03)	0.003	2.06 (1.56–2.72)	<0.001	1.24 (1.16–1.32)	<0.001
Model 2	Reference	1.38 (1.04–1.85)	0.03	1.48 (1.10–1.98)	0.009	1.11 (1.04–1.19)	0.003
Model 3	Reference	1.36 (1.02–1.82)	0.04	1.42 (1.06–1.91)	0.02	1.10 (1.03–1.18)	0.008
Model 4	Reference	1.34 (1.00–1.80)	0.05	1.38 (1.02–1.86)	0.03	1.09 (1.01–1.17)	0.02
All-cause death							
Event rate (per 1000 person-y)	39 (31–47)	47 (39–56)		73 (63–85)		53 (47–58)	
Unadjusted HR	Reference	1.22 (0.94–1.60)	0.13	1.94 (1.51–2.48)	<0.001	1.22 (1.15–1.29)	<0.001
Model 1	Reference	1.14 (0.87–1.50)	0.34	1.57 (1.21–2.04)	<0.001	1.15 (1.08–1.23)	<0.001
Model 2	Reference	1.01 (0.76–1.33)	0.97	1.19 (0.91–1.57)	0.20	1.07 (1.00–1.14)	0.06
Model 3	Reference	1.00 (0.76–1.33)	0.99	1.15 (0.87–1.52)	0.32	1.05 (0.98–1.13)	0.14
Model 4	Reference	1.00 (0.75–1.32)	0.97	1.13 (0.85–1.49)	0.40	1.05 (0.97–1.12)	0.21

Model 1: Adjusted for Framingham risk factors (age, sex, ethnicity, smoking, hypertension, diabetes, high-density lipoprotein/total cholesterol ratio) and heart rate.

Model 2: Model 1+medical history (heart failure, revascularization)+laboratory (estimated glomerular filtration rate, low-density lipoprotein, C-reactive protein, N-terminal pro-B-type natriuretic peptide).

Model 3: Model 2+medications (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, aspirin, statin).

Model 4: Model 3+echocardiography (left atrial end-systolic volume index, left ventricular end-systolic volume index, left ventricular ejection fraction, left ventricular mass index). eSVR indicates noninvasive systemic vascular resistance; and HR, hazard ratio.

systolic function, resistance reduction might be more important than BP reduction for the prevention of adverse cardiovascular outcomes.

Furthermore, we observed that repeatedly elevated vascular resistance was associated with worse cardiovascular outcomes. In clinical practice, there are various classifications of antihypertensive medications. Thiazide diuretics, calcium-channel blockers, and angiotensin-converting enzyme inhibitors are all recommended as Class I indication for blood pressure control.[22] Based on our observation, however, arteriole vasodilators may provide greater benefit than thiazide diuretics in reducing arterial resistance and augmenting forward stroke volume. In the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living With Systolic Hypertension) trial, the reduction in BP from baseline was similar between the benazepril-amlodipine arm and the benazepril-hydrochlorothiazide arm among high-risk patients with hypertension over the course of the trial, but the benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events.[23] This findings raise the concern that not every class of antihypertensive agents is equally protective. Our study illuminates a possible mechanism of cardiovascular benefits provided by arteriole vasodilators beyond their blood pressure lowering effects. If supported by subsequent research, management of blood pressure might include consideration of resistance, which carries the promise of decreasing both over- and undertreatment.

Limitations

Our results should be interpreted with caution in view of limitations. A direct correlation between the noninvasive eSVR derived from SBP and the invasively measured SVR has not been tested. However, the close correlation between SBP and peak MR makes it likely that a strong correlation exists. Despite this limitation,

