

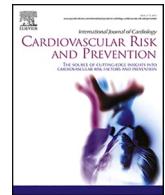


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## Prediction of stroke using an algorithm to estimate arterial stiffness



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### ABSTRACT

**Background:** Arterial stiffness is important because it is associated with adverse cardiovascular events including stroke. Methods that are based on pulse wave velocity have significant limitations in estimating arterial stiffness. The purpose of this paper is to present a novel easy to apply non-invasive method to estimate arterial stiffness that is based on pulse pressure.

**Methods:** Two indices to estimate arterial stiffness, (1) arterial stiffness 1 (AS1) and (2) arterial stiffness 2 (AS2) were developed and applied in two National Institutes of Health funded clinical trials, the Systolic Hypertension in the Elderly Program and the Systolic Blood Pressure Intervention Trial. These indices were developed by fitting individual survival models for selected predictor variables to the response, i.e. time to stroke, by selecting the coefficients that were statistically significant at the 0.05  $\alpha$  level after adjusting the variable weights. The indices were derived as the weighted linear combination of the coefficients.

**Results:** AS1 and AS2 performed well in two goodness of fit criteria i.e. overall model p-value and concordance correlation. Comparison of Cox models using indices AS1 and AS2 and chronological age indicated that AS1 and AS2 independently predicted the occurrence of stroke at five years better than chronological age. Nearly identical effects were observed when the analyses were limited to Black participants in SPRINT with a concordance correlation of 0.80 and log rank test p-value of 0.007.

**Conclusion:** These indices that are derived from pulse pressure predict the occurrence of stroke better than either pulse pressure or chronological age alone and may be used in designing new randomized clinical trials, and possibly incorporated in hypertension and stroke guidelines.

### 1. Introduction

Arterial stiffness is determined by the physical properties of the arterial wall that regulate how pressure and blood flow vary with changes in arterial diameter with every heartbeat. Pulse wave velocity (PWV) is influenced by the physical properties of the artery and is modulated by endothelial function, smooth muscle tone, nitric oxide, oxidative stress and inflammation [1,2]. Numerous studies on various disease-specific and community-based cohorts have demonstrated that higher carotid to femoral PWV (cfPWV) and brachial to femoral PWV (bfPWV) are associated with increased risk of major cardiovascular (CV) disease events [3–5]. An expert consensus document of the European Society of Hypertension Working Group on Vascular Structure and Function on the measurement of aortic stiffness in daily practice using

carotid-femoral pulse wave velocity states that, although carotid-femoral pulse wave velocity is considered the gold standard, standardization of its measurement is needed [6].

A scientific statement from the American Heart Association published on behalf of the AHA Council on Hypertension recommended that it is reasonable to measure arterial stiffness clinically by determining PWV. However, the statement includes an indication that single-point estimates of PWV are not recommended because there is a lack of prediction of CV outcomes in longitudinal studies. Use of pulse wave velocity in estimating the relationship of arterial stiffness with uric acid was associated with generally unsatisfactory results [7]. In addition, the statement mentions the need to examine the dependence of PWV to systolic blood pressure (SBP) and aging, as additional limitations of PWV methods. Also, measurement of PWV in different arterial segments such

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**Table 1**Measures of goodness of fit of the five indices of SHEP<sup>a</sup> data.

	P-value	Concordance	5%	95%
AS1†	2.028577e-15	0.6329524	0.6039712	0.6619336
AS1m‡	7.349576e-14	0.6269266	0.5972880	0.6565653
AS2§	1.084902e-17	0.6458316	0.6176189	0.6740444
AGE	3.726488e-07	0.5858519	0.5567674	0.6149364
PP	6.410814e-05	0.5700694	0.5400160	0.6001227

<sup>a</sup> Systolic Hypertension in the Elderly Program; †arterial stiffness 1; ‡arterial stiffness 1 modified; §arterial stiffness 2.

as carotid-radial was not recommended because it did not predict well clinical outcomes [8]. In addition, these methods have not been validated and much needs to be done to improve the utility of non-invasively determined PWV [9]. Thus, techniques based on PWV lack precision because they assume that arterial stiffness is uniform throughout the path of the pulse wave, and that it is constant throughout the cardiac cycle. The fact that the PWV depends on the SBP in the central arteries and the problems inherent to estimation of the length of pathway are additional limitations in estimating arterial stiffness based on PWV. In a comprehensive review of validation studies of PWV, Milan and associates stated that the methods to assess transit time and path length need validation in larger populations [10]. In summary, PWV methods are imprecise because of inaccuracies in measuring the length between the carotid (or the brachial artery) and the femoral artery and because of the short time intervals involved.

