

SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Sampling strategy

PREVENCION (acronym for Estudio Peruano de Prevalencia de Enfermedades Cardiovasculares y Factores de Riesgo Coronario) is a study undertaken in Arequipa, the second largest city in Peru. The first phase of PREVENCION was designed to determine the population-based prevalence of cardiovascular disease and cardiovascular risk factors. The sampling frame was based on the most recent population and household National Census at the time of study initiation. The sampling strategy was probabilistic, multistage, clustered and stratified according to geographic location and socioeconomic status. We aimed to enroll a minimum total of 1600 subjects with at least 200 subjects per sex in each pre-defined age group (20–34, 35–49, 50–64, and 65–80 years) to increase statistical power for age-group comparisons. This was achieved through deliberate oversampling of subjects aged >65 years to improve the precision of estimates in these groups. The first phase sample consisted of 1878 individuals (867 men and 1011 women). Following initial contact with participants, informed consent was obtained and a comprehensive evaluation was performed at the study headquarters.⁸⁻¹⁴ Further details regarding the main objectives, design and sampling strategy have been previously described.⁸

In contrast to the first phase of the study, which aimed to obtain precise estimates of the age and sex-stratified, weighted prevalence estimates of cardiovascular disease and cardiovascular risk factors, the second phase of the study was designed to increase the sample size, in order to achieve greater statistical power for assessments related to the relationship between cardiovascular phenotypes obtained at baseline and mortality. In the second phase of the study, 631 first-degree relatives of the first phase participants were invited to attend the study headquarters for a clinical and phenotypic evaluation that was similar to that implemented in the

first-phase study participants.

Impedance Cardiography (ICG) was implemented after enrollment in the parent study had been initiated; therefore, this analysis included a subset of phase 1 and phase 2 participants, as detailed in the supplemental section. All subjects signed a written informed consent. Subjects with a congestive heart failure (n=22) were excluded from this analysis, given that we aimed to assess the value of ICG to detect subclinical changes in ventricular and arterial function.

Table S2 presents a table that compares subjects with vs. without ICG data (excluding those with prevalent heart failure, as per our exclusion criteria for this analysis). As shown, subjects included in this sub-study were older (mean age 49 vs. 42.6 years) and demonstrated a slightly greater prevalence of various cardiovascular risk factors.

Blood pressure measurements

As previously described,^{8,9} blood pressure was measured between 7 AM and 10 AM using a mercury sphygmomanometer after a resting period of at least 5 minutes, with the auscultatory method, according to recommendations from the seventh report of the Joint National Committee for the diagnosis, evaluation and treatment of high BP.¹⁵ The cuff was placed on the participant's dominant arm and inflated in 10 mm Hg increments until the cuff pressure was 30 mm Hg above the level at which the radial pulse disappeared. At least 2 measurements were performed in each of 2 separate days, and a final mean value was obtained for systolic and diastolic BP.

Baseline biochemical measurements

Samples of venous blood were obtained after at least 8 h of fast and serum was used for biochemical measurements. Total cholesterol, serum glucose and triglycerides were measured

enzymatically by automated methods using a clinical Cobas Mira analyzer (Roche, Basel, Switzerland). Direct measurements of LDL-cholesterol and HDL-cholesterol were performed using the same analyzer. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL or pharmacological treatment with glucose-lowering drugs. Glomerular filtration rate was estimated with the Modification of Diet in Renal Disease (MDRD) equation.¹⁶

Hemodynamic assessments

Assessments were performed between 7-10 AM, with participants seated after a resting period of at least 5 minutes. ICG applies Ohm's relationship to the thorax to allow changes in voltage and impedance to be translated into hemodynamic parameters of cardiac function.^{3,4} Since blood is a much stronger conductor of current than the surrounding thoracic tissues, variations in blood volume in the thoracic great vessels results in a measurable change in impedance, which allows calculation of stroke volume, as described in detail in previous publications.^{3,4}

We utilized the BioZ ICG device (CardioDynamics, San Diego, CA) for hemodynamic recordings, with validated methods for estimation of stroke volume and cardiac output.¹⁷ Four dual ICG sensors were placed on the subject, two above the base of the neck and just below each ear and one on either side of the thorax in the mid-axillary line at the level of the xiphoid process. An integrated oscillometric BP cuff was attached to the patient's left arm and the patient was placed in the supine position (**Figure 1**). After confirmation of a visible ICG waveform on the ICG monitor screen, the patient was instructed to rest while ICG hemodynamic data was collected.