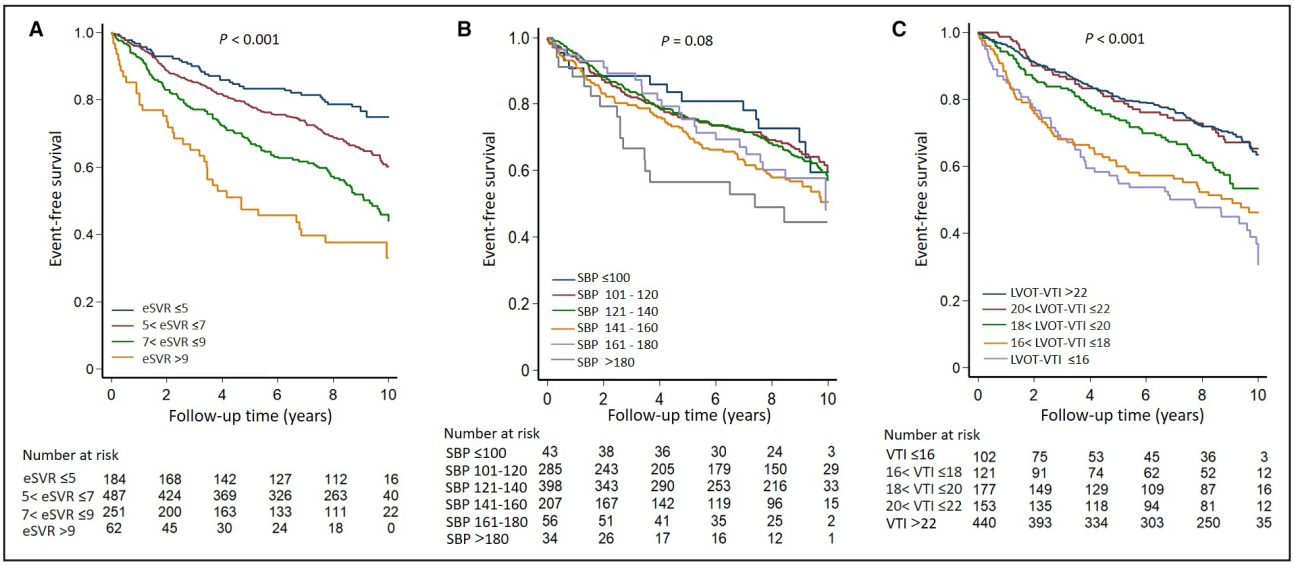

Figure 3. Kaplan–Meier curves of major cardiovascular events (MACE) stratified by (A) noninvasive systemic vascular resistance (eSVR), (B) systolic blood pressure (SBP), and (C) left ventricular outflow tract velocity time integral (LVOT-VTI).
The event-free survival of MACE decreased with every 2-unit increase of eSVR. On the contrary, the event-free survival curves did not show a stepwise change for every 20-mm Hg increment of SBP or every 2-cm decrease of LVOT-VTI.

our goal to augment the predictive value of clinically measured BP has been realized by demonstrating that the eSVR vascular resistance analog improves the prognostic power of clinically measured BP. Second, participants in the Heart and Soul Study were mainly men with stable CHD, so our results might not be generalizable to women or subjects without CHD. Third, the variation of eSVR during follow-up may be influenced by BP control, duration of hypertension, cardiac remodeling, or previous therapeutic intervention, all of

