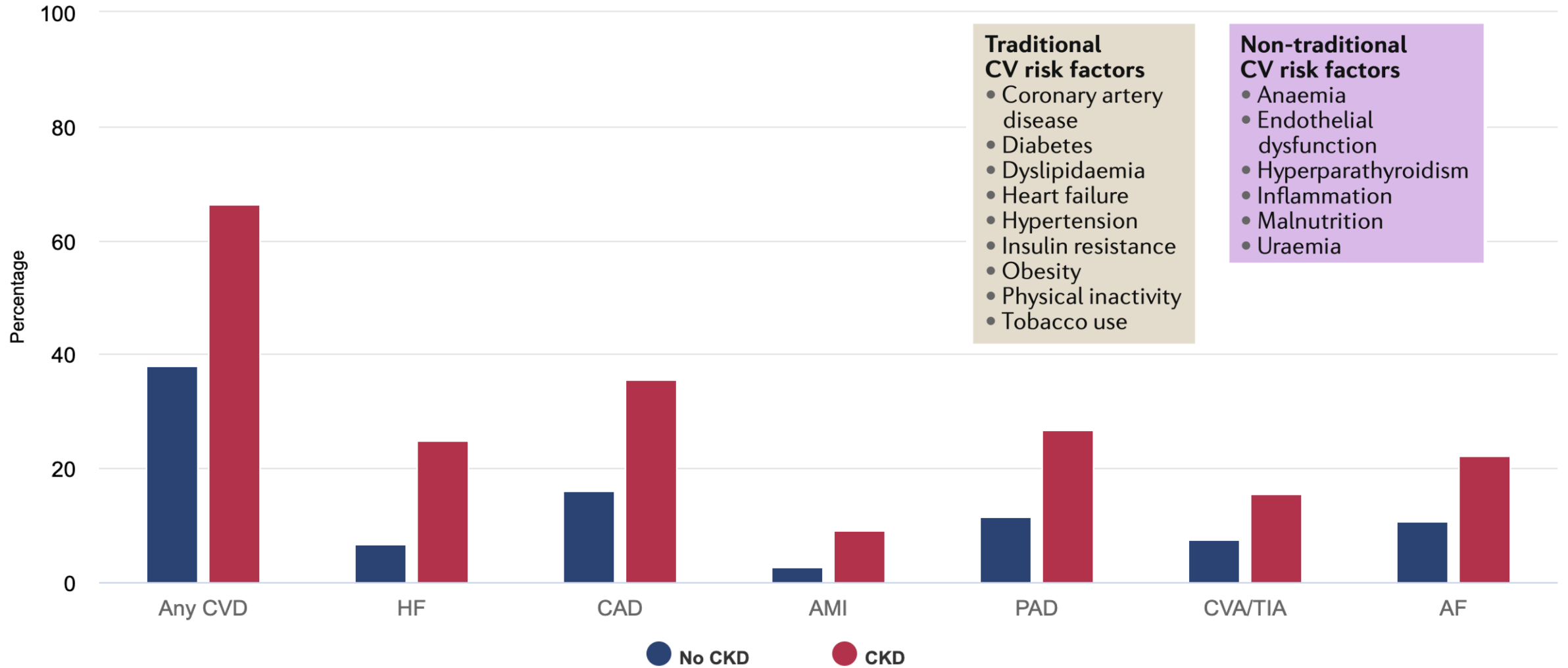
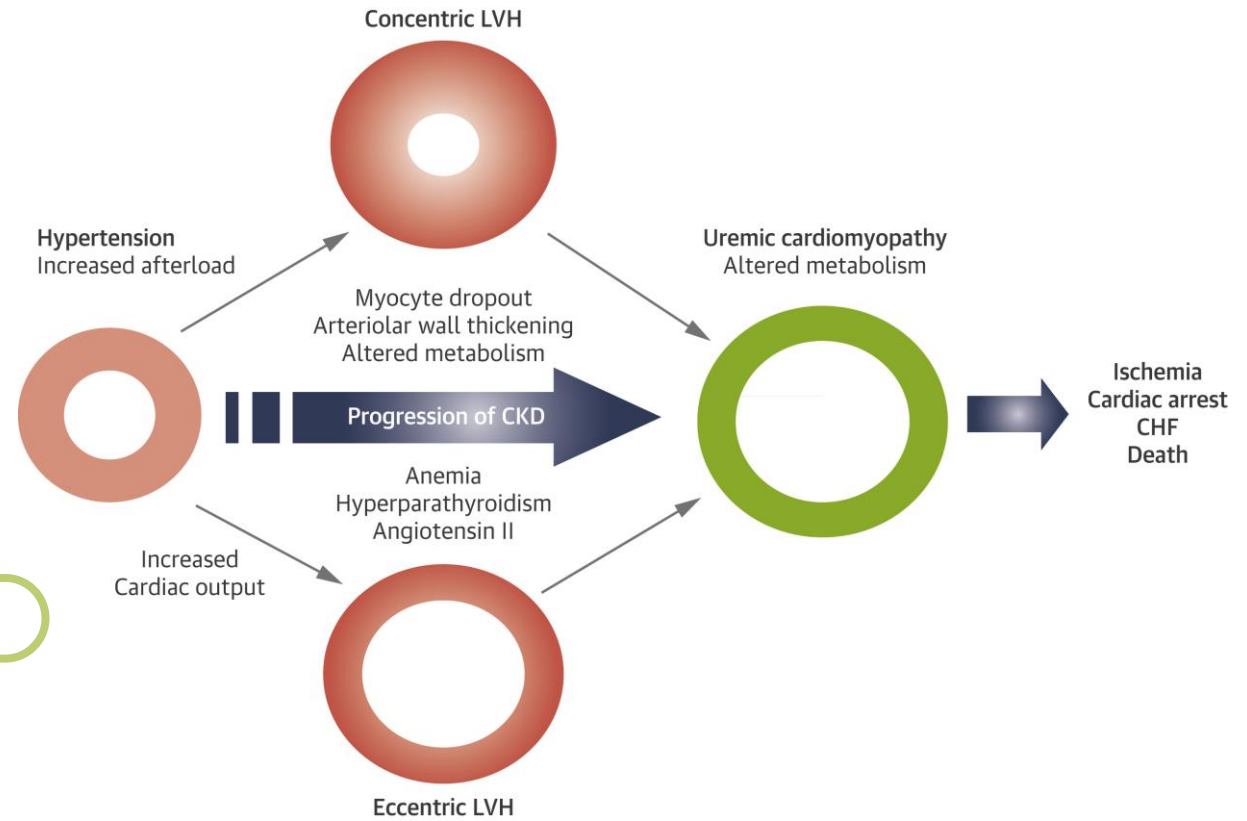
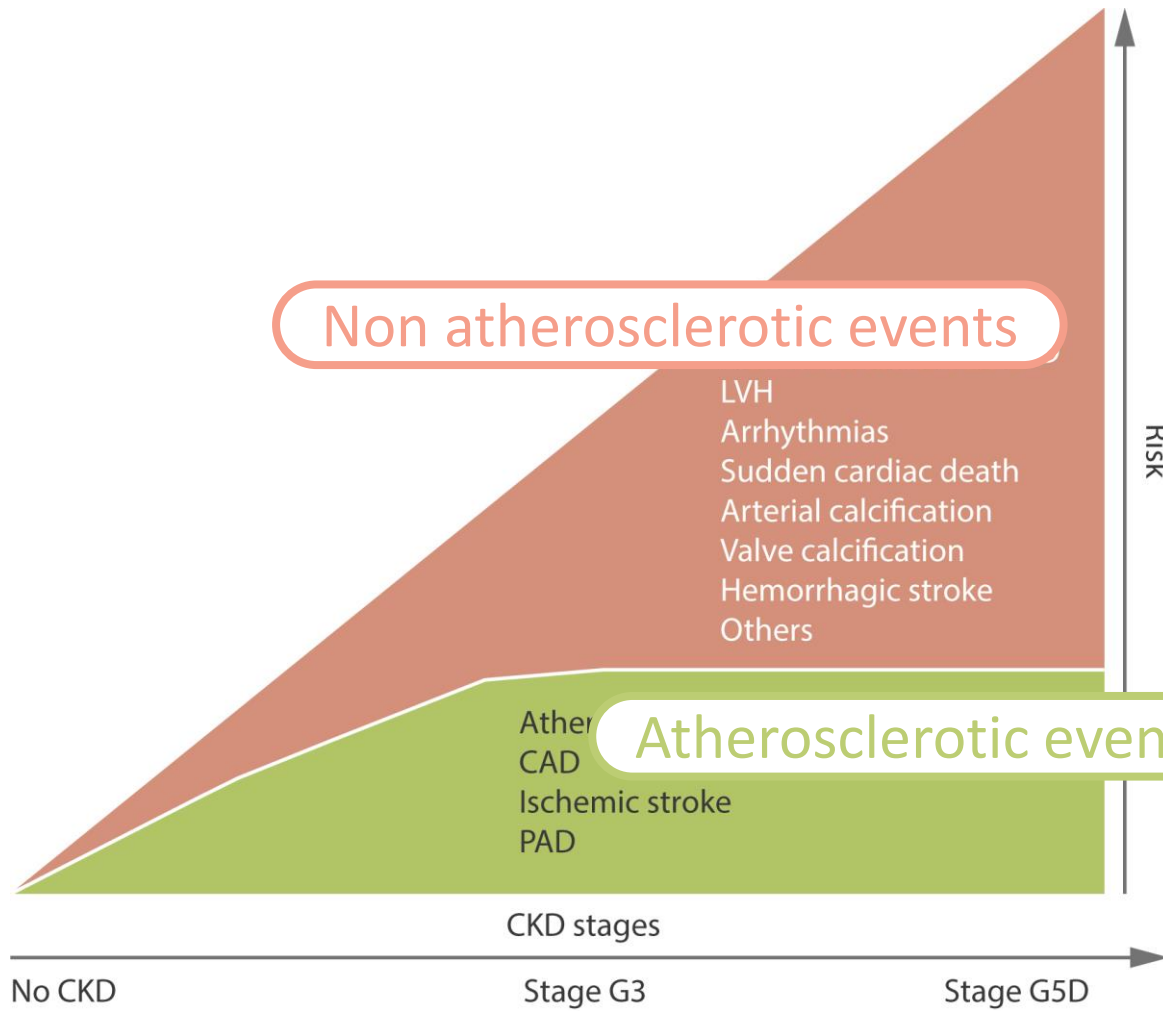