Methods based on pulse pressure have been used to estimate arterial stiffness in conjunction with stroke volume in ICU patients, and as a surrogate of arterial stiffness in relation to segmental relaxation, in heart failure in the elderly [5,11,12]. To our knowledge methods based on pulse pressure have not been used in large controlled clinical trials before. The purpose of this paper is to describe a novel pulse pressure based non-invasive, easy to apply method of estimating arterial stiffness derived from data from SHEP and SPRINT, two high quality hypertension NIH funded clinical trials. This new method does not have most of the limitations of PWV described above and was used to predict the occurrence of stroke up to five years in comparison to chronological age.

## 2. Methods

The overall plan was to develop estimates of arterial age based on pulse pressure adjusted for selected demographics and comorbidities in the Systolic Hypertension in the Elderly Program (SHEP) and the Systolic Blood Pressure Intervention Trial (SPRINT) and was used to evaluate whether arterial age is better than chronological age in predicting stroke.

### 2.1. Patient population

The patients included in this study were participants in the SHEP and the SPRINT [13,14]. SHEP was a 4736 participant multicenter randomized double-blind placebo controlled clinical trial designed to investigate whether chlorthalidone based stepped care therapy of patients older than 60 who had isolated systolic hypertension was better than placebo stepped care in preventing stroke [13]. Average age was 72, 48% were white women, 39% white men, 4% black women and 5% were black men. Blood pressure at baseline was 170/77 mm Hg, heart rate was 71 beats per minutes, body mass index was 28, 13% were smokers, 5% had history of myocardial infarction, 1% had history of stroke and 10% had history of diabetes. The randomized phase of the trial lasted 4.9 years at which time all participants were informed that chlorthalidone-based active therapy was superior to placebo and were advised to continue taking chlorthalidone. SHEP was supported by contracts with the National Heart Lung and Blood Institute and the National Institute of Aging.

SPRINT was a 9361 participant NIH sponsored study that examined the effect of intensive treatment (SBP target of <120 mm Hg) versus standard treatment (SBP target of <140 mm Hg) on CV events and mortality. The participants were at least 50 years old or older and had an SBP between 130 and 180 mm Hg at randomization. They had increased risk of CV events as defined by the following: clinical or subclinical CV disease other than stroke; estimated glomerular filtration rate of 20 or less; 10-year risk of CV disease of 15% or greater on the basis of the Framingham risk score; or an age of 75 years or older. Patients with diabetes mellitus or prior stroke were excluded. Patients had follow-up visits once every month for the first 3 months, and every 3 months thereafter.

In these two clinical trials the diagnosis of stroke was adjudicated by investigators blind to the randomized assignment.

To examine the congruence of the findings of the two clinical trials (SHEP and SPRINT) across PP levels, we compared the relationship of arterial stiffness indices with stroke to chronological age by investigating the subset of the intersection of the pulse pressures of SHEP and SPRINT.

### 2.2. Method for constructing indices for estimating arterial stiffness

In order to estimate vascular age, we constructed linear combinations of a basic list of variables selected from the literature that were associated with arterial stiffness and were available in the baseline datasets of SHEP and SPRINT as follows: PP: pulse pressure = SBP – DBP; Sex: male or female; Race: white or non-white; Smoker: current smoker; BMI: body mass index; MI: history of myocardial infarction; LVF: left ventricular failure; eduCOL: college education, or at least 16 years of education; eduHS: high school education, at least 12 years of education; DM: diabetes mellitus; GL: Glucose level; HistSMK: history of smoking; Response: Time from enrollment to stroke event in days.