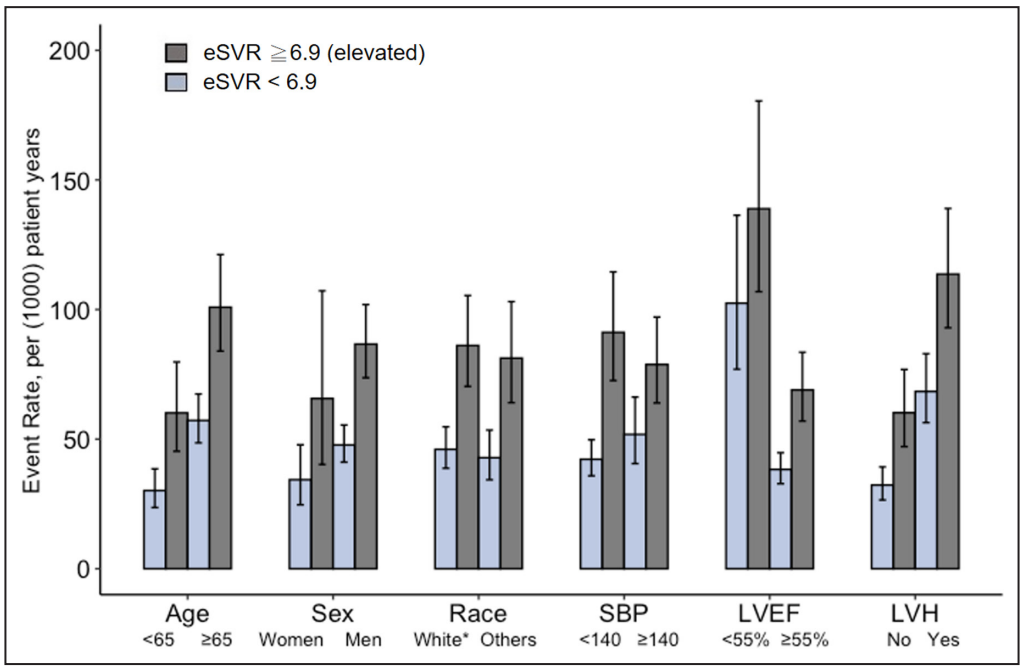

Figure 4. Event rate of major cardiovascular events (MACE) in study subjects stratified by age, sex, race, systolic blood pressure (SBP), left ventricular ejection fraction (LVEF), or left ventricular hypertrophy (LVH).
Subjects with an elevated noninvasive systemic vascular resistance (eSVR) had a higher event rate of MACE compared with their counterparts with an eSVR <6.9 in each subgroup (P<0.05 for each subgroup comparison). Others indicate participants who were not nonHispanic White.

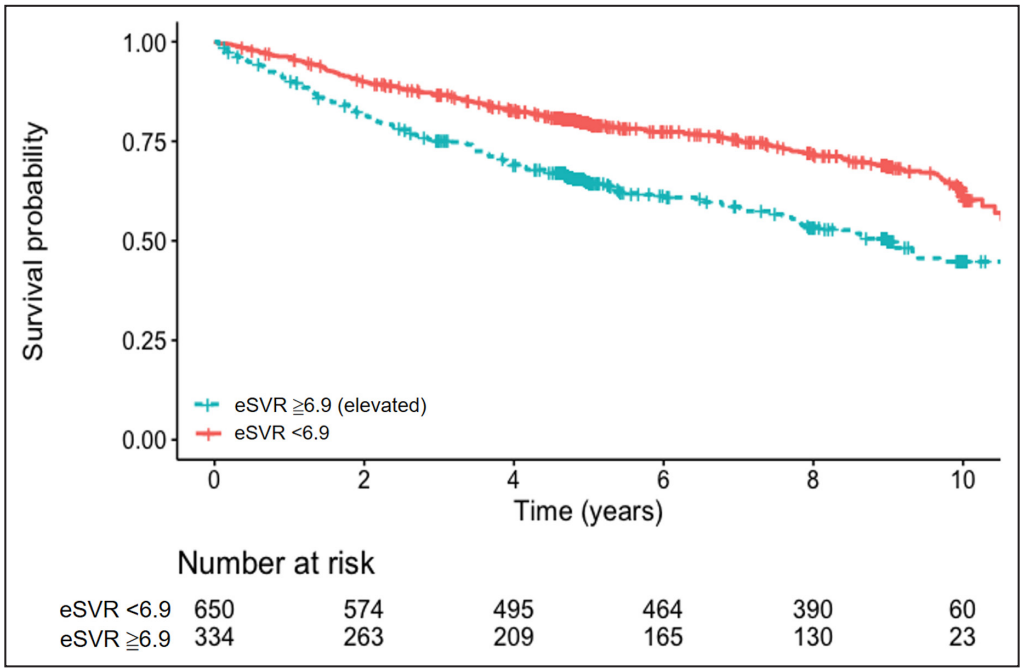

Figure 5. Extended Kaplan–Meier curves of major cardiovascular events (MACE) stratified by time-varying noninvasive systemic vascular resistance (eSVR).
A repeated elevated eSVR ≧6.9 (green) were associated with a higher risk of MACE compared with those who had an eSVR <6.9 (orange) at any time point during follow-up.

which could be potential confounders between association of eSVR and future adverse events. Given the observational nature of our cohort, it remains unknown whether such improvement of eSVR is a disease modifier or a disease marker of overall cardiovascular health. Prospective interventional studies are needed to answer this question. Finally, the peripheral resistance is determined by small arterioles but not by large arteries.[16] Speculation on the hemodynamic characteristics of large arteries and their impact on cardiovascular outcome is beyond the scope of this study. We have previously reported the association of ventricular-vascular coupling and HF admissions.[24] However, the association was mainly driven by LV end-systolic elastance but not arterial elastance. Whether large arteries or small arteries have greater impact on cardiac remodeling and outcomes remains uninvestigated.