2022.08.20 花蓮慈濟 郭秋煌

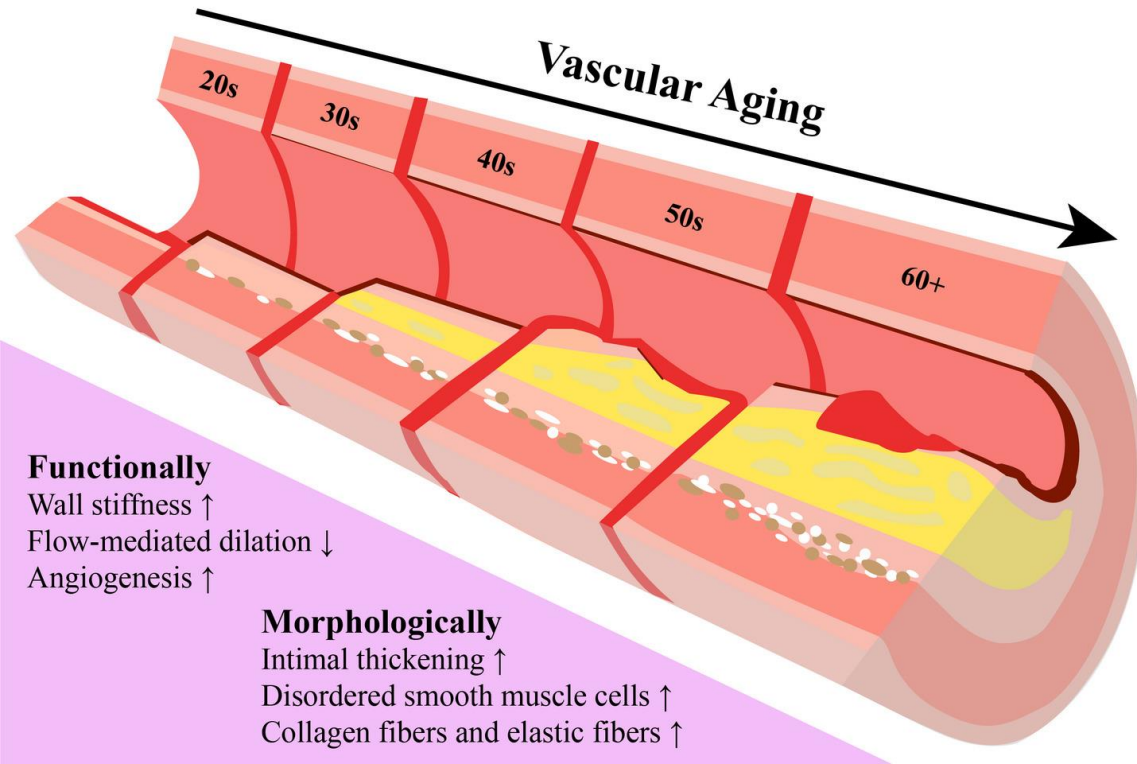
# Update of Arterial Stiffness in Nephrology

# Cardiovascular diseases prevalence among CKD and no CKD





# Vascular aging



- Mechanisms**
- Mitochondrial dysfunction
  - Oxidative stress
  - Inflammation
  - Loss of proteostasis
  - Genomic instability
  - Increased apoptosis and necroptosis
  - Epigenetic alterations
  - Dysregulated nutrient sensing pathways
  - Extracellular matrix remodeling
  - Exhaustion of progenitor cells

- Intima**
- Endothelial dysfunction
  - eNOS
  - ADMA
  - Arginase
  - BH4/BH2
  - SIRT-1
  - Thickening
  - Endothelial hyperplasia
  - Oxidative stress
  - Sympathetic nervous activity

- Media**
- Matrix degeneration
  - MMP
  - Elastin reduction
  - Collagen deposition
  - Cross linking
  - AGE
  - Calcification
  - Inflammation
  - Oxidative stress
  - Sympathetic nervous activity

- Adventitia**
- Collagen deposition

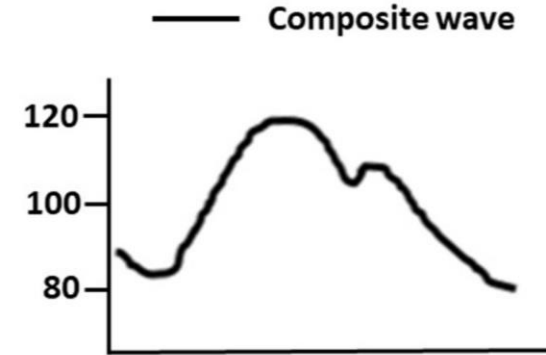
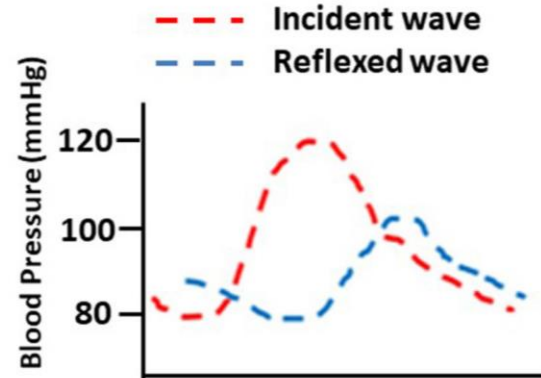
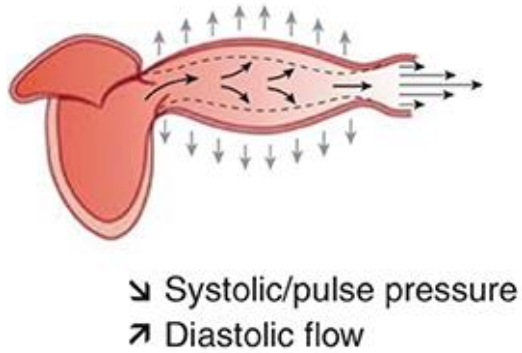
Aging Med (Milton). 2020 Oct 1;3(3):146-150; Int J Mol Sci. 2019 Jul 26;20(15):3664

# Vascular Biomarkers for Vascular Aging

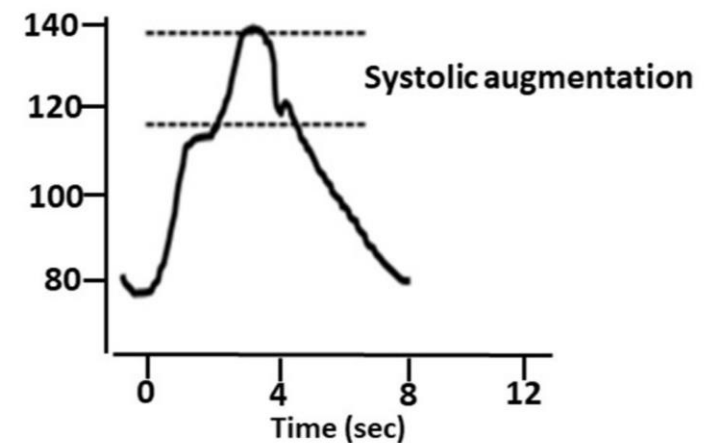
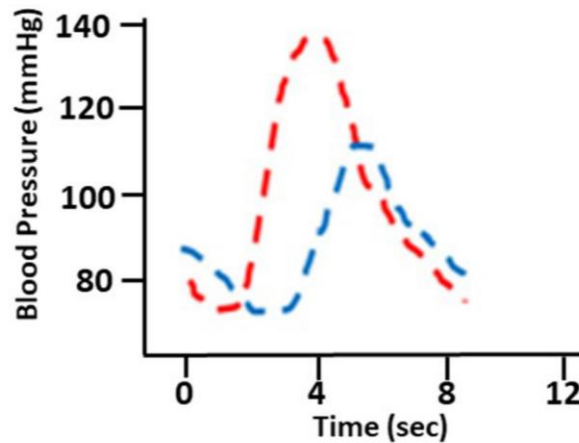
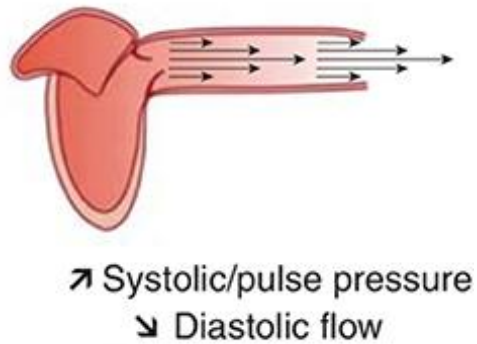
method		Guide for pharmacological therapy	Sensitivity for changes	Time to change	Prognostic value of changes
<b>Carotid ultrasonography</b>		++	Low	Slow	No
<b>Ankle-brachial index</b>		++	Low	No data	Moderate
<b>Arterial stiffness</b>	Carotid-femoral pulse wave velocity	+++	High	Moderate	Moderate
	Brachial-ankle pulse wave velocity	++	High	Moderate	No data
<b>Central hemodynamics/Wave reflections</b>		+++	High	Fast	Good guide for therapy, with the exception of patients with heart failure and a low ejection fraction
<b>Endothelial function</b>	Flow mediated dilatation	+++	Very high	Fast	Moderate
	Endothelial peripheral arterial tonometry	+	Very high	Fast	No data
<b>Circulating biomarkers</b>	High sensitivity C- reactive protein	+++	Moderate	Fast	No data