### 2.3. Algorithms for arterial stiffness indices

#### 2.3.1. AS1 (arterial stiffness 1)

This index was defined by the following algorithm.

- fitting individual survival models for each selected predictor variable and the response time to stroke.
- selecting the coefficients that were statistically significant at the  $\alpha$  0.05 significance level.
- forming the variable weights by dividing every coefficient by the coefficient of PP and rounding up the coefficients.
- forming the index as the weighted linear combination of the coefficients.

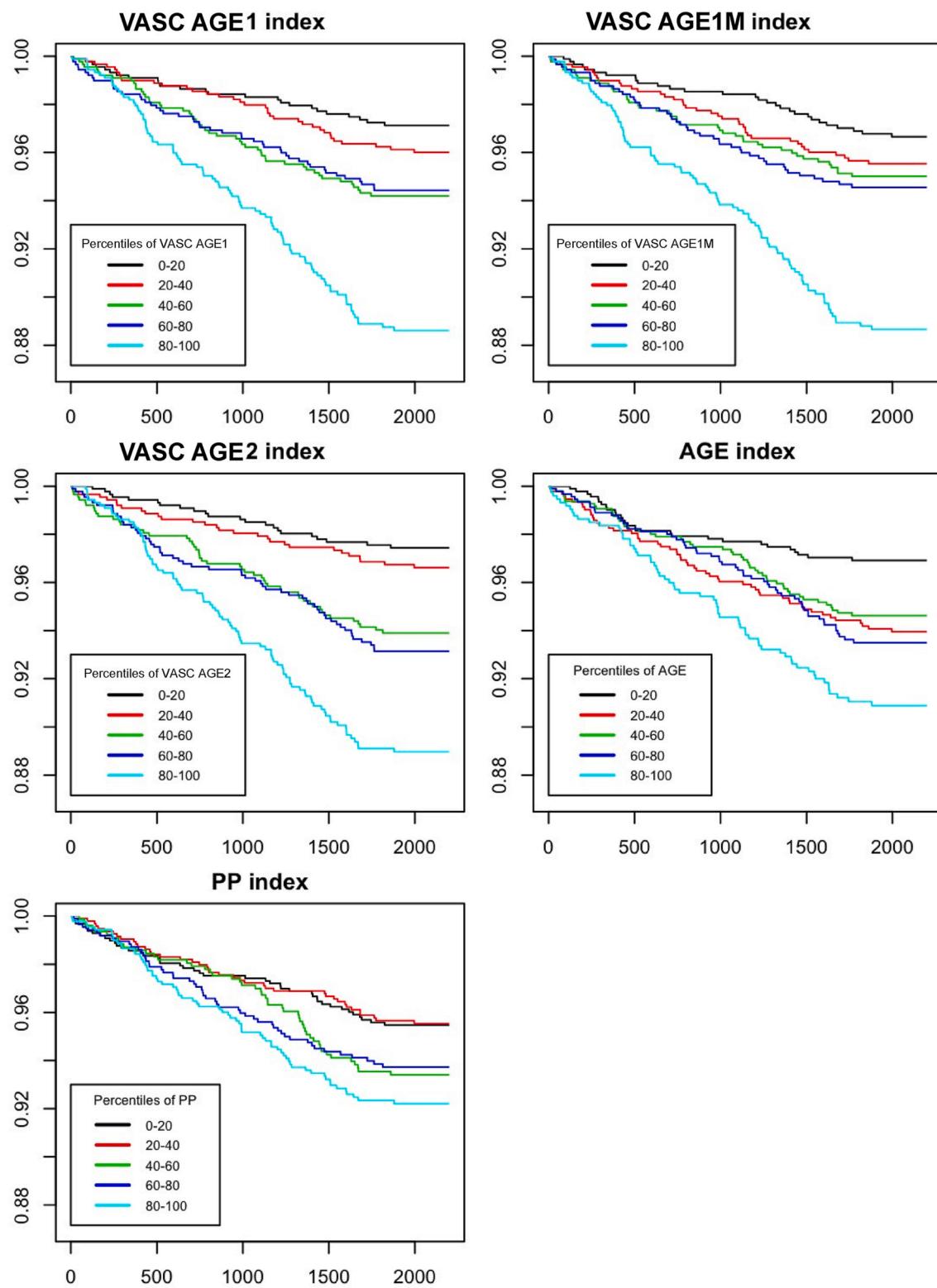
These steps were applied to the data from SHEP and SPRINT and produced the following index:

$$\text{AS1} = \text{PP} + 24 \text{ Smoker} + 54 \text{ LVF} + \text{GL}/3 + 27 \text{ Not (eduCOL)} + 41 \text{ DM.}$$

This index had the tendency to overfit because it emphasized linear combinations that were specific to the datasets that were used. To avoid this problem, we calculated the coefficients independently of each other. Other issues that may have influenced AS1 include that variables may have been correlated with the response by chance when many variables were tried. One way to avoid this overfitting is by false discovery adjustment using q-values. Amarntunga and Cabrera [15] proposed the idea of weight = -log (q-value) where a q-value is the p-value corrected for multiplicity. This yields a modified index AS1 using the weights obtained from the SHEP data.

$$\text{AS1m (modified AS1)} = \text{PP} + 15 \text{ Smoker} + 80 \text{ LVF} + \text{GL}/2 + 12 \text{ Not (eduCOL)} + 58 \text{ DM.}$$

Both AS1 and AS1m give prominence to LVF and DM/GL while AS1m reduced the impact of smoking and education by half. In theory AS1m reduces overfitting.



**Fig. 1.** Prediction of stroke up to 5 years using the three indices, chronological age and pulse pressure in SHEP. The subjects are divided into 5 groups by the 4 percentiles (20%, 40%, 60% and 80%) of the indices in predicting stroke. Each panel shows the survival curves for the 5 groups for each index.

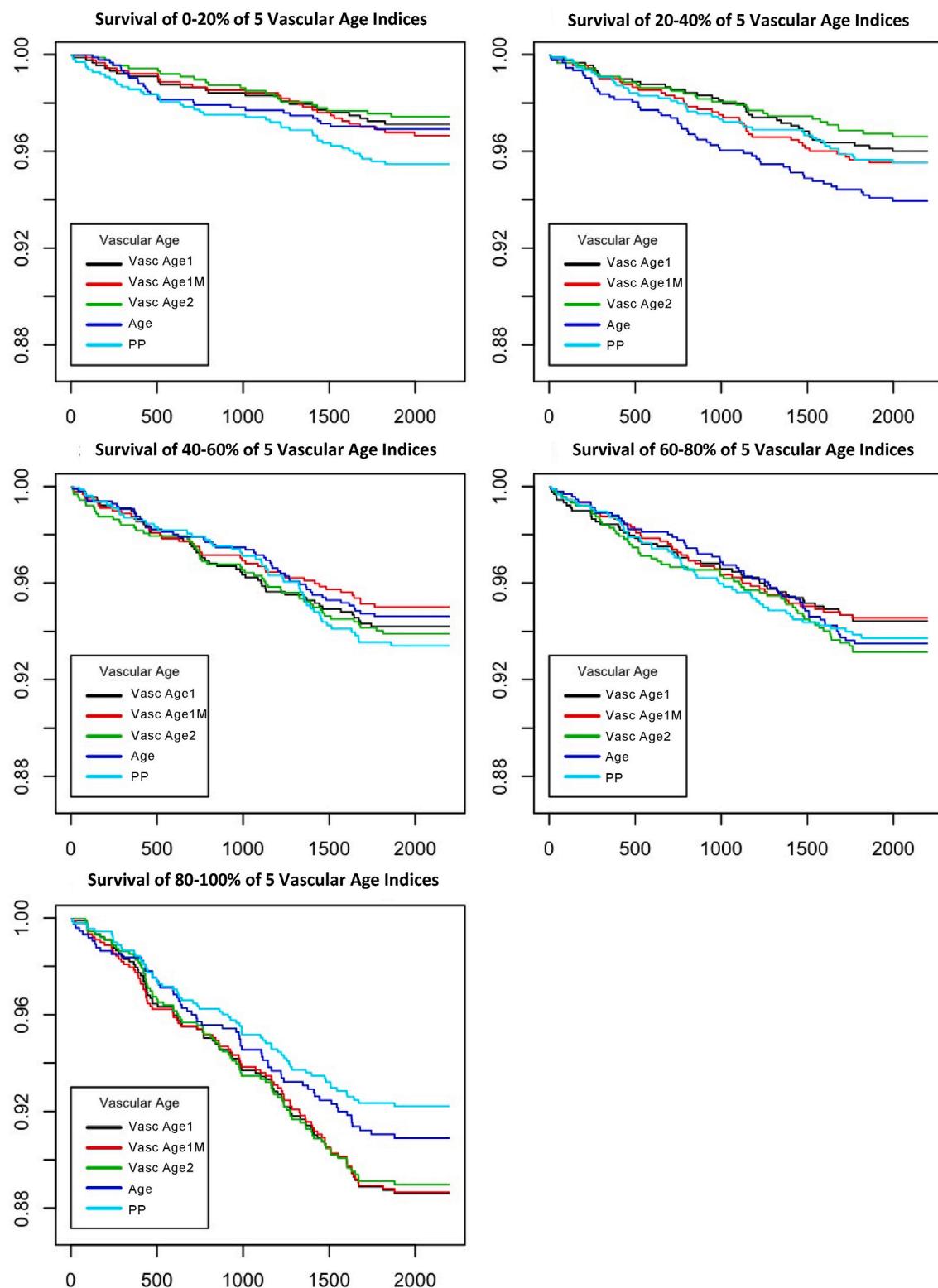
### 2.3.2. AS2 (arterial stiffness 2)