ICG provides measures of cardiac function (cardiac output, cardiac index, stroke volume, stroke volume index), in addition to indices of LV chamber contractility: velocity index (defined

as the maximum rate of impedance change, related to changes in aortic blood velocity and volume), acceleration index (maximum of the second derivative of impedance), pre-ejection period (measured interval from the onset of ventricular depolarization in the surface electrocardiogram to the beginning of ejection), LV ejection time, and the systolic time ratio (pre-ejection period divided by LV ejection time).^{3,4} The definition of these indices and the units of measurement are shown in **Table S2**.

Figure S1. Kaplan-Meier survival curves for quartiles of velocity index, acceleration index, total arterial compliance and total arterial compliance index.

Figure S1.

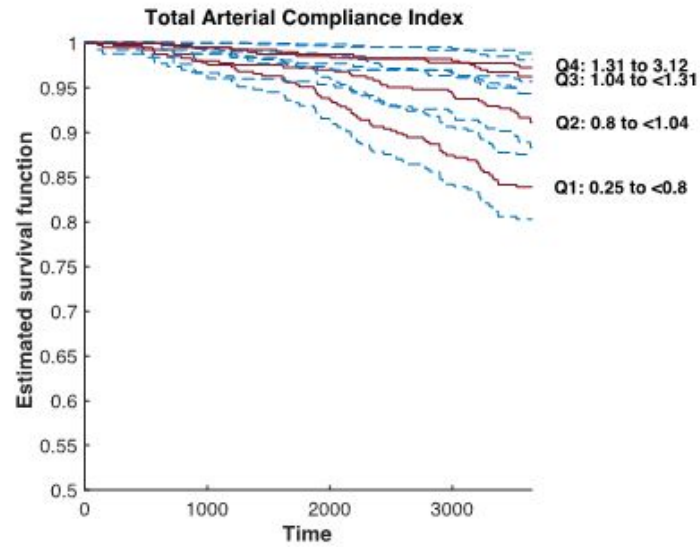
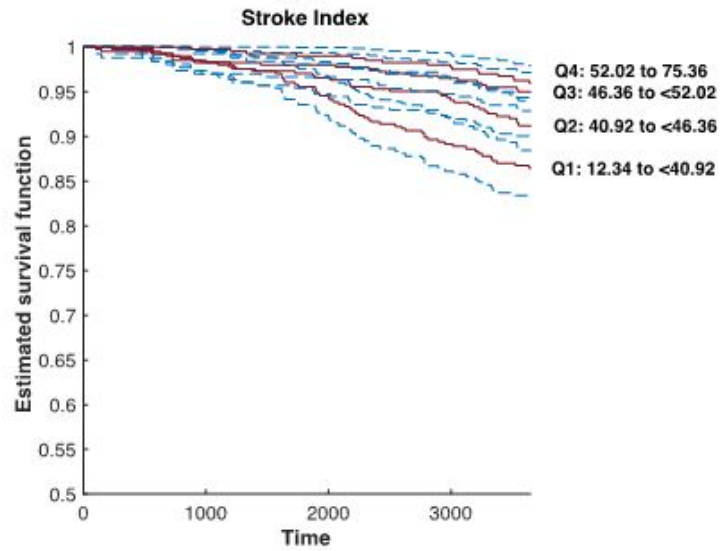
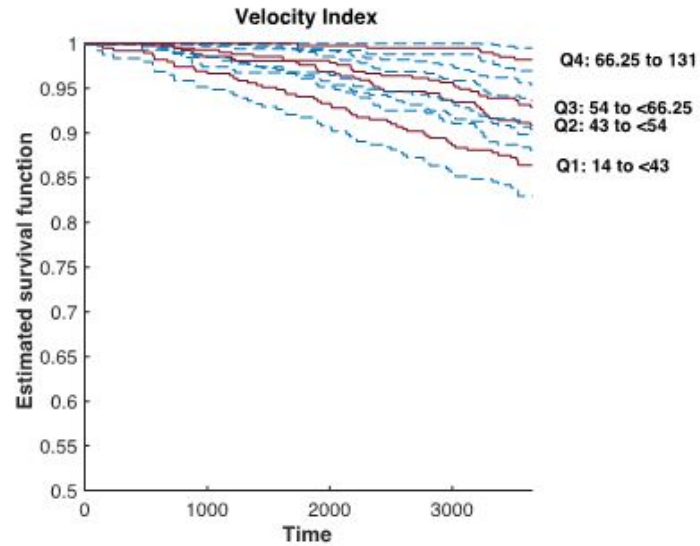
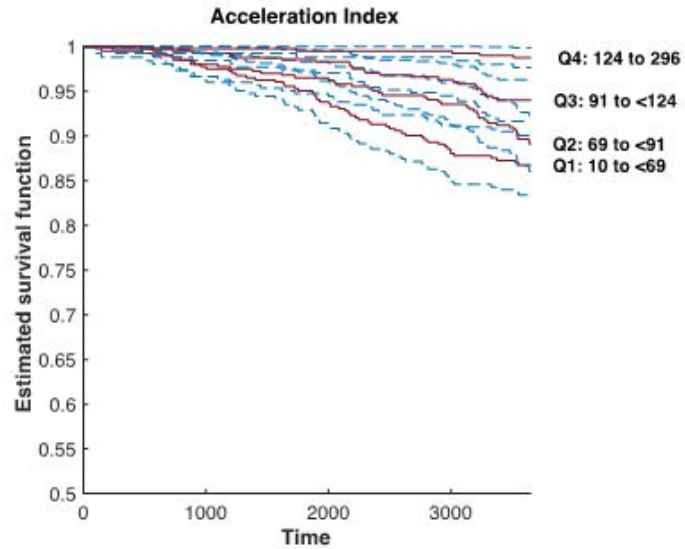