# Artery distensibility and pressure waveform

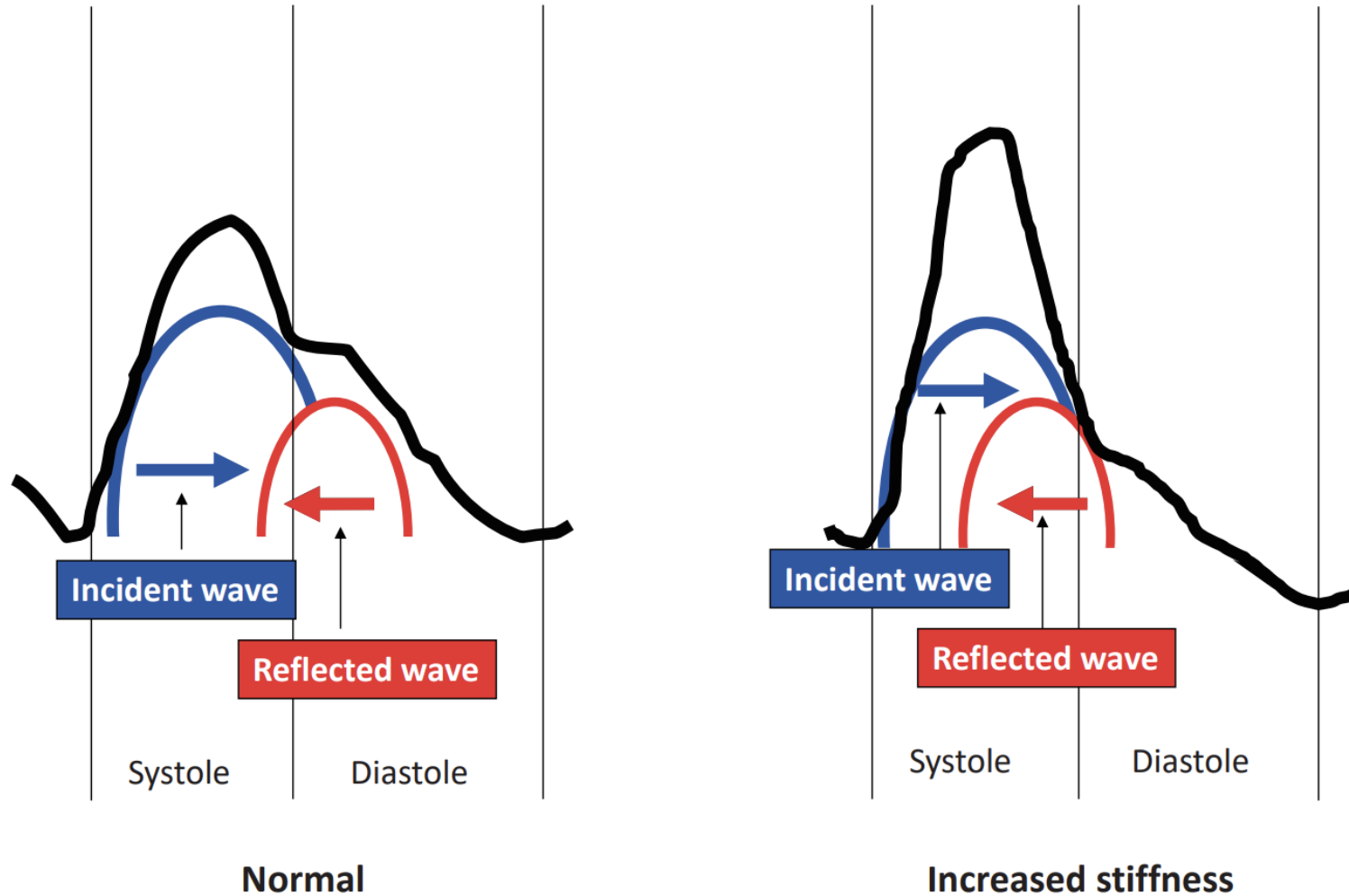
Elastic arteries



Stiff arteries



# Aortic stiffness: integrator of cumulative damages to the arterial wall



## Pulse wave velocity(PWV): Moens–Korteweg equation

E: arterial biomaterials elastic properties 血管壁的彈性

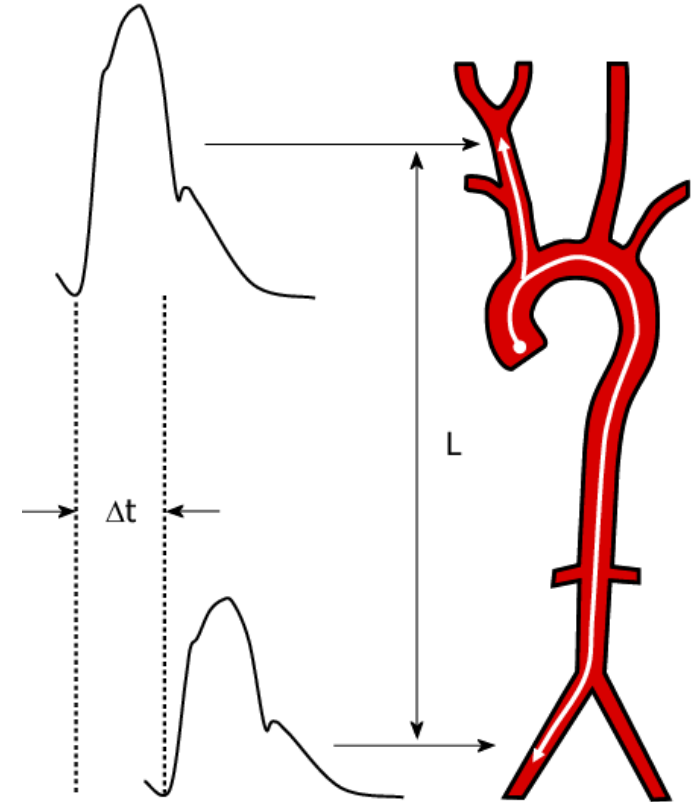
h: wall thickness 壁厚

r : radius 血管半徑

$\rho$ : tissue density 血液密度

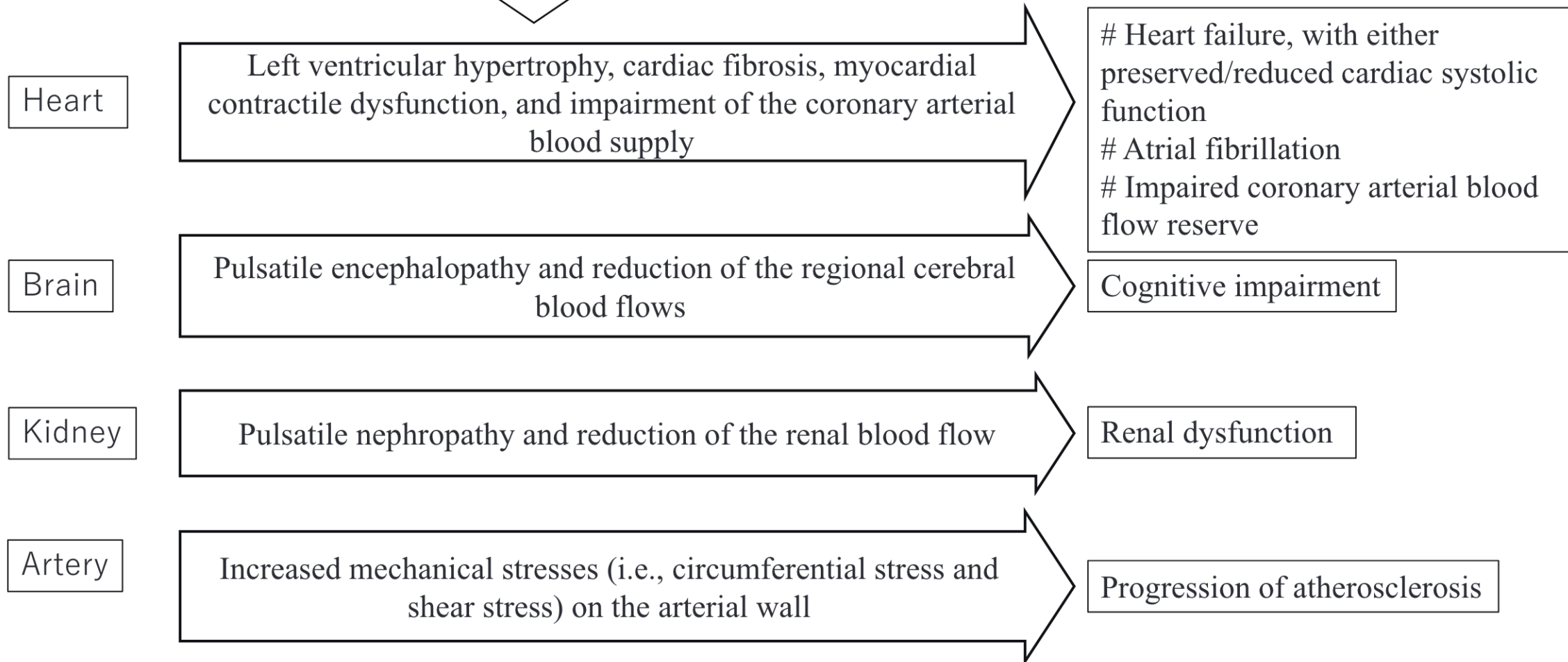
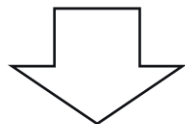
假設動脈壁是各向同性的並且隨著脈壓經歷等容變化

$$PWV = \sqrt{\frac{E_{inc} \cdot h}{2r\rho}} = \frac{Distance}{time} \quad (m/sec)$$