This index used the standard method in epidemiology, economics and other areas [16]. This index was defined by the following algorithm.

- (i) fitting multiple survival models with all the predictors combined and the response variable time to stroke, then multiplying the

coefficients by 100 and rounding them or by dividing the coefficients by the sum and multiplying them by 100.

- (ii) adjusting the variable weights by dividing every coefficient by the coefficient of PP.
- (iii) forming the index as the weighted linear combination of the coefficients.



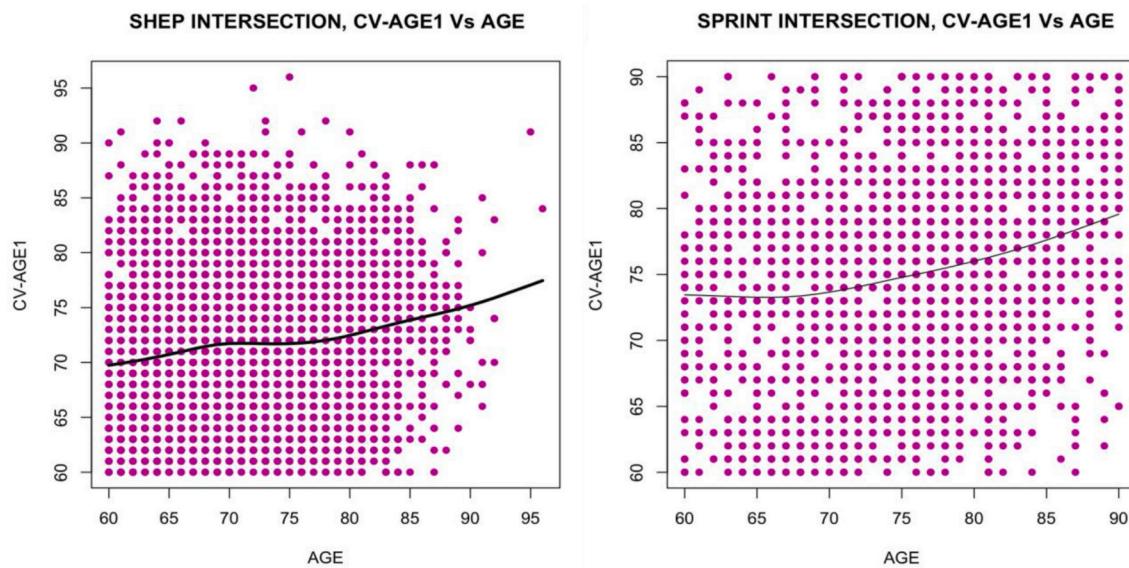
**Fig. 2.** Vascular age indices in predicting stroke up to 5 years in SHEP, compared to chronological age and pulse pressure. Each plot the survival curve for 5 groups by the 4 percentiles (20%, 40%, 60% and 80%) of the indices. Each panel shows the survival curves for one group from the five indices.