Table S1. General characteristics of subjects who were included vs. not included in this subanalysis, due to availability of ICG data. Subjects with prevalent heart failure are excluded from this comparison.

	Without ICG data (n=846)	With ICG data (n=1641)	P value
Age, years	42.6 (41.5 to 43.7)	49 (48.1 to 49.9)	<0.0001
Male sex	349 (41.25%)	782 (47.65%)	0.0024
Body Mass Index, kg/m²	26.2 (25.9 to 26.5)	26.4 (26.1 to 26.6)	0.3060
Body Surface Area, m²	1.73 (1.72 to 1.75)	1.77 (1.76 to 1.78)	<0.0001
Systolic Blood Pressure, mmHg	119 (118 to 121)	119 (118 to 120)	0.4534
Diastolic Blood Pressure, mmHg	76.7 (76 to 77.3)	77.5 (77 to 77.9)	0.0436
Pulse Pressure, mmHg	41.4 (40.5 to 42.4)	40 (39.4 to 40.7)	0.0126
Total Cholesterol, mg/dl	197 (194 to 199)	199 (197 to 201)	0.1114
LDL cholesterol, mg/dl	113 (111 to 115)	117 (115 to 118)	0.0070
HDL cholesterol, mg/dl	45.4 (44.8 to 46.1)	46.5 (46 to 47)	0.0071
Triglycerides mg/dl	145 (140 to 150)	155 (151 to 159)	0.0017
Fasting Glucose, mg/dl	80.2 (79.2 to 81.3)	81.9 (81.2 to 82.7)	0.0087
Impaired Fasting Glucose	26 (3.07%)	84 (5.12%)	0.0187
Diabetes Mellitus	32 (3.78%)	100 (6.09%)	0.0149
Serum creatinine, mg/dl	0.761 (0.75 to 0.772)	0.781 (0.773 to 0.789)	0.0033
Estimated GFR, ml/1.72 m² of BSA	93.9 (92.5 to 95.4)	90.3 (89.3 to 91.4)	<0.0001
Antihypertensive medication use	70 (8.27%)	287 (17.49%)	<0.0001
Aspirin use	0.011 (0.004 to 0.018)	0.019 (0.013 to 0.024)	0.0780
Current Smoking	160 (18.91%)	290 (17.67%)	0.4465
Peripheral arterial disease	13 (1.54%)	43 (2.65%)	0.0780

LDL=Low density lipoprotein; HDL=High density lipoprotein; GFR=glomerular filtration rate.