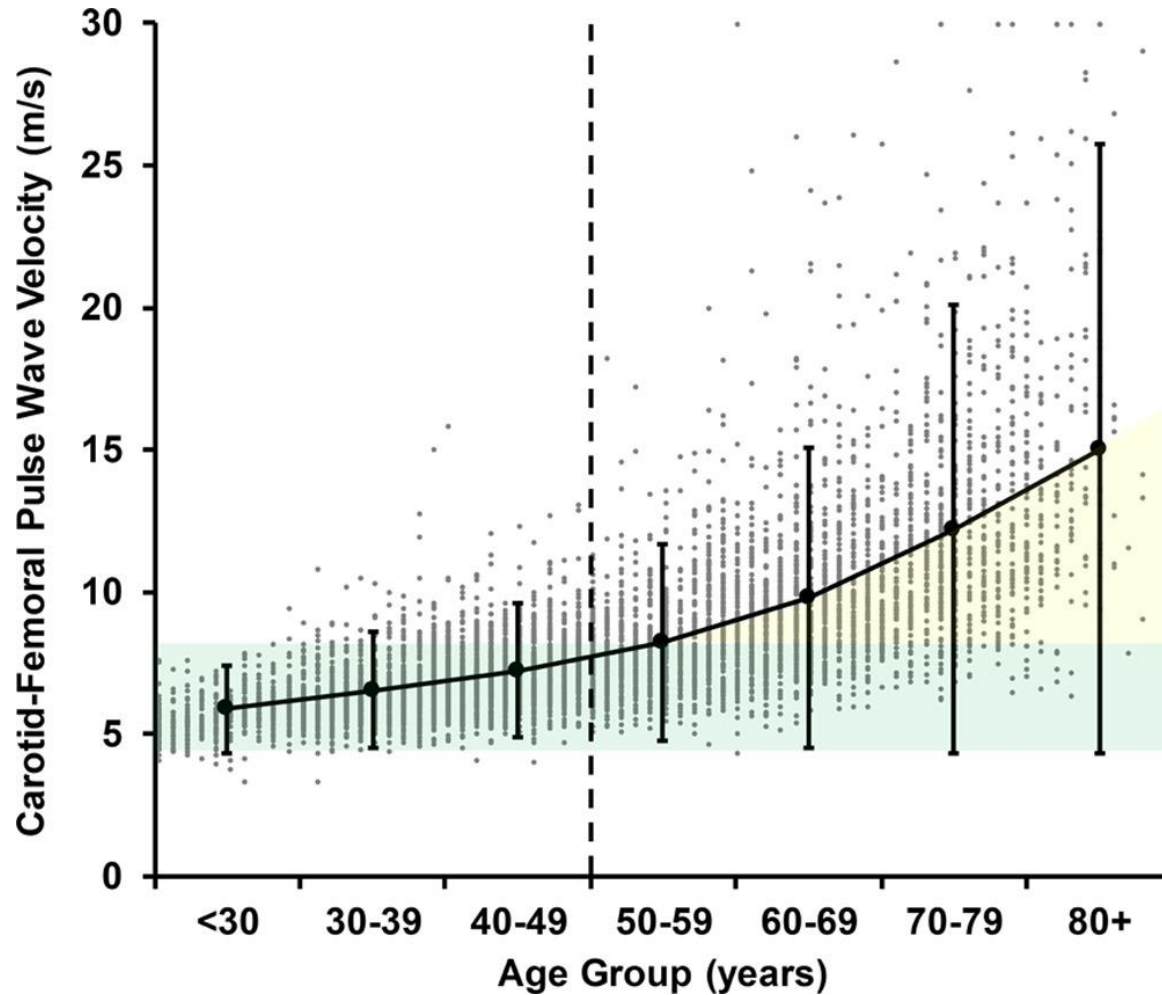




# Increased Arterial Stiffness contributes to CVD development

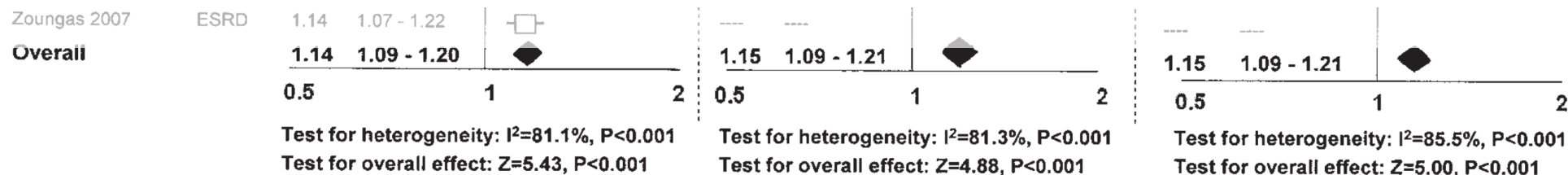
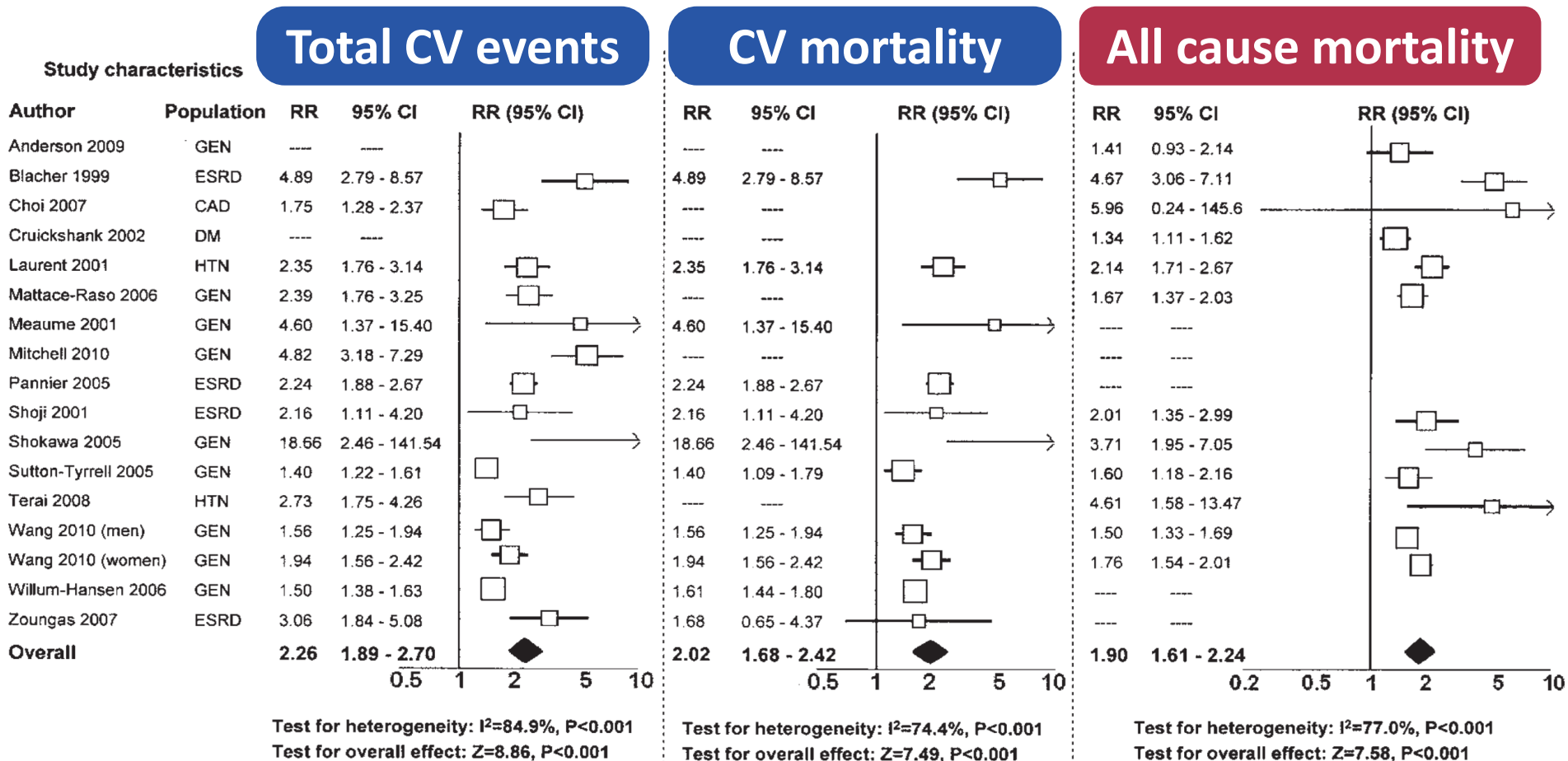


# Carotid-femoral pulse wave velocity (cfPWV) across the adult lifespan

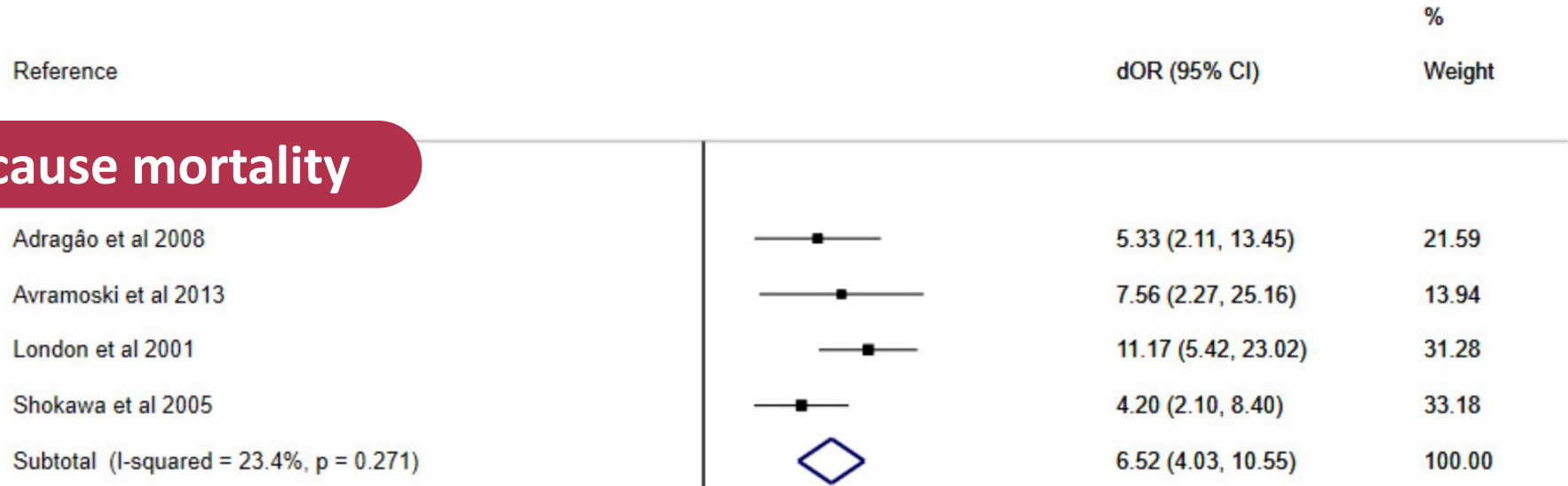


cfPWV increases moderately before 50 y of age ( $0.52 \pm 0.04$  m/s per decade) and markedly thereafter ( $2.05 \pm 0.03$  m/s per decade).

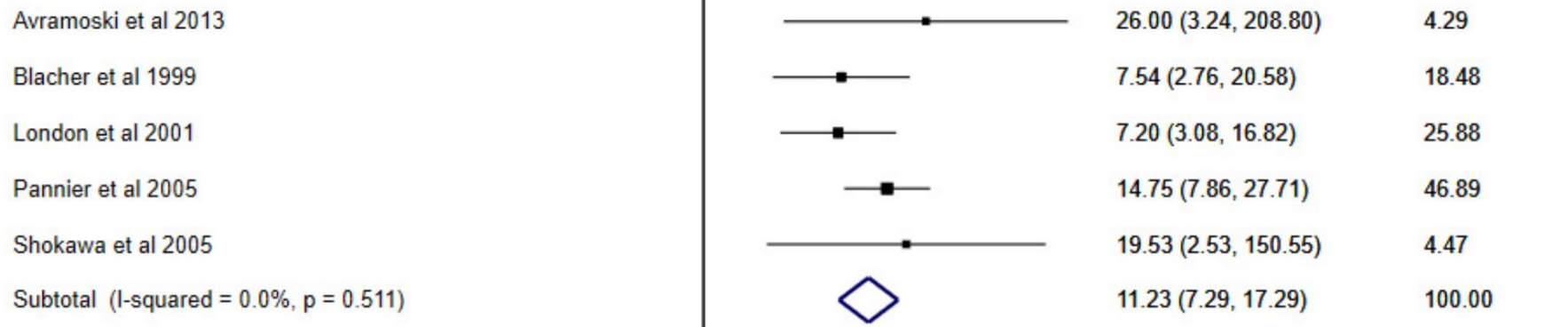
# 2010: Prediction of CV Events and All-Cause Mortality With Arterial Stiffness