CONCLUSIONS

From the Heart and Soul study, we demonstrated that an elevated eSVR, derived by the ratio of SBP and LVOT-VTI, was associated with adverse cardiovascular outcomes. Furthermore, repeatedly elevation of eSVR was associated with more adverse outcomes. Calculation of eSVR is promising as a simple but clinically useful marker of future adverse cardiovascular events in coronary artery disease. This simple index provides a more physiologic expression of blood pressure, and can be calculated mentally from the ratio of SBP to standard Doppler LVOT-VTI. With increasing clinical use of point-of-care ultrasound (bedside echocardiography), LVOT-VTI, the key component of eSVR, may be automatically measured, rendering eSVR as a routinely available bedside variable.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Association of eSVR tertile with clinical outcomes after patients with revascularization were excluded (remaining N= 407)

	eSVR tertile I	eSVR tertile II		eSVR tertile III	
Heart failure	(Reference)	HR (95% CI)	p value	HR (95% CI)	p value
Event rate (per 1000 person-years)	12 (7 - 20)	27 (18 - 40)		36 (25 - 52)	
Unadjusted HR	reference	2.16 (1.10 - 4.27)	0.03	2.91 (1.51 - 5.61)	0.001
Model 1	reference	2.37 (1.17 - 4.79)	0.02	2.71 (1.35 - 5.46)	0.005
Model 2	reference	2.48 (1.17 - 5.26)	0.02	1.53 (0.69 - 3.38)	0.29
Model 3	reference	2.60 (1.22 - 5.53)	0.01	1.38 (0.62 - 3.07)	0.44
Model 4	reference	2.46 (1.13 - 5.35)	0.02	1.23 (0.54 - 2.80)	0.62
MACE					
Event rate (per 1000 person-years)	25 (17 - 37)	52 (39 - 69)		73 (56 - 94)	
Unadjusted HR	reference	1.98 (1.22 - 3.20)	0.006	2.87 (1.82 - 4.55)	< 0.001
Model 1	reference	2.16 (1.31 - 3.57)	0.003	2.53 (1.54 - 4.15)	< 0.001
Model 2	reference	1.95 (1.14 - 3.34)	0.02	1.70 (0.98 - 2.94)	0.06
Model 3	reference	1.99 (1.16 - 3.41)	0.01	1.51 (0.87 - 2.65)	0.15
Model 4	reference	1.87 (1.08 - 3.24)	0.02	1.44 (0.82 - 2.55)	0.21
All-cause death					
Event rate (per 1000 person-years)	38 (28 - 51)	52 (39 - 68)		73 (57 - 93)	
Unadjusted HR	Reference	1.40 (0.93 - 2.11)	0.11	1.95 (1.32 - 2.88)	< 0.001
Model 1	Reference	1.29 (0.84 - 1.98)	0.25	1.52 (1.00 - 2.31)	0.05
Model 2	Reference	1.14 (0.73 - 1.78)	0.57	1.10 (0.70 - 1.73)	0.69
Model 3	Reference	1.17 (0.74 - 1.82)	0.50	1.03 (0.65 - 1.63)	0.91
Model 4	Reference	1.06 (0.67 - 1.67)	0.80	0.94 (0.59 - 1.50)	0.79

Model 1: Adjusted for Framingham risk factors (age, sex, ethnicity, smoking, HTN, DM, HDL/TC ratio) and heart rate.

Model 2: Model 1 + medical history (HF, revascularization) + laboratory (eGFR, LDL, CRP, NT-proBNP)

Model 3: Model 2 + medications (ACEI/ARB, aspirin, statin).

Model 4: Model 3 + echocardiography (LAESVI, LVESVI, LVEF, LVMI).

CI, confidence interval; eSVR, non-invasive systemic vascular resistance; HR, hazard ratio; MACE, major cardiovascular event (including heart failure hospitalization, myocardial infarction, stroke, and death from cardiovascular diseases).

Table S2. Association of eSVR trajectory with clinical outcomes using time-dependent covariates

	Non-persistently elevated eSVR group	Persistently elevated eSVR group	
	(Reference)	HR (95% CI)	P value
MACE			
Unadjusted	Reference	1.81 (1.47 - 2.21)	<0.001
Model 1	Reference	1.60 (1.28 - 1.99)	<0.001
Model 2	Reference	1.26 (0.99 - 1.60)	0.06
Model 3	Reference	1.25 (0.98 - 1.59)	0.08
Model 4	Reference	1.27 (0.99 - 1.63)	0.07
All-cause death			
Unadjusted	Reference	1.67 (1.38 - 2.02)	<0.001
Model 1	Reference	1.48 (1.21 - 1.82)	<0.001
Model 2	Reference	1.28 (1.03 - 1.59)	0.03
Model 3	Reference	1.23 (0.98 - 1.54)	0.07
Model 4	Reference	1.29 (1.02 - 1.63)	0.03

