

Original article

Carotid artery stiffness and risk of vascular events and mortality: the REGICOR study



Roberto Elosua,^{a,b,c,*} Andrea Toloba,^{a,b} Roman Arnold,^{b,d} Eric De Groot,^{e,f} Ruth Martí-Lluch,^g Irene R. Degano,^{a,b,c} Jaume Marrugat,^{a,b} and Rafel Ramos^{g,h}

^a Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain

^b Centro de Investigación en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

^c Facultat de Medicina, Universitat de Vic-Universitat Central de Catalunya, Vic, Barcelona, Spain

^d Instituto de Ciencias del Corazón/Unidad de Imagen Cardíaca (ICICOR/ICICORELAB), Hospital Clínico Universitario Valladolid, Valladolid, Spain

^e Imagemonline & Cardiovascular, Erichem, The Netherlands

^f Department of Gastroenterology and Hepatology, Amsterdam UMC - Academic Medical Center, Amsterdam, The Netherlands

^g Grup de Recerca en Salut Vascular (ISV-Girona), Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Girona, Spain

^h Departament de Ciències Mèdiques, Facultat de Medicina, Campus Salut, Universitat de Girona, Girona, Spain

Article history:

Received 28 March 2023

Accepted 15 September 2023

Available online 9 October 2023

Keywords:

Carotid stiffness

Ischemic heart disease

Cerebrovascular disease

Predictive capacity

ABSTRACT

Introduction and objectives: The aims of this study were to determine the dose-response association of carotid arterial stiffness with vascular outcomes and overall mortality, and to assess their added predictive capacity.

Methods: Population-based cohort study including 6468 individuals, with a median follow-up of 6.5 years. Six carotid artery stiffness indices were assessed: strain, stiffness, Peterson elasticity coefficient, compliance coefficient, distensibility coefficient, and pulse wave velocity (PWV). Incident coronary, cerebrovascular, global vascular, and total fatal events were identified.

Results: Carotid compliance and distensibility coefficients were not associated with any of the outcomes. Carotid stiffness, Peterson elasticity coefficient, and PWV showed a direct linear relationship to cerebrovascular disease: the risk increased by 8% (95%CI, 1–16) per stiffness unit increase, by 7% (95%CI, 2–13) per 10-unit Peterson elasticity coefficient increase, and by 26% (95%CI, 8–48) per PWV unit increase. Carotid strain showed a nonlinear association with ischemic heart disease. When strain was ≤ 0.09 units, each 0.01-unit increase was associated with a 15% lower risk of coronary events (95%CI, –33 to 6); above 0.09 units, each 0.01 increase in strain was associated with a 16% higher risk of coronary events (95%CI, 6–27). The addition of the stiffness indices did not improve the predictive capacity of validated risk functions.

Conclusions: Carotid stiffness, Peterson elasticity coefficient, and PWV have a direct linear association with cerebrovascular disease risk. Carotid strain is not linearly related to U-shaped ischemic heart disease risk. The inclusion of these indexes does not improve the predictive capacity of risk functions.

© 2023 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

Rigidez carotídea y riesgo de eventos vasculares y mortalidad: el estudio REGICOR

RESUMEN

Introducción y objetivos: Los objetivos son analizar la relación dosis-respuesta de la rigidez de la arteria carótida y la mortalidad y evaluar su capacidad predictiva.

Métodos: Estudio de cohorte poblacional que incluyó a 6.468 participantes, con una mediana de seguimiento de 6,5 años. Se evaluaron 6 índices de rigidez. Se identificaron los eventos coronarios y cerebrovasculares y la mortalidad.

Resultados: La rigidez carotídea, el coeficiente de Peterson y la velocidad de la onda de pulso (VOP) se asociaron de manera lineal y directa con los eventos cerebrovasculares: aumento del 8% (IC95%, 1–16%) por unidad de rigidez, del 7% (IC95%, 2–13%) cada 10 unidades del coeficiente de Peterson y del 26% (IC95%, 8–48%) por unidad de la VOP. La tensión carotídea se asoció de modo no lineal con el riesgo de enfermedad coronaria: en valores $< 0,09$ unidades, cada aumento de 0,01 unidades se asoció con una

Palabras clave:

Rigidez carotídea

Enfermedad coronaria

Enfermedad cerebrovascular

Capacidad predictiva

* Corresponding author.

E-mail address: relousa@imim.es (R. Elosua).

disminución de un 16% del riesgo (IC95%, -33 a +6%); por encima de 0,09 unidades, cada incremento de 0,01 unidades se asoció con un aumento de un 16% del riesgo (IC95%, 6-27%). La inclusión de estos índices no mejoró la capacidad predictiva de las funciones de riesgo.

Conclusiones: La rigidez carotídea, el coeficiente de elasticidad de Peterson y la VOP tienen una relación lineal y directa con el riesgo de enfermedad cerebrovascular. La tensión (*strain*) carotídea tiene una relación en U con el riesgo de enfermedad coronaria. Estos índices no contribuyen a mejorar la capacidad predictiva de las funciones de riesgo.

© 2023 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Abbreviations

CCA: common carotid artery
cNRI: continuous net reclassification index
DBP: diastolic blood pressure
IHD: ischemic heart disease
PWV: pulse wave velocity
SBP: systolic blood pressure

INTRODUCTION

Ischemic heart disease (IHD) and stroke remain the leading causes of the global burden of disease in the population older than 49 years.¹ Arterial stiffness has been proposed as a noninvasive imaging method to assess arterial wall damage and vascular aging, as well as a predictive biomarker of vascular risk. Although current guidelines do not recommend its use due to measurement difficulties,^{2,3} a meta-analysis including 10 studies (n = 22 472 individuals) showed that carotid arterial stiffness predicts cardiovascular and overall mortality and future cerebrovascular events and improves the predictive capacity of classic risk functions.⁴

Arterial stiffness can be estimated by measuring regional or local stiffness and several indices are available.³ The most popular index for calculating regional arterial stiffness is pulse wave velocity (PWV), generally the carotid-femoral PWV to estimate aortic stiffness. Local arterial stiffness can be quantified by indices based on changes in arterial diameters and their relationship to changes in arterial blood pressure.⁵ The linear and nonlinear pattern of the association of these indices with vascular outcomes and mortality has not been properly analyzed to date.