When these steps were applied to the data from SHEP, the result was the following index:

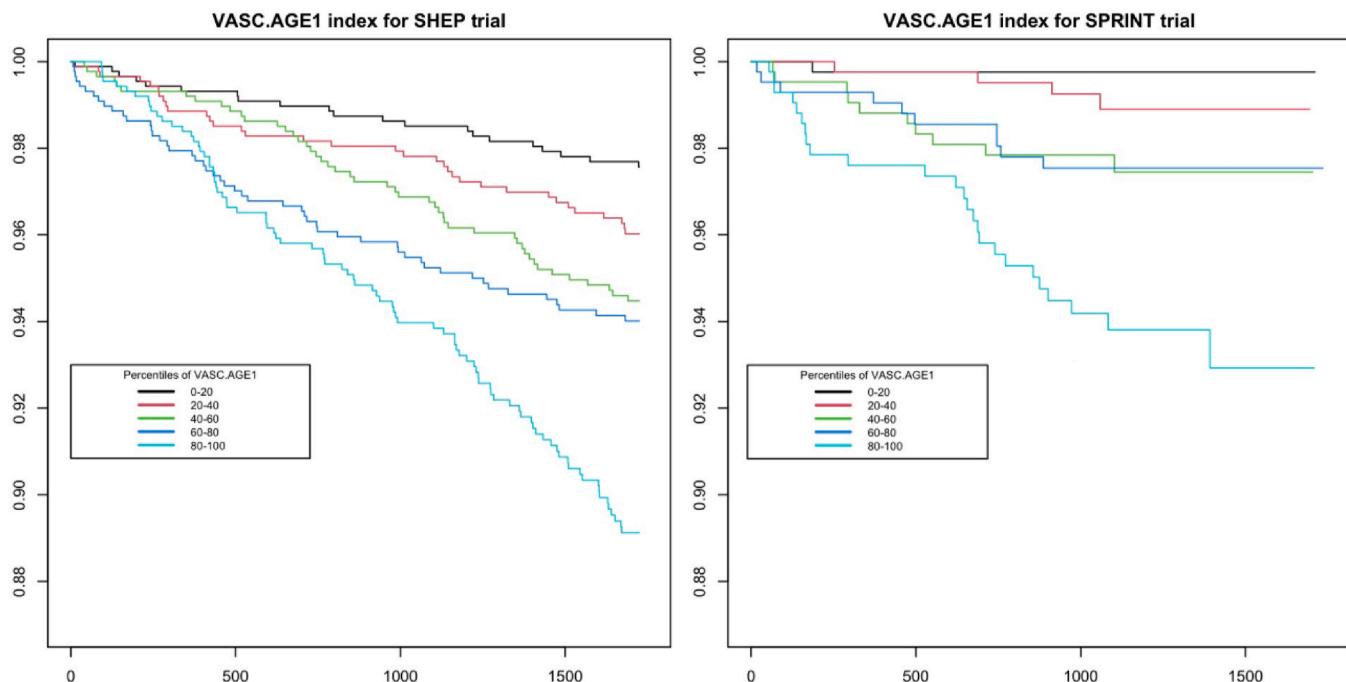
$$\text{AS2} = \text{PP} - 13.96 \text{ Sex} - 7.49 \text{ Race} + 32.14 \text{ Smoker} - 0.71 \text{ BMI} + 35.50 \text{ LVF} + 0.19 \text{ GL} - 30.20 \text{ MI} - 20.54 \text{ eduCOL} - 7.15 \text{ eduHS} - 7.15 \text{ DM} - 16.75 \text{ HisSMK}$$