Table S2. Physiologic Indices Derived from Impedance Cardiography (ICG)

Variable	Units	Computation
Blood flow		
Stroke volume	mL	derived from ICG waveform
Stroke index	mL/m ²	Stroke volume / body surface area
Cardiac output	L/min	Stroke volume × heart rate
Cardiac index	L/min/m ²	Cardiac output/body surface area
Arterial Properties		
Systemic vascular resistance	dyne sec cm ⁻⁵	Mean arterial pressure / cardiac output
Systemic vascular resistance index	dyne sec	Mean arterial pressure / cardiac index
Total Arterial Compliance	ml/mmHg	Stroke volume / pulse pressure
Total Arterial Compliance Index	ml mmHg/m ²	Stroke index / pulse pressure
Contractility /cardiac performance		
Velocity index	/1000/sec	1000 × first time derivative _{max} /baseline impedance
Acceleration index	/100/sec ²	100 × second time derivative _{max} /baseline impedance
Pre-ejection period	ms	ECG Q-wave to aortic valve opening in milliseconds
Left ventricular ejection time	ms	Aortic valve opening to closing
Systolic time ratio	unitless	Pre-ejection period / Left ventricular ejection time

Table S3. Comparison of ICG parameters between non-hypertensive, stage 1 hypertensive, and stage 2 hypertensive subjects in the study sample, after exclusion of hypertensive subjects receiving antihypertension medications

	ACC/AHA Blood Pressure Group			P value
	Non-Hypertensive Mean (95%CI) (n=704)	Stage 1 HTN Mean (95%CI) (n=471)	Stage 2 HTN Mean (95%CI) (n=179)	
Stroke Volume, ml	80.4 (79 to 81.8)	83.2 (81.4 to 84.9)	78 (75.3 to 80.7)	0.0037 * \$
Stroke Index, ml/m²	47.4 (46.8 to 48)	47 (46.3 to 47.8)	44.2 (43 to 45.5)	<0.0001 # \$
Cardiac Output, ml/min	5.01 (4.93 to 5.1)	5.22 (5.11 to 5.32)	5.04 (4.88 to 5.21)	0.0092 *
Cardiac Index, ml m²/min	2.91 (2.87 to 2.95)	2.91 (2.86 to 2.95)	2.78 (2.71 to 2.86)	0.0135 # \$
SVR, dyn s/cm⁵	1132 (1113 to 1152)	1183 (1157 to 1208)	1384 (1336 to 1433)	<0.0001 * # \$
SVR Index, dyn s m²/cm⁵	1954 (1925 to 1984)	2124 (2085 to 2164)	2507 (2431 to 2583)	<0.0001 * # \$
TAC, ml/mmHg	2.03 (1.98 to 2.08)	1.88 (1.83 to 1.94)	1.42 (1.35 to 1.49)	<0.0001 * # \$
TAC Index, ml m²/mmHg	1.17 (1.15 to 1.2)	1.05 (1.02 to 1.08)	0.79 (0.75 to 0.82)	<0.0001 * # \$
Velocity Index, 1/100 s	59.2 (57.8 to 60.6)	52 (50.5 to 53.5)	47.1 (44.9 to 49.4)	<0.0001 * # \$
Acceleration Index, 1/100 s²	104 (100.9 to 107.1)	88.8 (85.5 to 92)	80.7 (75.9 to 85.5)	<0.0001 * # \$
Systolic Time Ratio	0.248 (0.244 to 0.252)	0.235 (0.231 to 0.24)	0.226 (0.219 to 0.234)	<0.0001 * #
Pre-ejection Period, ms	85.7 (84.7 to 86.7)	84.9 (83.7 to 86.2)	81.7 (79.7 to 83.6)	0.0014 # \$
LV Ejection Time, ms	338 (335 to 342)	353 (349 to 357)	353 (346 to 359)	<0.0001 * #

Non-Hypertensive: BP<130/80 mmHg. Stage 1 hypertension: systolic BP 130-139 or diastolic BP 80-89 mmHg; Stage II hypertension: systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, or pharmacologic treatment for hypertension.