The aim of this analysis was to determine the dose-response association of several measurements of local carotid arterial stiffness with vascular outcomes and overall mortality in a population cohort in a region with a low incidence of cardiovascular disease (figure 1). We also assessed the added predictive capacity value of carotid arterial stiffness indices for those outcomes.

METHODS

Design and population

The Registre Gironí del Cor (REGICOR) study involves a prospective population-based cohort in Girona.⁶ Individuals living in the city of Girona and other cities and rural villages of Girona province were

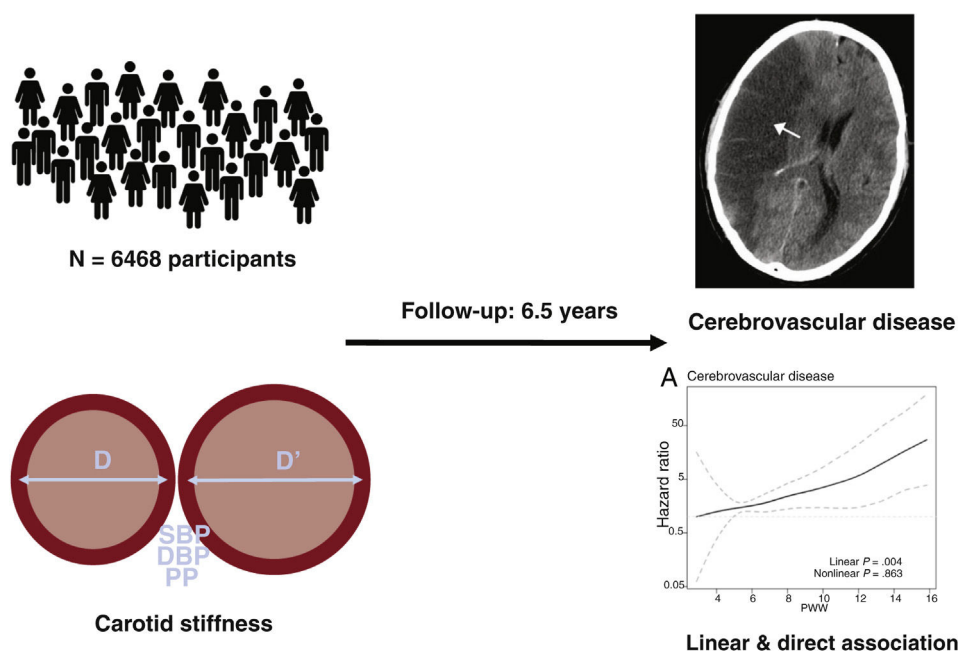


Figure 1. Central illustration. Summary of the design, aim and main results of the study. D, carotid artery diameter in diastole; D', carotid artery diameter in systole; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

randomly selected from the census and invited to participate in 3 different surveys (participation rate > 70.0%): 1748 individuals aged 25 to 74 years from 1994 to 1996; 3058 aged 25 to 74 years from 1999 to 2001; and 6352 aged 35 to 79 years from 2003 to 2006. All these participants were invited to attend a second visit between 2007 and 2013 in which carotid ultrasound was performed and were then followed up until December 31, 2016. The present analysis included all participants of the 3 surveys without a personal history of coronary or cerebrovascular disease who were not institutionalized, were living in the monitored area, and were attending the second visit with completion of carotid stiffness measurements.

All included participants were duly informed about the study and signed a written consent form. The study was approved by the local ethics committee.

Carotid artery stiffness measurements

As previously described,⁷ carotid scans were assessed by 3 certified sonographers using a standardized protocol and an Acuson XP128 ultrasound instrument (Acuson-Siemens, Germany) equipped with an L7 5–12 MHz linear array transducer. The scans were conducted at a specific site within each city or village, generally at a primary care center. Inter- and intrasonographer variability were evaluated in 42 participants, using repeated intima-media thickness (IMT) measurements obtained at 2 visits 2 weeks apart. The intraclass correlation coefficients for the mean IMT of the common carotid artery (CCA) were > 0.82 for both inter- and intrasonographer variability; the correlation and the mean difference between the M-mode right and left mean CCA diameter was 0.73 and 0.10, respectively.

During the carotid ultrasound scan, the anterior and posterior walls of the distal right and left CCA were visualized in B-mode. To obtain the M-mode anterior wall intima-lumen and posterior wall lumen-intima tracings, the sonographer switched from the full B-mode to a 1/3 B-mode 2/3 M-mode image of the distal CCA. The 1/3 B-mode image guides the M-mode. The movements of the arterial walls on the 2/3 M-mode image shows waveforms with the double-line patterns of the arterial walls over time. Bilaterally, images were saved as a DICOM (digital information and communication in medicine) stills. These still images were analyzed offline using validated “eTrack” software in 2 imaging laboratories Imagelabonline & Cardiovascular, The Netherlands, n = 3182 images; and Instituto de Ciencias del Corazón (ICICOR/ICICORELAB), Spain, n = 3286 images), applying the same processing protocol and software.⁸ The eTrack software traces the waveforms of the leading edges of anterior wall intima-lumen and posterior wall lumen-intima interfaces. If the contours of both walls are identified for at least 2 heartbeats, the software can calculate lumen diameter changes and calculate parameters and heart rates according to international recommendations.⁹ Systolic and diastolic blood pressure were determined twice after a 5 minute rest; the mean value was calculated before performing the study and considered for further calculations.

Several local carotid arterial stiffness indices were calculated in the right and the left CCA:

$$\text{a.-Strain} = \frac{\Delta D}{DD} \quad \text{Equation 1}$$

$$\text{b.-Stiffness}(\beta) = \frac{\ln\left(\frac{SBP}{DBP}\right)}{\text{Strain}} \quad \text{Equation 2}$$

$$\text{c.-Peterson elasticity coefficient (Ep, kPa)} = \frac{\frac{PP}{7.6}}{\text{Strain}} \quad \text{Equation 3}$$

$$\text{d.-Compliance coefficient (CC, kPa}^{-1}\text{)} = \frac{\pi * ((2 * DD * \Delta D) + \Delta D^2)}{4 * \frac{PP}{7.6}} \quad \text{Equation 4}$$

$$\text{e.-Distensibility coefficient (DC, kPa}^{-1}\text{)} = \frac{(2 * DD * \Delta D) + (\Delta D)^2}{\frac{PP}{7.6} * DD^2} \quad \text{Equation 5}$$

$$\text{f.-Pulse wave velocity (PWV)} = \frac{1}{\sqrt{DC * \rho}} \quad \text{Equation 6}$$

Where: ΔD is the increment of the CCA diameter in systole (diameter in systole – diameter in diastole), DD is the diastolic CCA diameter, SBP is the systolic blood pressure, DBP is the diastolic blood pressure, PP is the pulse pressure ($SBP - DBP$), and ρ is blood density, assumed as 1.050 kg/m³.