### 3. Results

The results are presented in Table 1 and 2 and Figs. 1–4. Overall, AS1 and AS2 predicted the occurrence of stroke up to 5 years better than either chronological age or PP. AS1m validated the data by indicating that the results of AS1 were not appreciably different after correction for



**Fig. 3.** Scatter plot of AS1 and chronological age in the subset of the pulse pressure intersection of SPRINT and SHEP.



**Fig. 4.** AS1 index of the intersection of pulse pressure in the SPRINT and SHEP subset up to 5 years. The subjects are divided into 5 groups at the 4 percentile cutoffs (20%, 40%, 60% and 80%) of the indices. Each panel shows the survival curves for the 5 groups.

**Table 2a**  
Concordance correlation for SPRINT and SHEP using their corresponding fitted model.

SPRINT Intersection				SHEP Intersection					
	C.Cor	SE	2.50%	97.50%		C.Cor	SE	2.50%	97.50%
AGE	0.591	0.018	0.556	0.625	AGE	0.622	0.039	0.546	0.697
AS1	0.64	0.018	0.605	0.675	AS1	0.732	0.036	0.662	0.801
AS2	0.648	0.018	0.613	0.682	AS2	0.753	0.032	0.69	0.816

multiplicity

Fig. 1 shows that the three indices AS1, AS1m and AS2 are better than age alone and PP alone in that they better predict and better quantify the risk of time to stroke. The first group contains the subjects

whose index value is in the 0%–20% of the index, the second group is of subjects whose index is in the 20%–40% range, and the ranges of 40–60%, 60–80% and 80–100%. The following algorithm was applied to construct the graphs:

**Table 2b**

Concordance correlation using SHEP<sup>†</sup> as training set and SPRINT<sup>‡</sup> as testing set and using SPRINT<sup>‡</sup> as training set and SHEP<sup>†</sup> as testing set.

SPRINT <sup>‡</sup> Intersection				SHEP <sup>†</sup> Intersection					
	C.Corr	SE	2.50%	97.50%		C.Corr	SE	2.50%	97.50%
AGE	0.591	0.018	0.556	0.625	AGE	0.622	0.039	0.546	0.697
AS1 <sup>§</sup>	0.608	0.018	0.573	0.642	AS1 <sup>§</sup>	0.666	0.037	0.595	0.738
AS2 <sup>  </sup>	0.565	0.018	0.529	0.601	AS2 <sup>  </sup>	0.61	0.044	0.525	0.696

<sup>†</sup>Systolic Hypertension in the Elderly Program; <sup>‡</sup>Systolic Blood Pressure Intervention Trial; <sup>§</sup>arterial stiffness 1; <sup>||</sup>arterial stiffness 2.

1. Divide the data into 5 equal groups by the index (0–20%, 20–40%, 40–60%, 60–80%, 80–100%)
2. Plot survival curves by group by color: B-R-G-B-C (black, red, green, blue, cyan)

The differences in the stroke rate across low to high AS1, AS1m and AS2 are higher than the differences for chronological age alone and for PP alone.

Fig. 2 shows in each panel the survival curves of the 5 indices split by quintiles.

As expected, the stroke rates of AS1, AS1m and AS2 conform to the prediction within each quintile (0–20%, 20–40%, 40–60%, 60–80% and 80–100%).

### 3.1. Comparing indices by prediction of “time to stroke event”

To compare the indices, we calculated the model performances to predict time to stroke. Two goodness of fit criteria were used (i) overall model p-value (ii) concordance correlation with confidence intervals. Table 1 shows the summary of the results for the goodness of fit for the 5 models. The 3 indices performed better than age alone or PP alone and that the performance of the 3 indices were similar. Correction for multiplicity did not indicate that index AS1m was no different from the other two indices.