SVR=Systemic vascular resistance; TAC=total arterial compliance.

* Post-hoc pairwise comparison different between non-hypertensive and Stage 1 HTN.

Post-hoc pairwise comparison different between non-hypertensive and Stage 2 HTN.

\$ Post-hoc pairwise comparison different between Stage 1 and Stage 2 HTN

Table S4. ICG parameters as predictors of all-cause mortality in unadjusted and adjusted proportional hazards regression models among subjects without ACC/AHA stage 2 hypertension

	Non-Adjusted Standardized Hazard Ratios	<i>P</i> value	Standardized Hazard Ratios, Adjusted for Confounders	<i>P</i> value	Standardized Hazard Ratios, Further Adjusted for BP	<i>P</i> value
Systolic Blood Pressure	1.63 (1.35-1.97)	<0.0001	0.97 (0.77-1.22)	0.81	---	---
Diastolic Blood Pressure	1.32 (1.06-1.65)	0.0142	1.02 (0.81-1.30)	0.84	---	---
Mean Arterial Pressure	1.45 (1.17-1.8.)	0.0008	0.98 (0.77-1.25)	0.85	---	---
Pulse Pressure	1.55 (1.30-1.87)	<0.0001	0.95 (0.76-1.19)	0.66	---	---
Stroke Volume	0.68 (0.53-0.86)	0.0012	0.90 (0.69-1.16)	0.42	0.92 (0.71-1.2)	0.56
Stroke Index	0.65 (0.52-0.80)	<0.0001	0.86 (0.68-1.08)	0.19	0.87 (0.69-1.11)	0.27
Cardiac Output	0.74 (0.60-0.92)	0.0075	1.01 (0.79-1.28)	0.97	1 (0.78-1.28)	0.99
Cardiac Index	0.72 (0.60-0.88)	0.0009	0.97 (0.77-1.21)	0.76	0.96 (0.76-1.2)	0.72
SVR	1.43 (1.24-1.63)	<0.0001	1.00 (0.83-1.21)	0.98	1 (0.82-1.23)	0.97
SVR Index	1.43 (1.25-1.64)	<0.0001	1.01 (0.84-1.22)	0.93	1.02 (0.83-1.25)	0.85
TAC	0.51 (0.39-0.66)	<0.0001	1.01 (0.75-1.37)	0.95	0.98 (0.66-1.47)	0.93
TAC Index	0.48 (0.37-0.63)	<0.0001	0.98 (0.72-1.33)	0.89	0.91 (0.59-1.41)	0.68
Velocity Index	0.32 (0.23-0.44)	<0.0001	0.61 (0.42-0.88)	0.008	0.62 (0.43-0.91)	0.014
Acceleration Index	0.31 (0.22-0.44)	<0.0001	0.62 (0.41-0.94)	0.023	0.63 (0.41-0.95)	0.026
Systolic Time Ratio	0.64 (0.48-0.84)	0.0014	0.75 (0.58-0.97)	0.028	0.74 (0.57-0.95)	0.018
Pre-ejection Period	0.69 (0.53-0.91)	0.0078	0.71 (0.54-0.92)	0.011	0.69 (0.53-0.9)	0.0065
LV Ejection Time	1.33 (1.06-1.68)	0.0138	0.98 (0.79-1.21)	0.85	0.99 (0.8-1.22)	0.91

SVR=Systemic vascular resistance; TAC=total arterial compliance; LV=left ventricle.

* Adjusted for age, sex, body mass index, LDL-cholesterol, HDL-cholesterol, triglycerides, fasting plasma glucose, diabetes mellitus, serum creatinine and smoking history.

** Further adjusted for systolic and diastolic blood pressure.