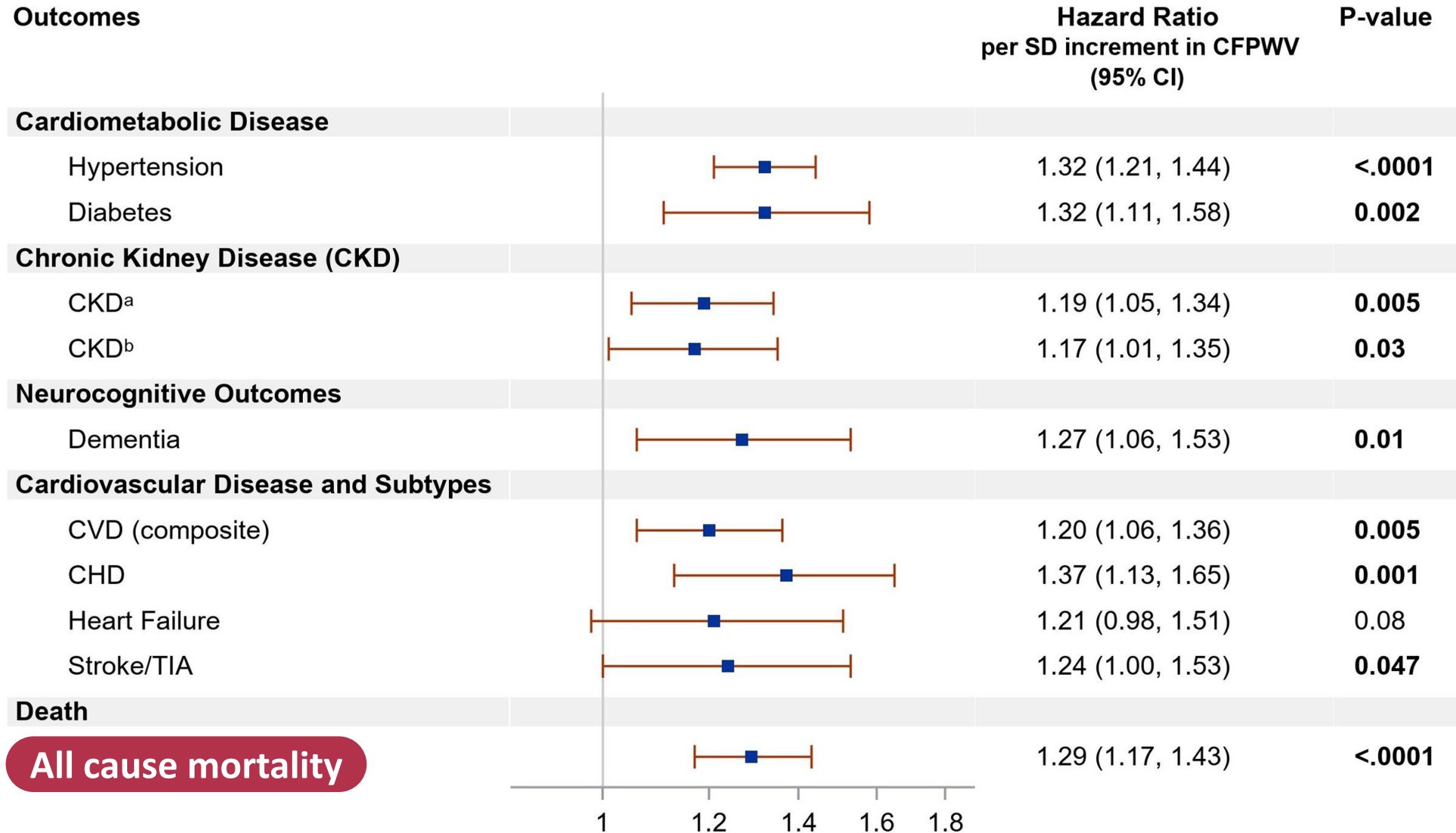
## All cause mortality



## CV mortality



# Arterial Stiffness and Long-Term Risk of Health Outcomes: The Framingham Heart Study

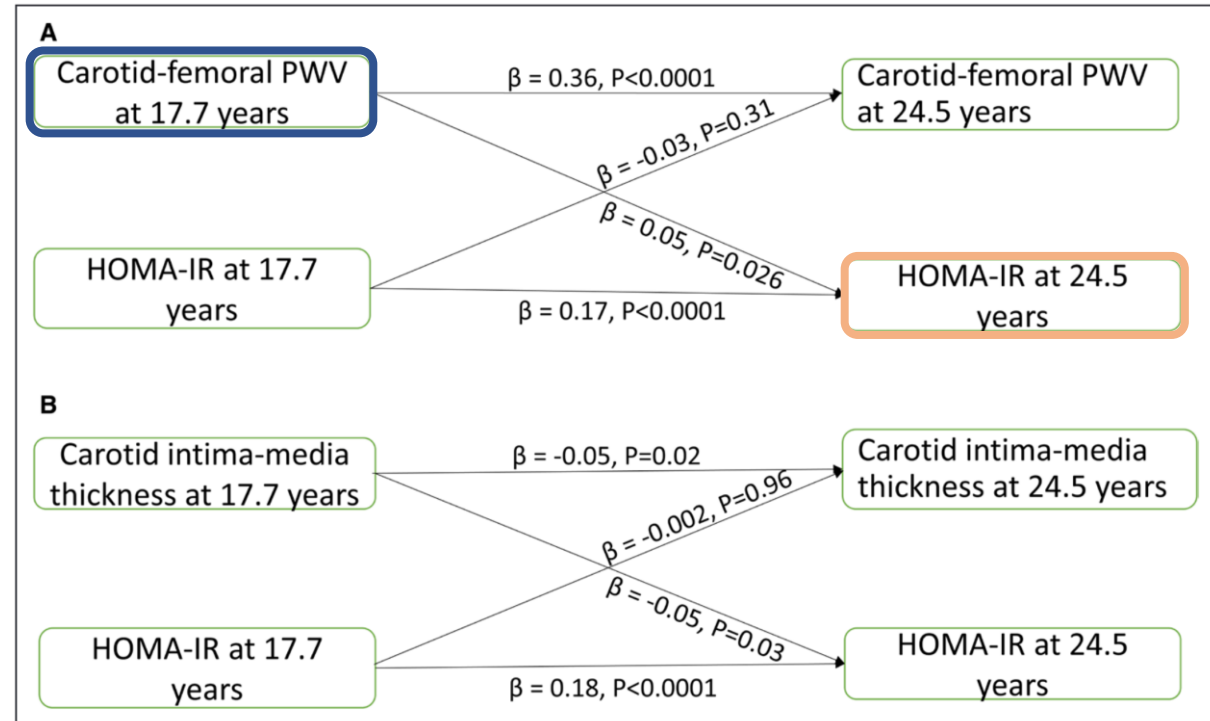


7283 participants; median follow up 15 yr

# Arterial Stiffness effect on Adolescence ?

cfPWV				
Autoregressive	B	$\beta$	SE	P value
LDL T1 $\Rightarrow$ LDL T2	0.729	0.580	0.026	<0.0001
HDL T1 $\Rightarrow$ HDL T2	0.868	0.623	0.027	<0.0001
Triglyceride T1 $\Rightarrow$ triglyceride T2	0.475	0.404	0.029	<0.0001
Insulin T1 $\Rightarrow$ insulin T2	0.216	0.194	0.030	<0.0001
Glucose T1 $\Rightarrow$ glucose T2	0.743	0.678	0.021	<0.0001
HOMA-IR T1 $\Rightarrow$ HOMA-IR T2	0.194	0.170	0.030	<0.0001
HOMA-% $\beta$ T1 $\Rightarrow$ HOMA-% $\beta$ T2	0.259	0.241	0.027	<0.0001
cfPWV T1 $\Rightarrow$ cfPWV T2	0.496	0.356	0.033	<0.0001
LDL T1 $\Rightarrow$ cfPWV T2	0.0001	0.003	0.003	0.900
cfPWV T1 $\Rightarrow$ LDL T2	0.347	0.023	0.304	0.253
HDL T1 $\Rightarrow$ cfPWV T2	0.0001	-0.002	0.007	0.942
cfPWV T1 $\Rightarrow$ HDL T2	-0.300	-0.036	0.154	0.051
Triglyceride T1 $\Rightarrow$ cfPWV T2	-0.014	-0.031	0.013	0.278
cfPWV T1 $\Rightarrow$ triglyceride T2	0.088	0.024	0.080	0.272
Insulin T1 $\Rightarrow$ cfPWV T2	-0.014	-0.048	0.009	0.118
cfPWV T1 $\Rightarrow$ insulin T2	0.286	0.055	0.116	0.014
Glucose T1 $\Rightarrow$ cfPWV T2	0.011	0.093	0.003	<0.0001
cfPWV T1 $\Rightarrow$ glucose T2	0.075	0.006	0.254	0.767
HOMA-IR T1 $\Rightarrow$ cfPWV T2	-0.009	-0.029	0.008	0.310
cfPWV T1 $\Rightarrow$ HOMA-IR T2	0.275	0.050	0.123	0.026
HOMA-% $\beta$ T1 $\Rightarrow$ cfPWV T2	-0.015	-0.052	0.008	0.069
cfPWV T1 $\Rightarrow$ HOMA-% $\beta$ T2	0.248	0.048	0.113	0.028

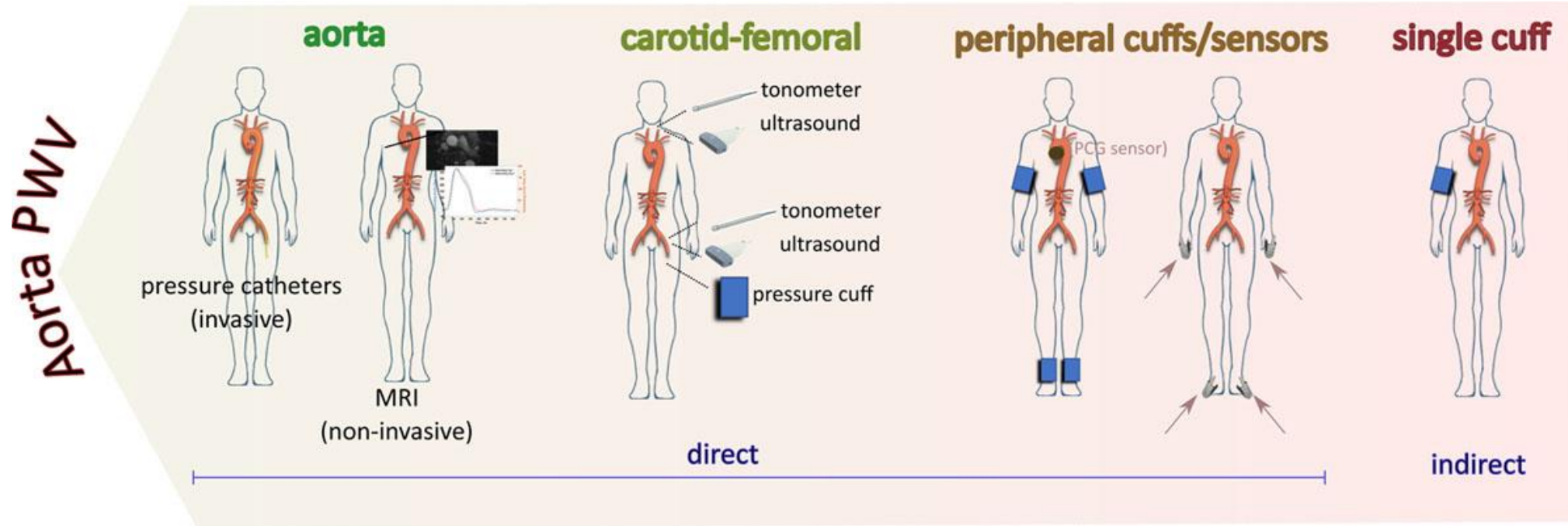
## Analyses of cfPWV at 17.7 and 24.5 Years of Age