Persistently elevated eSVR group: subjects always had an eSVR ≥ 6.9 during the entire study period

Non-persistently elevated eSVR group: subjects had a eSVR **<** 6.9 at any time point

Model 1: Adjusted for Framingham risk factors (age, sex, ethnicity, smoking, HTN, DM, HDL/TC ratio) and heart rate.
Model 2: Model 1 + medical history (HF, revascularization) + laboratory (eGFR, LDL)
Model 3: Model 2 + medications (ACEI/ARB, aspirin, statin).
Model 4: Model 3 + echocardiography (LAESVI, LVESVI, LVEF, LVMI).
CI, confidence interval; eSVR, non-invasive systemic vascular resistance; HR, hazard ratio; MACE, major cardiovascular event (including heart failure hospitalization, myocardial infarction, stroke, and death from cardiovascular diseases).

Table S3. Association of MeSVR with clinical outcomes

	MeSVR tertile I	MeSVR tertile II		MeSVR tertile III		MeSVR per unit	
	(Reference)	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Heart failure hospitalization							
Event rate (per 1000 person-years)	18 (14 - 24)	29 (23 - 37)		38 (31 - 48)		28 (25 - 32)	
Unadjusted HR	Reference	1.74 (1.19 - 2.54)	0.004	2.19 (1.51 - 3.17)	<0.001	1.40 (1.25 - 1.58)	<0.001
Model 1	Reference	1.92 (1.30 - 2.82)	0.001	2.20 (1.48 - 3.25)	<0.001	1.43 (1.26 - 1.62)	<0.001
Model 2	Reference	1.50 (1.01 - 2.24)	0.05	1.39 (0.91 - 2.11)	0.13	1.13 (0.99 - 1.29)	0.07
Model 3	Reference	1.43 (0.96 - 2.15)	0.08	1.39 (0.91 - 2.11)	0.13	1.13 (0.99 - 1.29)	0.07
Model 4	Reference	1.33 (0.88 - 2.00)	0.17	1.29 (0.84 - 1.97)	0.24	1.11 (0.97 - 1.27)	0.13
MACE							
Event rate (per 1000 person-years)	38 (31 - 47)	57 (48 - 68)		77 (66 - 90)		57 (52 - 63)	
Unadjusted HR	Reference	1.49 (1.14 - 1.95)	0.004	2.03 (1.56 - 2.63)	<0.001	1.34 (1.23 - 1.46)	<0.001
Model 1	Reference	1.54 (1.17 - 2.03)	0.002	1.96 (1.48 - 2.58)	<0.001	1.33 (1.21 - 1.46)	<0.001
Model 2	Reference	1.32 (1.00 - 1.76)	0.05	1.50 (1.13 - 2.01)	0.006	1.16 (1.05 - 1.28)	0.002
Model 3	Reference	1.28 (0.96 - 1.71)	0.09	1.49 (1.11 - 2.00)	0.007	1.15 (1.04 - 1.27)	0.006
Model 4	Reference	1.26 (0.94 - 1.68)	0.12	1.44 (1.07 - 1.93)	0.02	1.13 (1.02 - 1.25)	0.02
All-cause death							
Event rate (per 1000 person-years)	40 (33 - 49)	52 (44 - 62)		66 (56 - 77)		53 (47 - 58)	
Unadjusted HR	Reference	1.32 (1.02 - 1.70)	0.04	1.71 (1.34 - 2.20)	<0.001	1.25 (1.15 - 1.36)	<0.001
Model 1	Reference	1.30 (1.00 - 1.70)	0.05	1.54 (1.19 - 2.01)	0.001	1.21 (1.11 - 1.33)	<0.001
Model 2	Reference	1.09 (0.83 - 1.44)	0.52	1.25 (0.95 - 1.65)	0.10	1.10 (1.00 - 1.21)	0.04
Model 3	Reference	1.06 (0.81 - 1.40)	0.66	1.24 (0.94 - 1.63)	0.13	1.09 (0.99 - 1.20)	0.09
Model 4	Reference	1.05 (0.80 - 1.39)	0.73	1.21 (0.91 - 1.61)	0.18	1.08 (0.97 - 1.19)	0.15

Model 1: Adjusted for Framingham risk factors (age, sex, ethnicity, smoking, HTN, DM, HDL/TC ratio) and heart rate.

Model 2: Model 1 + medical history (HF, revascularization) + laboratory (eGFR, LDL, CRP, NT-proBNP)

Model 3: Model 2 + medications (ACEI/ARB, aspirin, statin).