### 3.2. Comparison of arterial stiffness indices with stroke to chronological age using the pulse pressure intersection of SHEP and SPRINT

We expected that the indices derived from data from SHEP and SPRINT would be different since these trials were carried out in different time periods and with different populations and that the SHEP inclusion criteria limited the level of PP to above 70. Thus, the intersection dataset was restricted to PP ranging from 70 to 190 mm Hg.

### 3.3. Correlation of AS1 and AS2 indices with chronological age

Fig. 3 shows the correlation between AS1 and chronological age in the PP intersection subset of SHEP and SPRINT. The AS1 index was normalized to the distribution of age in the PP intersection subset. Both plots show only a small correlation between AS1 and chronological age indicating that AS1 is very different than age. Nearly identical effects were observed when the analyses were limited to Black participants in SPRINT with a concordance correlation of 0.80 and log rank test p-value of 0.007.

### 3.4. Concordance correlations of AS1 index with stroke in the pulse pressure overlap subset compared to chronological age

To study the performance of AS1 and AS2 indices further, we compared the concordance correlations of the indices for predicting stroke with the corresponding concordance correlations for chronological age in the intersection dataset of SHEP and SPRINT including participants with PP between 70 and 190 mm Hg. We fitted 3 Cox models to the response time-to-stroke using AS1, AS2 and chronological age. The results are shown in Table 2A where the estimates of concordance correlation for AS1 and AS2 are well above the upper confidence interval

for the concordance correlation for chronological age. The goodness of fit of this model is presented in Fig. 4. To validate the performance of AS1 and AS2 we used the SHEP fitted model to predict SPRINT stroke outcome and the SPRINT fitted model to predict SHEP stroke outcome. This may be analogous to using SHEP as training set and SPRINT as testing set and vice-versa. The estimates of concordance correlation are shown in Table 2B. This further validates the strong performance AS1.

## 4. Discussion

This study indicates that the two indices described above are successful in predicting the occurrence of stroke, in participants of the SHEP and SPRINT randomized clinical trials. These indices are based on pulse pressure, a variable that is easily measured in routine physical examinations and is not affected by the limitations of methods based on PWV. However, the method described in this report also has limitations including the lack of application to other data sets, by gender, age groups, in persons with different comorbidities, different blood pressure ranges and different ethnicities. AS1 and AS2 predict the occurrence of stroke better than chronological age probably because of the superiority of the methods presented here compared to methods based on PWV. These (PWV) methods depend on exact measurements of small time and distance which cannot be measured with the required accuracy and are estimated from the shape of the blood pressure curve during the cardiac cycle.

The indices described in this report are based on the well-known relationship between PP and arterial stiffness and are superior to chronological age in predicting stroke. The estimates of concordance correlation for AS1 and AS2 are well above the upper confidence interval for the concordance correlation for chronological age.

To further validate the performance of AS1 and AS2, we used the SHEP fitted model to predict SPRINT stroke outcome and the SPRINT fitted model to predict SHEP stroke outcome. This may be analogous to using the outcomes derived from SHEP data as a training set and the outcomes derived from SPRINT data as a testing set.

The indices described here, AS1 or AS2, are helpful in the management of individual patients with hypertension, and may help in the design and performance of new randomized clinical trials. They (AS1 and AS2) were based on easily obtained demographic and comorbidity variables and predicted stroke better than chronological age. These indices apply only to patients with hypertension where there are no published algorithms predicting stroke using the variables entered in the respective models.

## 5. Conclusion

In conclusion, these easy to derive indices from pulse pressure, AS1 and AS2, predict the occurrence of stroke better than either pulse pressure or chronological age alone and may be used in designing new randomized clinical trials, and possibly incorporated in hypertension and stroke guidelines.

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This study was supported in part by the New Jersey Health Foundation, Inc.

## Declaration of competing interest

We state that this manuscript is not under consideration elsewhere and that the research reported will not be submitted for publication elsewhere until a final decision is made as to the acceptability of the manuscript. There is no financial or other relationship that influenced the outcome of this paper. In addition, this manuscript represents original work without fabrication, fraud, plagiarism and has been read and approved by all authors.

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