Some of these indices (β , Ep, PWV) are directly related to stiffness, whereas others (strain, CC, DC) are inversely related to stiffness. For each participant, right and left M-mode carotid values for each of the stiffness indices were averaged.⁵ If M-mode data of a given one site were missing, we used data of the available site only.

Follow-up and outcomes

We used several data sources to identify the clinical outcomes of interest in the follow-up of the participants: physical re-exams, telephone contact, medical records review, and linkage with the program of analytical data for research and innovation in health (PADRIS) of the Government of Catalonia, which includes all hospital admissions, primary care diagnosis, and the official mortality register. At the time of data collection, the follow-up was updated December to 31, 2016. For participants who relocated outside Catalonia, the follow-up date was censored at the time of change of residence.

Four main outcomes were defined: a) IHD events, including fatal and nonfatal myocardial infarction or angina (ICD9 codes 410–414 or ICD10 codes I20–I25 in the medical or mortality records); b) cerebrovascular events, including fatal and nonfatal stroke (ICD9 codes 431–437 or ICD10 codes I69.1–I69.9, in the medical or mortality records); c) overall vascular disease events, including fatal and nonfatal IHD and cerebrovascular events, and other fatal vascular conditions (ICD9 codes 390–459 and 798 or ICD10 codes I00–I99 in the mortality register); and d) all-cause mortality. All the events were classified by an event committee according to standardized criteria. This committee consisted of 3 investigators from the study who were blinded to any relevant exposures of interest. If there were multiple events in the same participant, the first occurring event was considered in defining the composite global vascular outcome.

Other covariates

A group of trained nurses and interviewers used standardized and validated questionnaires and measurement methods to collect other variables of interest.¹⁰ Tobacco consumption and educational level were self-reported on standard questionnaires. Hypertension was considered when previously diagnosed by a physician, was under treatment, or showed values of $SBP \geq 140$ mmHg or $DBP \geq 90$ mmHg. Fasting blood samples were collected and total cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose concentrations were determined. Low-density lipoprotein cholesterol levels were estimated using the Friedewald equation when triglycerides were < 300 mg/dL. Diabetes was defined if previously diagnosed, was under treatment, or showed fasting

glucose values ≥ 126 mg/dL. Previous vascular events were self-reported and validated by hospital and ambulatory-clinic records.

Statistical analysis

Categorical data are expressed as counts and percentages. Continuous variables are expressed as mean (standard deviation) or median [interquartile range]. The student t-test or nonparametric Mann-Whitney test were used to identify differences in continuous traits between groups. The chi-square test was used to assess differences in categorical variables between groups. The bivariate association between continuous variables was assessed with the Spearman correlation coefficient.

To explore the linear and nonlinear dose-response pattern of the relationship between carotid stiffness indices and vascular outcomes or all-cause mortality, we used Cox or Fine-Gray (considering competing risk for events) regression models with penalized spline smoothing for each stiffness variable of interest. Noncardiovascular mortality was considered a competing event for cardiovascular events, noncoronary mortality a competing

event for coronary events, and noncerebrovascular mortality a competing event for cerebrovascular events. When the relationship included a significant nonlinear component ($P < .05$), we used morphological curve analysis to define the best knot at which a change in the linear dose-response was observed. The analyses were then segmented according to this knot and Cox or Fine-Gray regression modeling considered the stiffness index of interest as a continuous variable in each of the defined segments, assuming a linear risk in each of the segments. All the models were fully adjusted a priori for age, sex, classic cardiovascular risk factors (body mass index, smoking, diabetes, SBP, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides), and diabetes, hypertension, and dyslipidemia treatments.

The added predictive value of carotid stiffness indices was assessed by analyzing improvement in discrimination (area under the ROC curve [AUC]) and in categorical net reclassification index (NRI), considering 5% and 10% as a cutoff points, when each was included in validated and specific IHD (REGICOR)¹¹ and cerebrovascular (FRESCO)¹² risk functions.