Model 4: Model 3 + echocardiography (LAESVI, LVESVI, LVEF, LVMI).

CI, confidence interval; eSVR, non-invasive systemic vascular resistance; HR, hazard ratio; MACE, major cardiovascular event (including heart failure hospitalization, myocardial infarction, stroke, and death from cardiovascular diseases); MAP, mean arterial pressure.

MeSVR is defined as the ratio of mean arterial pressure and left ventricular outflow tract velocity-time integral.

Figure S1. Distribution of eSVR

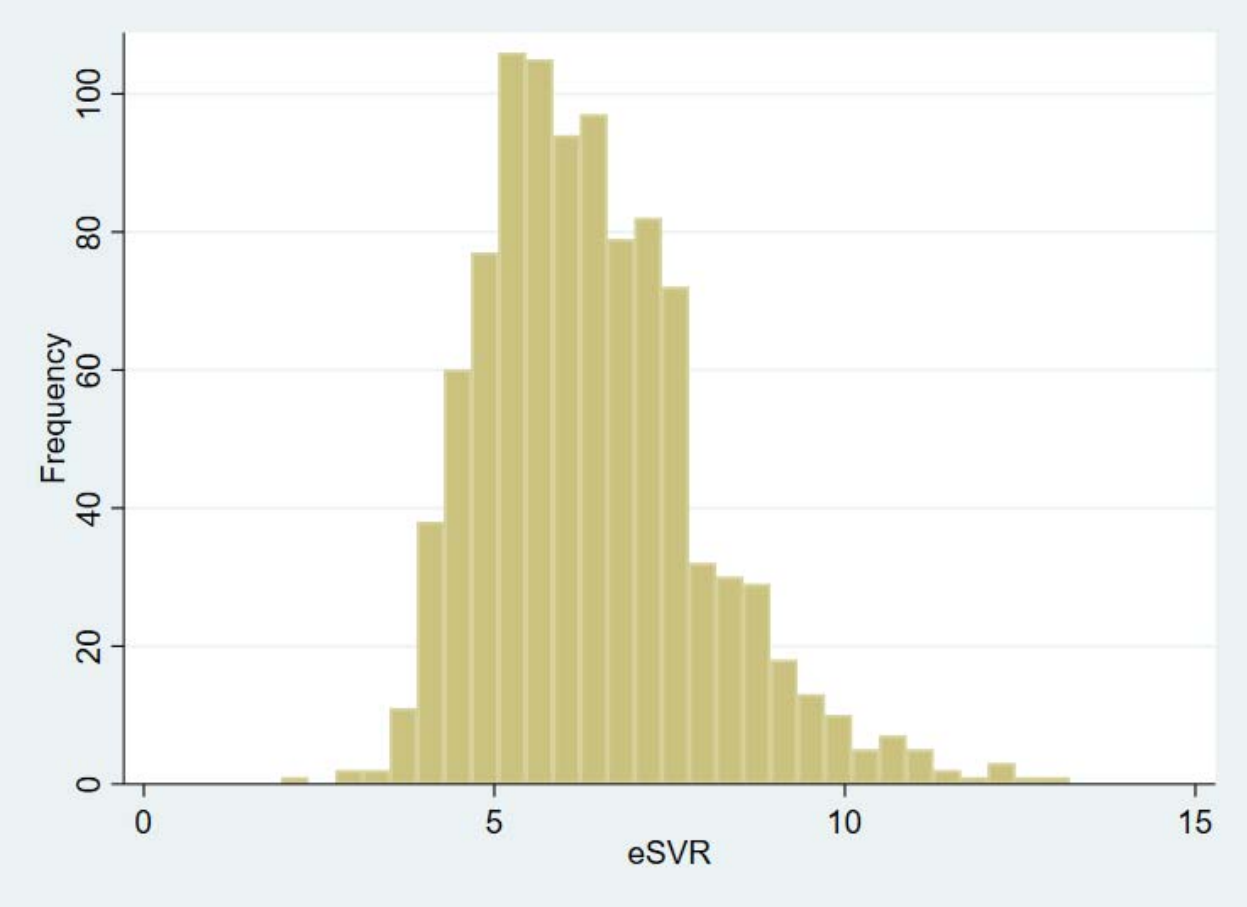

Figure S2. The hazard ratio (HR) and 95% confidence interval (CI) of major cardiovascular events (MACE) by (A) systolic blood pressure and (B) non-invasively estimated systemic vascular resistance (eSVR)