# Different methods of PWV measurement

	Method	Description	Measure
Non-invasive methods	Applanation tonometry	Apply a pressure sensor through the skin and appanate a superficial artery by applying a downward pressure sufficient to flatten the artery.	baPWV, cfPWV
	Computerized oscillometry	Simultaneous acquisition and analysis of the pulsation of the artery, which is caused by the heart, as the pressure oscillation in the cuff.	Heart-brachial PWV, heart-ankle PWV, brachial-ankle PWV, cfPWV
	Mechanotransducer	Two dedicated piezoelectric pressure mechanotransducers directly applied to the skin in a simultaneous measurement of pressure pulses	carotid–femoral, carotid–brachial or femoral–dorsalis pedis PWV
	Ultrasound	Doppler pulses are recorded sequentially in 2 different arterial sites and compared using the R-wave of the ECG	baPWV, cfPWV
	Photoplethysmography	DVP measured by the photoplethysmography transducer	DVP associated with aPWV
	Magnetic Resonance Imaging	Assessment of the blood flow velocity with an enough temporal and spatial resolution to study the propagation of the aortic systolic flow wave	Local PWV
Invasive methods	Aortic angiography	Intra-aortic catheter measurements	Local PWV

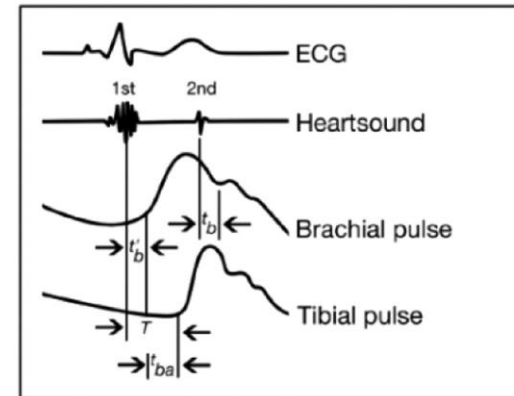
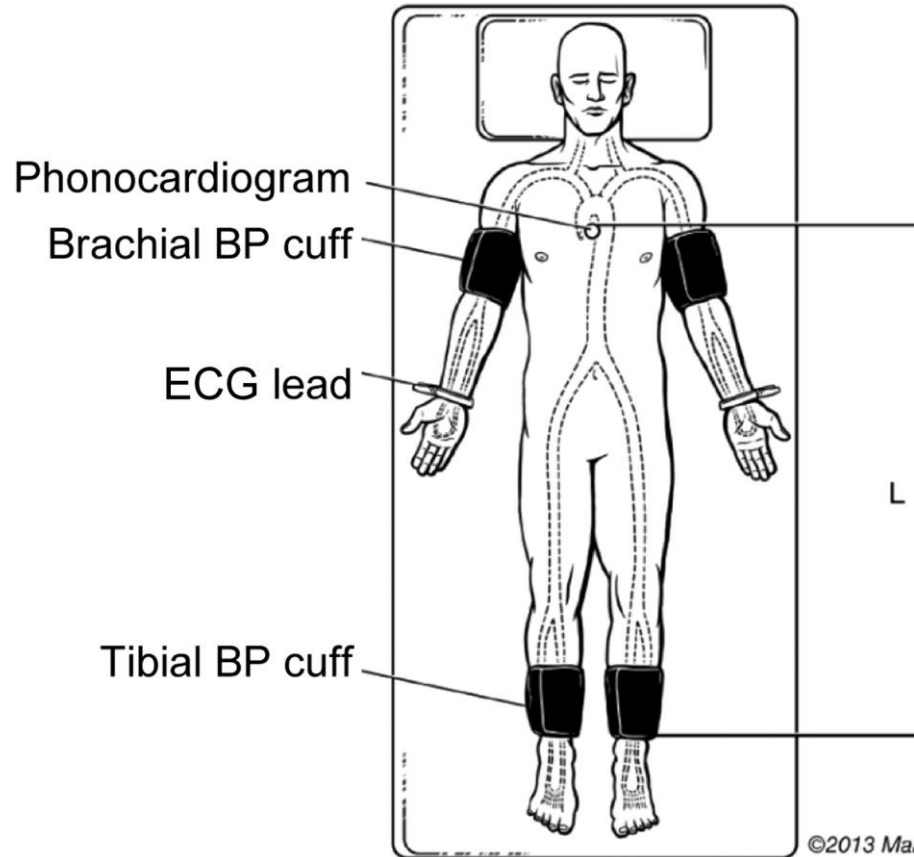
# Different methods of PWV measurement



- Arterial stiffness measured noninvasively by PWV have been recognized as independent predictors for cardiovascular morbidity and mortality.
- PWV is the most validated index to quantify arterial stiffness.



# Brachial-ankle PWV



$$PWV = L/T$$

$$T = t_b + t_{ba}$$

$$CAVI = \frac{2p}{\Delta P} \left[ \ln \frac{P_s}{P_d} \right] PWV^2$$

- The formula for baPWV calculation based on data from Asians, which may differ from data in Western populations.
- Brachial-ankle PWV has also demonstrated a predictive value for CV events and is recommended in the 2019 Japanese Society of Hypertension guidelines for the management of hypertension



## CLINICAL INVESTIGATION AND REPORTS

### Impact of Aortic Stiffness Attenuation on Survival of Patients in End-Stage Renal Failure

Alain P. Guerin, Jacques Blacher, Bruno Pannier, Sylvain J. Marchais, Michel E. Safar, and Gérard M. London

**TABLE 3. Proportional Hazard Regression Analyses of All-Cause and Cardiovascular Mortality**

Variable	RR (95% CI)	z Statistic	P	Pseudo- $r^2$
<b>All-cause mortality</b>				
Age (10 y)	1.69 (1.32–2.17)	4.15	0.00003	0.15346
LV mass index (10-g increase)	1.08 (1.04–1.15)	2.27	0.02322	0.05144
$\Delta$ PWV (1=positive/0=negative)	2.59 (1.51–4.43)	3.46	0.00053	0.11215
ACE inhibitor (1=yes/0=no)	0.19 (0.14–0.43)	–3.93	0.00027	0.13956
<b>Cardiovascular mortality</b>				
CVD (yes/no)	4.72 (1.91–11.61)	3.36	0.00077	0.13097
LV mass index (10-g increase)	1.11 (1.03–1.19)	2.63	0.00844	0.00847
$\Delta$ PWV (1=positive/0=negative)	2.35 (1.23–4.51)	2.57	0.01004	0.08110
ACE inhibitor (1=yes/0=no)	0.18 (0.06–0.55)	–3.00	0.00274	0.10689

#### Results—

115 ESRF patients (aged  $52 \pm 16$  years) monitored for  $51 \pm 38$  months. PWV were measured ultrasonographically. BP was controlled

59 deaths

40 cardiovascular and 19 noncardiovascular events.

The risk ratio for the absence of PWV decrease was 2.59 (95% CI 1.51 to 4.43) for all-cause mortality and 2.35 (95% CI 1.23 to 4.41) for cardiovascular mortality.