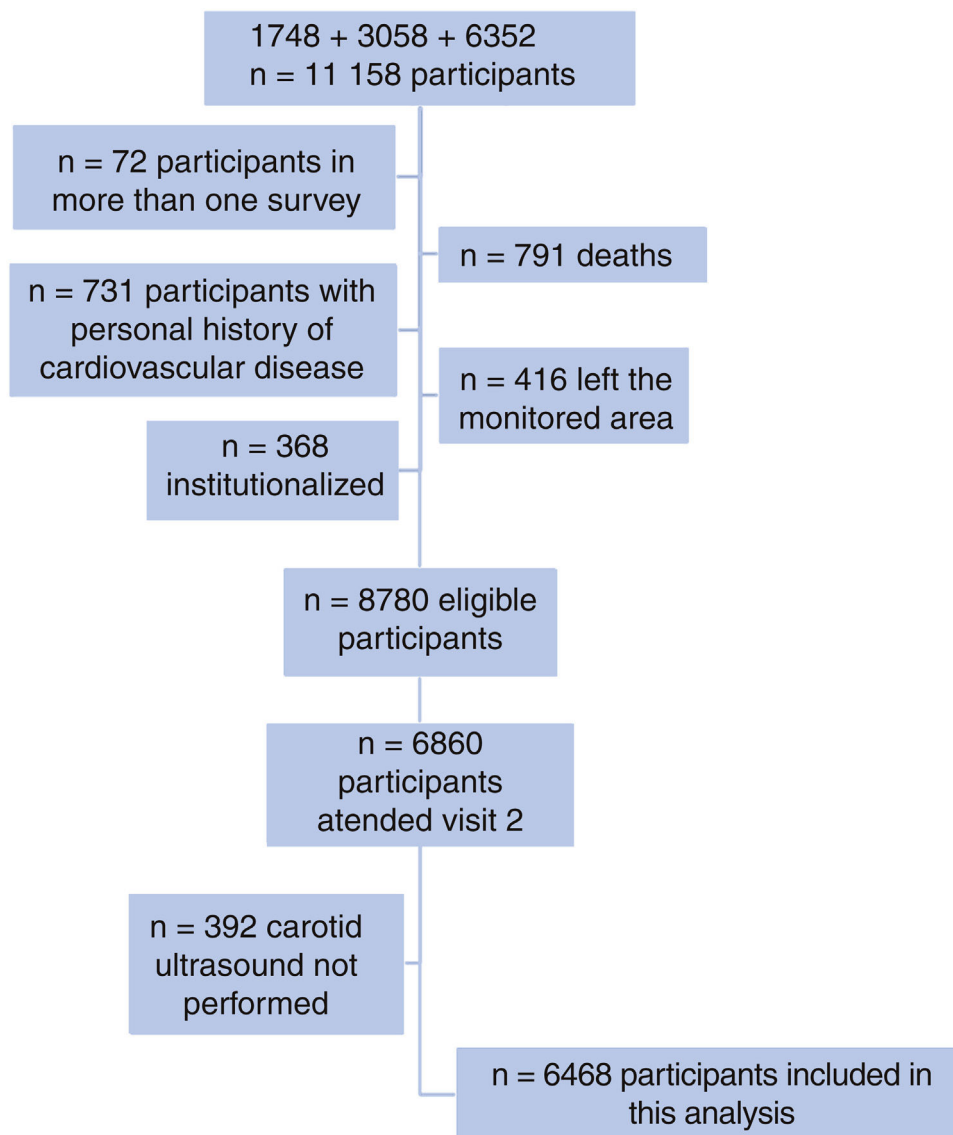


Figure 2. Flow chart of the participants included in this study.

Table 1

Clinical characteristics and carotid stiffness values in participants without and with a vascular event during follow-up

Clinical characteristics	No event n = 6287	Overall vascular disease n = 181	P	N
Age, y	58.8 ± 12.0	68.5 ± 10.9	< .001	6468
Female sex	3518 (56.0)	77 (42.5)	< .001	6468
Body mass index, kg/m ²	27.2 ± 4.45	28.5 ± 4.63	< .001	6462
Smoking			.642	6429
Never	3440 (55.0)	97 (53.9)		
Current or former < 1 y	1116 (17.9)	29 (16.1)		
Former > 1 y	1693 (27.1)	54 (30.0)		
Diabetes mellitus	649 (10.3)	47 (26.1)	< .001	6456
Glycemia, mg/dL	92.0 [85.8;101]	96.0 [88.9;109]	< .001	6411
Diabetes treatment	544 (8.7)	44 (24.3)	< .001	6456
Hypertension	2992 (47.7)	139 (76.8)	< .001	6459
Systolic blood pressure, mmHg	129 ± 19.6	140 ± 20.1	< .001	6466
Diastolic blood pressure, mmHg	77.5 ± 10.1	79.6 ± 10.1	.004	6466
Hypertension treatment	1524 (24.3)	94 (51.9)	< .001	6456
Total cholesterol, mg/dL	207 ± 35.8	211 ± 39.2	.203	6411
LDL cholesterol, mg/dL	134 ± 30.8	139 ± 33.7	.073	6343
HDL cholesterol, mg/dL	53.4 ± 12.0	50.6 ± 11.5	.001	6411
Triglycerides, mg/dL	86.0 [63.0;118]	104 [75.5;128]	< .001	6412
Dyslipidemia treatment	1000 (15.9)	37 (20.6)	.118	6456
Carotid stiffness indices				
Strain x 100	9.49 [7.99;11.1]	8.92 [6.82;10.8]	.001	6468
Stiffness parameter	5.64 [4.63;7.03]	6.80 [5.27;9.10]	< .001	6467
Peterson elasticity coefficient, x 0.1 kPa	7.12 [5.66;9.17]	9.13 [6.82;12.2]	< .001	6467
Compliance coefficient, kPa ⁻¹	0.82 [0.66;1.02]	0.74 [0.56;0.92]	< .001	6468
Distensibility coefficient, x 1000 kPa ⁻¹	30.1 [23.3;38.1]	23.5 [17.6;31.6]	< .001	6466
Pulse wave velocity	5.74 [5.10;6.55]	6.46 [5.61;7.64]	< .001	6467

LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

Continuous traits distribution is shown as mean ± standard deviation or median [interquartile range: quartile 1; quartile 3]. Categorical traits are shown as No. (%).

All statistical tests were based on 2-tailed hypothesis testing and *P* values below 0.05 were considered statistically significant. Statistical analysis was performed with R version 4.1.2, and pspline function, survival, cmprsk and mstate R packages were also used.

For sensitivity analysis, the potential role of the laboratory where the images were analyzed was explored in 3 ways: *a*) including the interaction between the laboratory and the stiffness variable in the multivariate model; *b*) stratifying the analysis by

Table 2

Spearman correlation between clinical variables and stiffness indices

	Age	BMI	Gluc	SBP	DBP	T-Cho	LDL	HDL	TG	DC	PWV	Strain	Stiff	Compl	PE
Age	1	0.190	0.240	0.467	0.002	0.075	0.043	0.015	0.180	−0.621	0.634	−0.290	0.618	−0.446	0.633
BMI	< .001	1	0.371	0.361	0.321	0.027	0.042	−0.282	0.361	−0.258	0.269	−0.097	0.186	−0.085	0.265
Gluc	< .001	< .001	1	0.344	0.222	0.043	0.030	−0.197	0.330	−0.274	0.281	−0.098	0.212	−0.125	0.280
SBP	< .001	< .001	< .001	1	0.598	0.061	0.041	−0.116	0.280	−0.588	0.590	−0.115	0.406	−0.361	0.599
DBP	.872	< .001	< .001	< .001	1	0.113	0.108	−0.099	0.227	−0.271	0.272	−0.189	0.068	−0.159	0.271
T-Cho	< .001	.034	.001	< .001	< .001	1	0.940	0.324	0.281	−0.056	0.056	−0.023	0.026	−0.100	0.057
LDLc	.001	.001	.018	.001	< .001	< .001	1	0.132	0.206	−0.036	0.035	−0.018	0.010	−0.064	0.036
HDLc	.220	< .001	< .001	< .001	< .001	< .001	< .001	1	−0.412	0.077	−0.082	0.043	−0.062	−0.066	−0.080
TG	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	1	−0.224	0.233	−0.102	0.170	−0.108	0.230
DC	< .001	< .001	< .001	< .001	< .001	< .001	.005	< .001	< .001	1	−0.990	0.703	−0.931	0.773	−0.992
PWV	< .001	< .001	< .001	< .001	< .001	< .001	.005	< .001	< .001	< .001	1	−0.696	0.948	−0.767	0.995
Strain	< .001	< .001	< .001	< .001	< .001	.060	.147	.001	< .001	< .001	< .001	1	−0.743	0.615	−0.682
Stiff	< .001	< .001	< .001	< .001	< .001	.035	.427	< .001	< .001	< .001	< .001	< .001	1	−0.753	0.936
Compl	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	1	−0.766
PE	< .001	< .001	< .001	< .001	< .001	< .001	.004	< .001	< .001	< .001	< .001	< .001	< .001	< .001	1