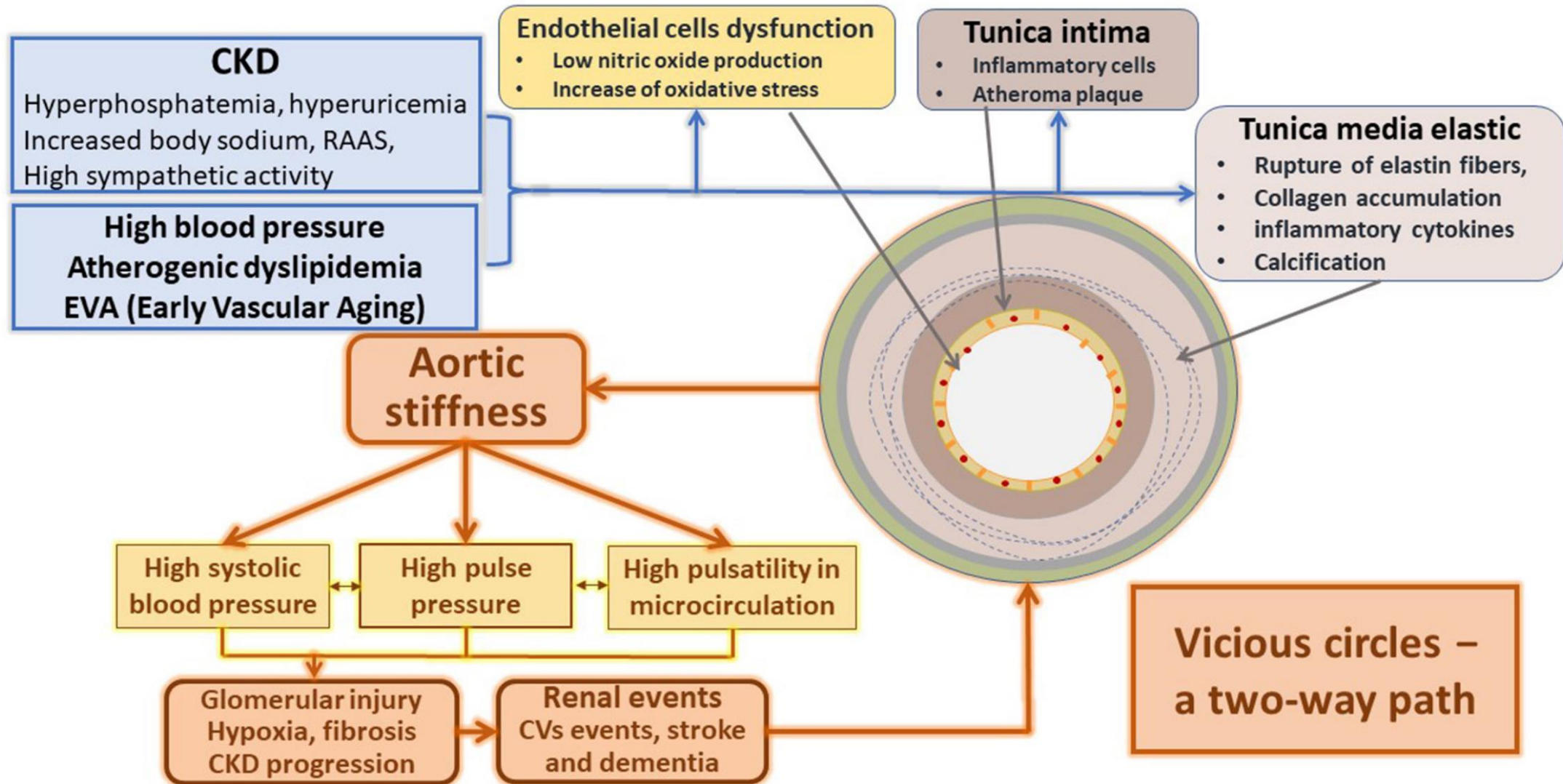
#### Conclusions—

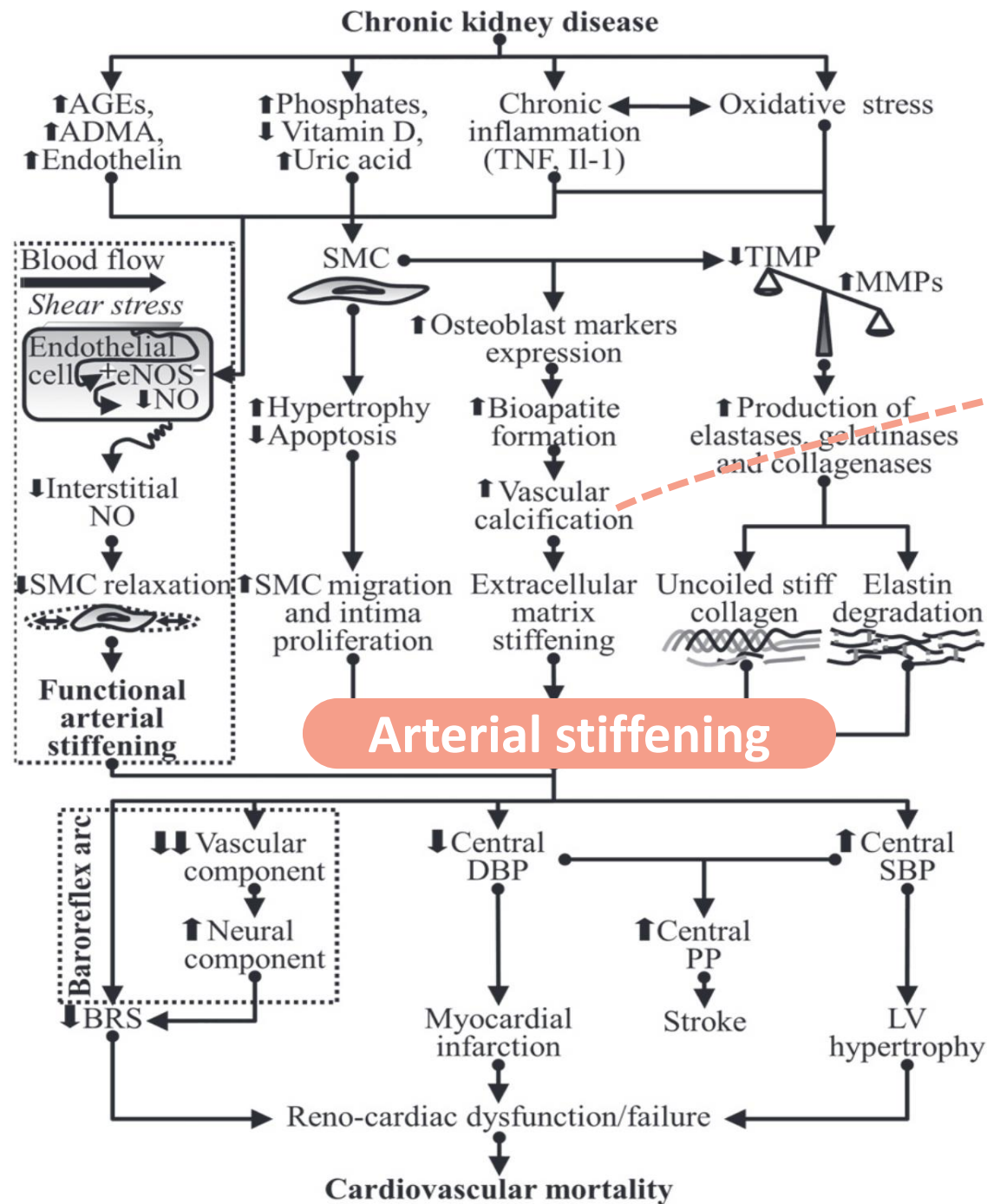
In ESRF patients, the insensitivity of PWV to decreased BP is an independent predictor of mortality ...

## We already know...

- Arterial stiffness independently predicts death (**all causes mortality and CV causes mortality**) and CV outcomes in healthy elderly people, diabetic patients, hypertensive patients, general adult populations, and patients with end-stage renal disease [ESRD]
- [CKD]CRIC
  - ✓ Arterial stiffness predicts death and CKD **progression to ESRD**.
  - ✓ Arterial stiffness worsens as **kidney function declines** irrespective of cause of CKD.
  - ✓ Arterial stiffness is linked to **proteinuria** in diabetic patients with CKD.
  - ✓ Arterial stiffness is linked to **bone & mineral disorders**.
  - ✓ Arterial stiffness predicts **new-onset HF** in CKD.
  - ✓ Arterial stiffness is worse in CKD patients with masked hypertension.
- [KTx] Large-artery stiffness of chronic kidney disease is partially **reversed** within 12 months of KT and appears unrelated to renal function.
- [early CKD] Higher indices of arterial stiffness are associated with steeper decline in kidney function in general population.

# Main mechanisms for the structural and functional changes of the arteries in CKD





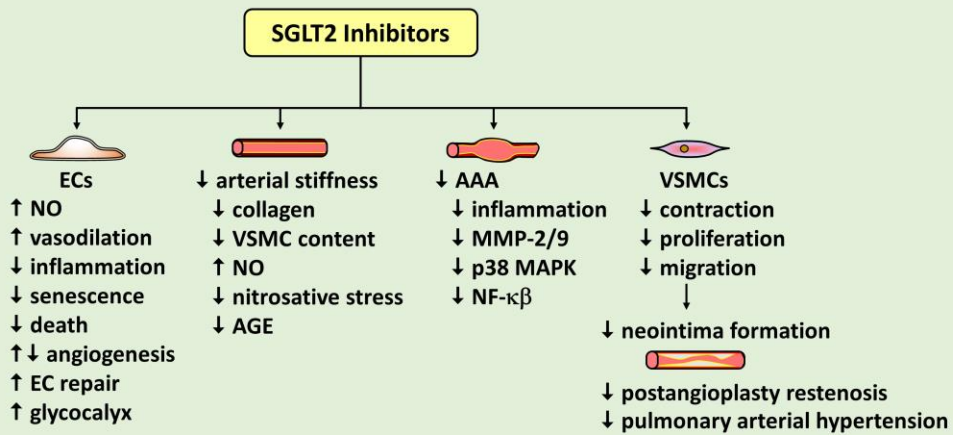
**Endothelia Function**

**Vascular Calcification promotor**

**Baroreflex**

# Evidence on the drugs used in nephrology on arterial wall properties

Drug(s)	Effect on Arterial Wall Properties	Best Level of Evidence	Level of Evidence in CKD or KTx
Antihypertensive drugs			
ACEi	↓ AS	+++	++
ARBs	↓ AS	+++	++
b-blockers	Doubtful		
Calcium channel blockers	↓ AS	+++	+
Diuretics (spironolactone)	↓ AS	+	+
Endothelin-1 antagonists	↓ AS, ↑ EF	+	+
Immunosuppressive drugs			
Anti-TNF	↓ AS	+++	
Cyclosporine	↑ AS	++	++
Mycophenolate mofetil	↓ AS	+	+
Corticosteroids	↑ AS	+	
Statins	↑ EF	+	
Noncalcium-containing phosphate binders	↓ AS	+	+
Parathyroid hormone	Doubtful		
Vitamin D analogs			
Vitamin D <sub>2</sub>	None	+++	++
Vitamin D <sub>3</sub>	None	+++	++
Paricalcitol	↑ EF	+++	++



> *Vasc Med.* 2022 Jun 27;1358863X221101653. doi: 10.1177/1358863X221101653.  
Online ahead of print.

## Effect of sodium-glucose co-transporter-2 inhibitors on arterial stiffness: A systematic review and meta-analysis of randomized controlled trials

Dimitrios Patoulas<sup>1</sup>, Christodoulos Papadopoulos<sup>2</sup>, George Kassimis<sup>3</sup>, Nikolaos Fragakis<sup>2</sup>, Vassilios Vassilikos<sup>2</sup>, Asterios Karagiannis<sup>1</sup>, Michael Doumas<sup>1</sup>

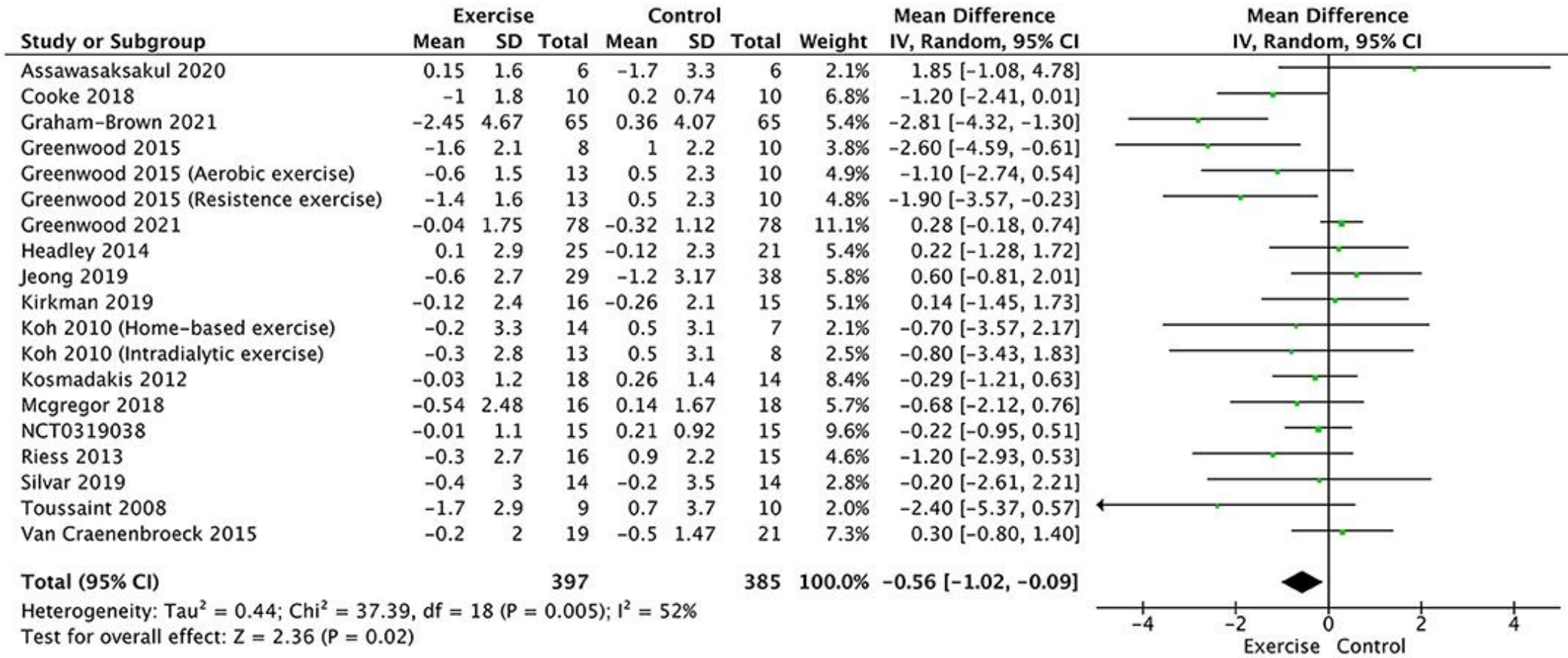
Affiliations + expand

PMID: 35754338 DOI: 10.1177/1358863X221101653

### Result:

- Six trials, 452 enrolled participants
- Overall, SGLT-2 inhibitor treatment compared to control resulted in a **nonsignificant decrease in PWV**.
- Exclusion of a trial utilizing cardiac magnetic resonance imaging for the assessment of PWV demonstrated that SGLT-2 inhibitors induce a significant reduction in PWV by 0.21 m/s.
- When we restricted our analysis to RCTs enrolling subjects with T2DM, we observed that SGLT-2 inhibitor compared to control resulted in a significant decrease in PWV by 0.17 m/s.