BMI, body mass index; Compl, compliance coefficient; DBP, diastolic blood pressure; DC, distensibility coefficient; Gluc, glucose; HDLc, high density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; PE, Peterson elasticity coefficient; PWV, pulse wave velocity; SBP, systolic blood pressure; Stiff, stiffness; T-Cho, total cholesterol; TG, triglycerides.

Spearman correlation (rho coefficient, above the diagonal; *P* value, below the diagonal) between clinical variables and stiffness indices of interest.

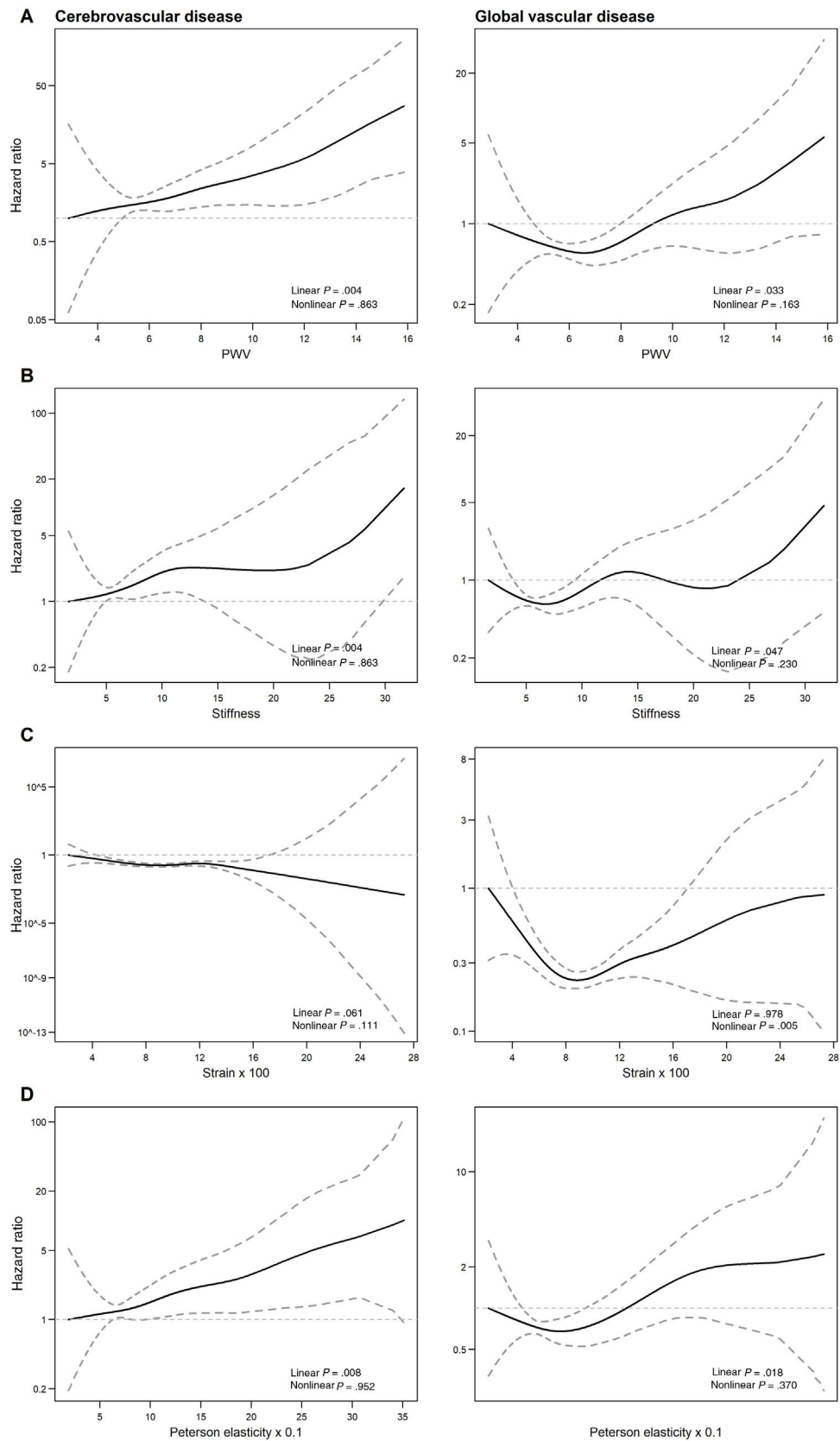


Figure 3. Predicted relative risk (with 95% confidence limits – dotted lines) of cerebrovascular disease, and overall vascular disease related to several stiffness indices (A-D). The graph was produced using a Cox regression model with spline smoothing functions and 2 degrees of freedom. PWV, pulse wave velocity.

Table 3

Multivariate adjusted association between each of the carotid stiffness indices and the outcomes of interest considering competing risk.

	Strain HR (95% CI) (per 0.01 units)	Stiffness HR (95%CI) (per 1 unit)	Peterson elasticity coefficient HR (95%CI) (per 10 units)	Compliance coefficient HR (95%CI) (per 1 unit)	Distensibility coefficient HR (95%CI) (per 0.001 units)	Pulse wave velocity HR (95%CI) (per 1 unit)
<i>Linear association assumption</i>						
Ischemic heart disease	—	1.01 (0.91-1.12)	1.01 (0.93-1.09)	1.75 (0.77-4.02)	1.02 (0.98-1.05)	0.98 (0.77-1.26)
Cerebrovascular disease	0.91 (0.83-1.00)	1.09 (1.03-1.16) ^a	1.08 (1.02-1.14) ^b	0.50 (0.17-1.43)	0.97 (0.93-1.00)	1.29 (1.10-1.51) ^b
Overall vascular disease	—	1.06 (1.00-1.12) ^c	1.05 (1.01-1.10) ^a	1.10 (0.56-2.18)	1.00 (0.97-1.02)	1.15 (0.99-1.33)
Overall mortality	1.03 (0.89-1.16)	1.01 (0.88-1.16)	1.03 (0.95-1.13)	1.88 (0.56-6.32)	1.02 (0.97-1.06)	1.07 (0.77-1.47)
<i>Nonlinear association assumption</i>						
	Strain ≤ 0.09 HR (95%CI) (per 0.01 units)	Strain > 0.09 HR (95%CI) (per 0.01 units)				
Ischemic heart disease	0.85 (0.66-1.08)	1.16 (1.05-1.28) ^b				
Overall vascular disease	0.80 (0.69-0.93) ^c	1.09 (1.00-1.19) ^a				

95%CI, 95% confidence interval; HR, hazard ratio.

Adjusted for age, sex, body mass index, smoking, diabetes, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides. Competing risk: noncardiovascular mortality as a competitive event for ischemic heart disease and cerebrovascular disease, ischemic heart disease mortality as a competitive event for cerebrovascular diseases, and cerebrovascular disease mortality as a competitive event for ischemic heart disease. Linear association assumption: a linear association assumption is considered for all the indices. Nonlinear association assumption: analysis of the association between strain and global vascular disease/ischemic heart disease was segmented according to the knot at which a change in the linear dose-response is observed (0.09), and strain is considered as a continuous variable in each of the defined segments, assuming a linear risk in each of the segments.

^a P-value < .025.^b P-value < .01.^c P-value < .05.

laboratory; and c) including the laboratory as a covariate in the multivariate model.

RESULTS

The flow chart of the individuals finally included in the analysis is shown in [figure 2](#) (n = 6468; 73.67% of the originally eligible participants included). No clinically significant differences between those included (n = 6468) and not included (n = 2312) were observed ([table 1 of the supplementary data](#)).

The median follow-up was 6.5 years, and 97, 85, 181 and 311 IHD, cerebrovascular, overall vascular, and fatal events, respectively, were observed. These events represent a cumulative

incidence rate of 1.50%, 1.31%, 2.80%, and 4.81%, respectively, during the follow-up. The characteristics of the participants included in the study, stratified by the incidence of overall vascular disease, are shown in [table 1](#). Participants with overall vascular disease were older, with a higher proportion of men and higher prevalence of vascular risk factors. They also presented with higher levels of stiffness, Peterson's elasticity coefficient, and PWV and lower strain, compliance, and distensibility coefficients. Participant characteristics stratified by the presence of IHD, cerebrovascular disease, and overall mortality are shown in [tables 2 to 4 of the supplementary data](#). The correlation between carotid stiffness indices and vascular risk factors is shown in [table 2](#).

The dose-response association between carotid artery stiffness indices and the outcomes of interest showed 3 patterns ([figure 3](#);

Table 4

Analysis of the added predictive capacity of carotid stiffness indices for ischemic heart disease and cerebrovascular events

		Strain		Stiffness		Peterson elasticity coefficient		Pulse wave velocity	
		c-statistic (95%CI)	NRI (95%CI)	c-statistic (95%CI)	NRI (95%CI)	c-statistic (95%CI)	NRI (95%CI)	c-statistic (95%CI)	NRI (95%CI)
Ischemic heart disease	REGICOR	0.774 (0.734; 0.815)	—	—	—	—	—	—	—
	+ carotid stiffness index	0.789 (0.749; 0.829)	−0.014 (−0.084; 0.055)	—	—	—	—	—	—
	P value	.070	.492	—	—	—	—	—	—
Cerebrovascular disease	FRESCO	—	—	0.817 (0.761; 0.873)	—	0.817 (0.761; 0.873)	—	0.817 (0.761; 0.873)	—
	+ carotid stiffness index	—	—	0.811 (0.755; 0.868)	−0.009 (−0.087; 0.070)	0.809 (0.753; 0.866)	−0.028 (−0.139; 0.083)	0.808 (0.751; 0.865)	−0.001 (−0.086; 0.083)
	P value	—	—	.143	.828	.074	.621	.066	.974

95%CI, 95% confidence interval; NRI, categorical net reclassification index (0-4.99%; 5-9.99%; ≥ 10% were used to define the low, intermediate and high risk categories).

figure 1 of the supplementary data): a) compliance and distensibility coefficients were not associated with any of the outcomes of interest; b) PWV, stiffness, and Peterson elasticity coefficient were linearly and directly related to cerebrovascular and overall vascular disease (figure 3A,B,D); and c) strain showed a nonlinear U-shaped relationship to overall vascular disease and IHD (figure 2C; figure 1C of the supplementary data), with an initial risk decrease up to values of 0.09 and a subsequent risk increase from strain values > 0.09.

In the multivariate Cox regression model, the risk of cerebrovascular disease increased by 9% (95%CI, 3% to 16%) per stiffness unit increase, by 8% (95%CI, 2–14) per 10-unit increase in Peterson elasticity coefficient, and by 29% (95%CI, 10–51) per PWV unit increase (table 3). When overall vascular disease was analyzed, the risk increase per corresponding stiffness and Peterson elasticity was 6% (95%CI, 0–12), and 5% (95%CI, 1–10%), respectively (table 3).

As the association between strain and overall vascular disease was not linear, the analysis was stratified by the point that best differentiated the 2 patterns of the association: ≤ 0.09 and > 0.09 (figure 2C, table 3). When strain was ≤ 0.09 units, each 0.01 increase was associated with a lower risk of vascular events (HR, 0.80; 95%CI, 0.69–0.93), whereas when strain was > 0.09 , each 0.01 increase in strain was associated with a higher risk of vascular events (HR, 1.09; 95%CI, 1.00–1.19). This nonlinear pattern was mainly dependent on IHD risk: when strain was ≤ 0.09 units, each 0.01 increase was associated with a lower risk of coronary events (HR, 0.85; 95%CI, 0.66–1.08), whereas above this value, each 0.01 increase in strain was associated with a higher risk of coronary events (HR, 1.16; 95%CI, 1.05–1.28). Carotid artery stiffness indices were not associated with all-cause mortality.

The addition of strain, stiffness, Peterson elasticity coefficient, or PWV on validated IHD or cerebrovascular predictive models did not improve the discrimination or the reclassification of the clinical risk models (table 4).

The results stratified by sex (tables 5 and 6 of the supplementary data) and the sensitivity analyses were consistent with those observed in the main analysis.

DISCUSSION

In this study, we analyzed the linear and nonlinear dose-response association of several indices of local carotid artery stiffness with vascular clinical outcomes and overall mortality. We report an independent, linear, and direct association between cerebrovascular disease and carotid stiffness, Peterson elasticity coefficient, and PWV. We also report an independent and nonlinear association between carotid strain and overall vascular disease and IHD, with a clear change in the direction of the association at a strain value of 0.09: an inverse association below this value and direct association above this cutoff. The addition of these indices to specific coronary or cerebrovascular risk functions did not improve predictive capacity.

The association between local carotid stiffness indices and vascular outcomes has been analyzed in previous studies. Three systematic reviews published from 2015 to 2016 summarize the evidence,^{4,13,14} supporting the association between stiffer carotid arteries and cerebrovascular disease risk in most of the studies^{15–19} but not in all of them.^{20–21} These studies also report a lack of association between most of the carotid stiffness indices and IHD risk.^{4,13,22}

In our study, we incorporated one of the largest sample sizes and one of the longest follow-ups to evaluate the correlation between carotid stiffness and vascular disease. Furthermore, we

examined both linear and nonlinear dose-response patterns in this relationship. This analysis is crucial in identifying nonlinear patterns that may define specific stiffness values where the effect size of the association shows exponential increase or decline, reaches a plateau, or even changes the direction of the association. We replicated the linear association between some carotid stiffness indices and cerebrovascular disease. The mechanisms explaining this association have been related to an increased pulsatile pressure and flow load, characterized by increased pulse pressure.⁴

It is difficult to disentangle whether carotid stiffness is a cause or consequence of vascular dysfunction. On the one hand, antihypertensive drugs reduce pulse pressure, improving vascular function, and on the other hand, increased pulse pressure induces vascular and endothelial dysfunction,^{23,24} and artery hypertrophic remodeling and rarefaction of small cerebral arteries, decreasing vascular relaxation capacity.²⁵ Other proinflammatory, proliferative, pro-oxidant and hemostatic factors²⁶ and carotid intraplaque hemorrhage through rupture-prone atherosclerotic carotid plaques²⁷ have also been proposed as potential actors in this complex relation between arterial stiffness, vascular dysfunction, and clinical events.

Interestingly, we also report a nonlinear association between carotid strain and overall vascular disease, mainly dependent on IHD risk. Carotid strain has not been previously related to IHD risk,^{4,14} although usually the nonlinear dose-response relationship has not properly been explored, and a linear relation has been assumed. This finding was unexpected (mainly the direct association observed above values of 0.09 units of strain and IHD risk) and we cannot exclude a spurious association as the local carotid stiffness indices could not reflect the local coronary vascular dysfunction. Nevertheless, this nonlinear pattern of association deserves assessment and potential replication in other studies.

Finally, the inclusion of carotid stiffness indices in specific coronary or cerebrovascular risk functions did not improve the predictive capacity of those functions. A previous meta-analysis with individual data reported an improvement in reclassification (continuous NRI, integrated discrimination index) but not in the discrimination capacity of the original model.⁴ Therefore, the limited added predictive value along with the lack of standardized techniques and reference values could hamper the usefulness of these indices in clinical practice.

The main strength of our study is the population-based sampling, the standardized methodology and the complete follow-up of the participants. However, there are some limitations. First, despite the recommendations of expert consensus to measure pulse pressure at the site of distension,³ we determined pulse pressure from brachial artery measurements, which may not reflect the local pressure conditions at the carotid arteries. Carotid stiffness indices were measured in 2 laboratories, which could introduce some misclassification of the main exposure variables, even though the same methodology was used. However, no differences between laboratories were observed and the results were consistent in sensitivity analyses. Inter- and intrasonographer variability were evaluated using repeated intima-media thickness (IMT) measurements but not stiffness indices. Cerebrovascular events included fatal and nonfatal stroke, but we did not have information related to the type of stroke.

CONCLUSIONS

Carotid stiffness, Peterson elasticity coefficient, and PWV are linearly and directly associated with cerebrovascular disease risk.

Carotid strain presents a nonlinear U-shaped relation with IHD risk; an initial inverse association up to values of 0.09 and a direct association above this value were observed. However, the inclusion of these stiffness indexes did not improve the predictive capacity of risk functions.

WHAT IS KNOWN ABOUT THE TOPIC?

- The association between carotid stiffness and cerebrovascular disease has already been documented.
- However, the dose-response pattern of this associations has not been properly assessed.

WHAT DOES THIS STUDY ADD?

- Several carotid stiffness measurements (stiffness, Peter-son elasticity coefficient, and PWV) are positively and linearly related to cerebrovascular but not to IHD risk.
- The nonlinear association between carotid strain and IHD should be replicated in other studies.
- Addition of the stiffness indices did not improve the predictive capacity of validated IHD or cerebrovascular risk models.

FUNDING

This work was supported by the Carlos III Health Institute–European Regional Development Fund [CIBERCV]; PERIS from *Agència de Gestió d'Ajuts Universitaris i de Recerca* [SLT002/16/00088]; and the Government of Catalonia through the Agency for Management of University and Research Grants [2017SGR946].

ETHICAL CONSIDERATIONS

All the participants were duly informed and signed a written consent form. The study was approved by the *Parc de Salut Mar* ethics committee (2016/7075/I). Gender dimensions have been considered in the recruitment, data collection and analyses.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

During the preparation of this work the authors did not use any artificial intelligence tool.

AUTHORS' CONTRIBUTIONS

Substantial contribution to the conception and design of the work: R. Elosua, R. Arnold, E. de Groot, I. R. Degano, J. Marrugat, R. Ramos. Substantial contribution to the acquisition of the data of the work: R. Elosua, R. Arnold, E. de Groot, R. Martí-Lluch, I. R. Degano, J. Marrugat, R. Ramos. Substantial contribution to the analysis and interpretation of the work: R. Elosua, A. Toloba, R. Ramos. Drafting the work: R. Elosua, R. Ramos. Reviewing the work critically for important intellectual content: A. Toloba, R. Arnold, E. de Groot, R. Martí-Lluch, I. R. Degano, J. Marrugat. Final approval of the version to be published: R. Elosua, A. Toloba, R. Arnold, E. de Groot, R. Martí-Lluch, I. R. Degano, J. Marrugat, R. Ramos. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: R.

Elosua, A. Toloba, R. Arnold, E. de Groot, R. Martí-Lluch, I. R. Degano, J. Marrugat, R. Ramos.

CONFLICTS OF INTEREST

None.

ACKNOWLEDGMENTS

We thank Elaine M. Lilly, PhD, for her critical reading and revision of the English text.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.1016/j.rec.2023.09.004>

REFERENCES

1. GBD 2019. Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204–22.
2. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;1–111. 00.
3. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–2605.
4. Van Sloten TT, Sedaghat S, Laurent S, et al. Carotid Stiffness Is Associated With Incident Stroke. A Systematic Review and Individual Participant Data Meta-Analysis. *J Am Coll Cardiol*. 2015;66:2116–2125.
5. Van Bortel LM, Duprez D, Starmans-Kool MJ, et al. Clinical applications of arterial stiffness, task force III: Recommendations for user procedures. *Am J Hypertens*. 2002;15:445–452.
6. Grau M, Subirana I, Elosua R, et al. Trends in cardiovascular risk factor prevalence (1995–2000–2005) in northeastern Spain. *Eur J Cardiovasc Prev Rehabil*. 2007;14:653–9. Erratum in: *Eur J Cardiovasc Prev Rehabil*. 2008;15:502.
7. Zabalza M, Subirana I, Lluís-Ganella C, et al. Association Between Coronary Artery Disease Genetic Variants and Subclinical Atherosclerosis: An Association Study and Meta-analysis. *Rev Esp Cardiol*. 2015;68:869–877.
8. de Groot E, van Leuven SI, Duivenvoorden R, et al. Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. *Nat Clin Pract Cardiovasc Med*. 2008;5:280–288.
9. Stein JH, Korcarz CE, Hurst RT, et al. Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Disease Risk: A Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force Endorsed by the Society for Vascular. *J Am Soc Echocardiogr*. 2008;21:93–111.
10. Baena-Díez JM, Alzamora-Sas MT, Grau M, et al. Validez del cuestionario cardiovascular MONICA comparado con la historia clínica. *Gac Sanit*. 2009;23:519–525.
11. Marrugat J, Vila J, Baena-Díez JM, et al. Validity of the 10-year cardiovascular risk estimate in a population cohort of the REGICOR Study. *Rev Esp Cardiol*. 2011;64:385–394.
12. Marrugat J, Subirana I, Ramos R, et al. Derivation and validation of a set of 10-year cardiovascular risk predictive functions in Spain: the FRESKO Study. *Prev Med*. 2014;61:66–74.
13. Boesen ME, Singh D, Menon BK, Frayne R. A systematic literature review of the effect of carotid atherosclerosis on local vessel stiffness and elasticity. *Atherosclerosis*. 2015;243:211–222.
14. Yuan C, Wang J, Ying M. Predictive value of carotid distensibility coefficient for cardiovascular diseases and all-cause mortality: a meta-analysis. *Plos One*. 2016;11:e0152799.
15. Hosomi N, Ohshima H, Takahashi T, et al. Plasma adrenomedullin and carotid atherosclerosis in atherothrombotic ischemic stroke. *J Hypertens*. 2004;22:1945–1951.
16. Dijk JM, Van Der Graaf Y, Grobbee DE, Bots ML. Carotid stiffness indicates risk of ischemic stroke and TIA in patients with internal carotid artery stenosis: the SMART study. *Stroke*. 2004;35:2258–2262.
17. Zhang PF, Su HJ, Yao GH, et al. Plaque volume compression ratio, a novel biomechanical index, is independently associated with ischemic cerebrovascular Events. *J Hypertens*. 2009;27:348–356.
18. Yang EY, Chambless L, Sharrett AR, et al. Carotid arterial wall characteristics are associated with incident ischemic stroke but not coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 2012;43:103–108.
19. Mitsumura H, Sakuta K, Bono K, et al. Stiffness parameter beta of cardioembolism measured by carotid ultrasound was lower than other stroke Subtypes. *J Stroke Cerebrovasc Dis*. 2014;23:1391–1395.

20. Dijk JM, Algra A, van der Graaf Y, Grobbee DE, Bots ML. Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease. The SMART study. *Eur Heart J*. 2005;26:1213–1220.
21. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation*. 2006;113:657–663.
22. Leone N, Ducimetiere P, Gariepy J, et al. Distension of the carotid artery and risk of coronary events: the three-city study. *Arterioscler Thromb Vasc Biol*. 2008;27:1392–1397.
23. Beigel R, Dvir D, Arbel Y, et al. Pulse pressure is a predictor of vascular endothelial function in middle-aged subjects with no apparent heart disease. *Vasc Med*. 2010;15:299–305.
24. McEniery CM, Wallace S, Mackenzie IS, et al. Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. *Hypertension*. 2006;48:602–608.
25. Ryan SM, Waack BJ, Weno BL, et al. Increases in pulse pressure impair acetylcholine-induced vascular relaxation. *Am J Physiol*. 1995;268:H359–H363.
26. Prasad M, Lerman LO, Lerman A. Carotid Stiffness and Cerebrovascular Disease. The Physiology Beyond the Anatomy. *J Am Col Cardiol*. 2015;66:2126–2128.
27. Selwaness M, van den Bouwhuijsen Q, Mattace-Raso FU, et al. Arterial stiffness is associated with carotid intraplaque hemorrhage in the general population: the Rotterdam study. *Arterioscler Thromb Vasc Biol*. 2014;34:927–932.