# Exercise training on PWV in CKD (include dialysis) ?



Front Med (Lausanne). 2022 Jul 6;9:904299

18 RCTs with 817 patients  
 three to four times per week  
 exercise duration varied from 10 to 65 min

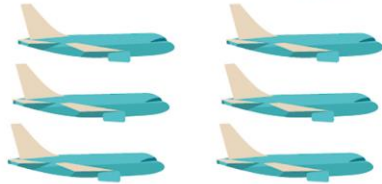




2015

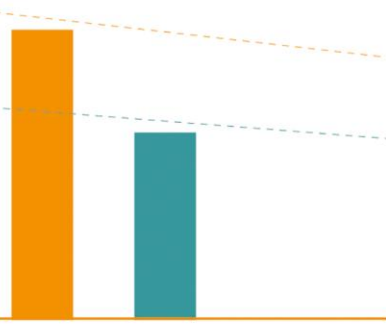
NOISE LEVEL

$L_{DEN} = 61$  dB



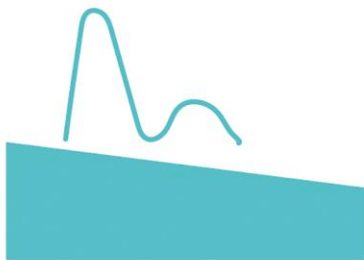
BP mm Hg

SBP DBP



PWV m/s

10.2



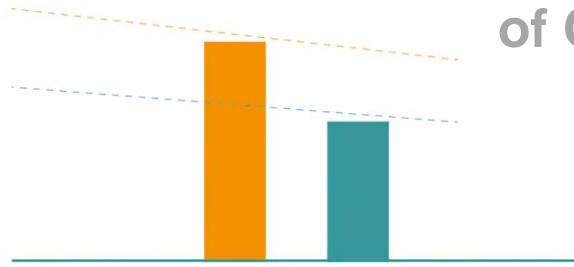
2020

NOISE LEVEL

$L_{DEN} = 47$  dB



SBP DBP



8.8



Hypertension. 2022 Feb;79(2):325-334.

## Blood Pressure and Arterial Stiffness in Association With Aircraft Noise Exposure: Long-Term Observation and Potential Effect of COVID-19 Lockdown

[Home](#) > [Journal of the American Heart Association](#) > [Vol. 11, No. 6](#) > [Effects of Magnesium Citrate, Magnesium Oxide, and Magnesium Sulfate Supplementation on Arterial Stiffness: A Randomize...](#)

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RESEARCH ARTICLE

 PDF/EPUB

## Effects of Magnesium Citrate, Magnesium Oxide, and Magnesium Sulfate Supplementation on Arterial Stiffness: A Randomized, Double-Blind, Placebo-Controlled Intervention Trial

Joëlle C. Schutten , Peter J. Joris, Iris Groendijk, Coby Eelderink, Dion Groothof, Yvonne van der Veen, Ralf Westerhuis, Frans Goorman, Richard M. Danel, Martin H. de Borst and Stephan J. L. Bakker

Originally published 5 Mar 2022 | <https://doi.org/10.1161/JAHA.121.021783>   | Journal of the American Heart Association. 2022;11:e021783

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 Tools  Share

# Clinical Usefulness of Arterial Stiffness

Focus	Objective	Challenge
<b>Risk stratification</b>	Defining disease end points most closely related to PWV as a measure of arteriosclerosis rather than atherosclerosis	Heterogeneity of disease end points
<b>Measurement technology</b>	Improving ease of measurement	Maintain reproducibility and accuracy
<b>Guiding antihypertensive Tx</b>	A PWV threshold for initiating treatment	Defining threshold; requires RCT to demonstrate benefit
<b>Selection of antihypertensive Tx</b>	Defining specific effects of antihypertensive drugs on PWV	
<b>Titration of antihypertensive Tx</b>	Requires RCT to demonstrate benefit	
<b>Arterial stiffness specific therapies</b>	Definitive evidence of specific BP-independent effects of established and novel drugs for AS	Long-term RCT required
<b>Kidney specific ?</b>		



OPEN

## Photoplethysmogram based vascular aging assessment using the deep convolutional neural network

Hangsik Shin<sup>1✉</sup>, Gyujeong Noh<sup>2,3</sup> & Byung-Moon Choi<sup>2✉</sup>

Arterial stiffness due to vascular aging is a major indicator during the assessment of cardiovascular risk. In this study, we propose a method for age estimation by applying deep learning to a photoplethysmogram (PPG) for the non-invasive assessment of the vascular age. The proposed deep learning-based age estimation model consists of three convolutional layers and two fully connected layers, and was developed as an explainable artificial intelligence model with Grad-Cam to explain the contribution of the PPG waveform characteristic to vascular age estimation. The deep learning model was developed using a segmented PPG by pulse from a total of 752 adults aged 20–89 years, and the performance was quantitatively evaluated using the mean absolute error, root-mean-squared-

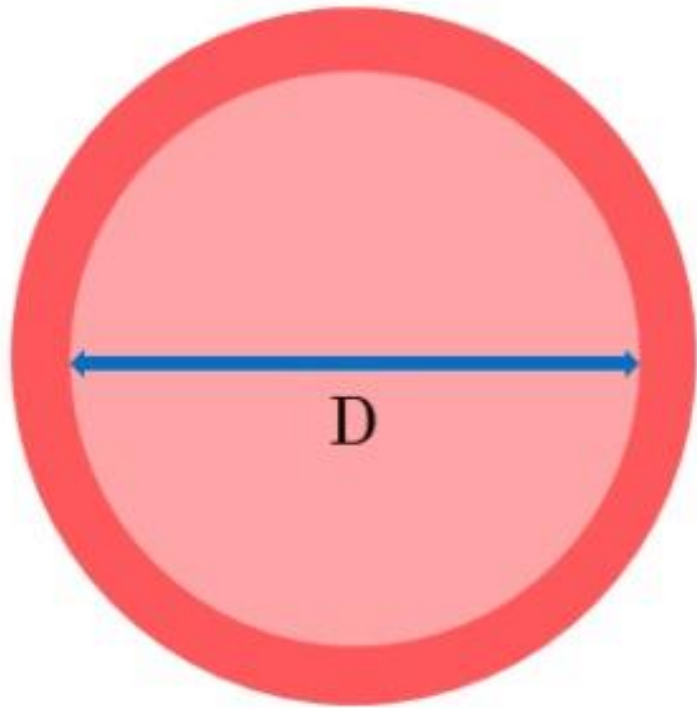


*“A man is as old as his arteries.”*

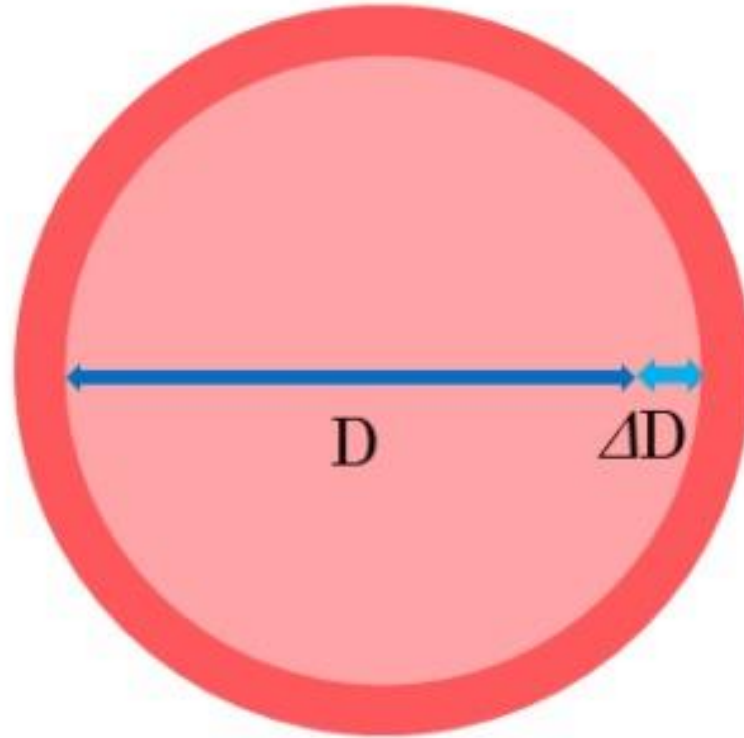
**Thomas Sydenham**

## Biomechanical Metrics for and Related to Stiffness

Stress	A measure of the intensity of an applied force that depends on its magnitude, direction, and area over which it distributes. The common unit of measurement is the Pascal =1 N/m <sup>2</sup> .
Intramural stress	Arises from applied loads such as the blood pressure within and the axial force acting on a blood vessel. Important both mechanobiologically and structurally.
Wall shear stress	Arises from the frictional interaction between the flowing viscous blood and the luminal surface of the blood vessel. Important mechanobiologically.
Strain	A measure of normalized changes in lengths or changes in angles within a material when acted upon by an applied load. Dimensionless by definition.
Stiffness	A measure of resistance to applied loads. The unit of measurement depends on the precise definition but can include N/m <sup>2</sup> (material) and N/m (structural) among others.
Material stiffness	An intrinsic property of a material that depends both on its composition and the internal organization of and interactions between the different constituents. This stiffness appears to be highly mechano-regulated by arterial cells for it defines their local mechano-environment. It is calculated as a change in stress with respect to a change in a conjugate strain.
Structural stiffness	A property of a structure depending both on its intrinsic material stiffness and its geometry. For example, a thin-walled materially stiff vessel can have the same structural stiffness as a thick-walled materially compliant vessel. This stiffness is a critical determinant of hemodynamics.
Strength	A measure of the maximum applied load or stress that can be sustained before failure, as, for example, via dissection or rupture. Fundamentally, material failure occurs when stress exceeds strength.
Compliance	The inverse of stiffness, either material or structural. One clinical measure of compliance is the inverse of distensibility.



Systolic phase



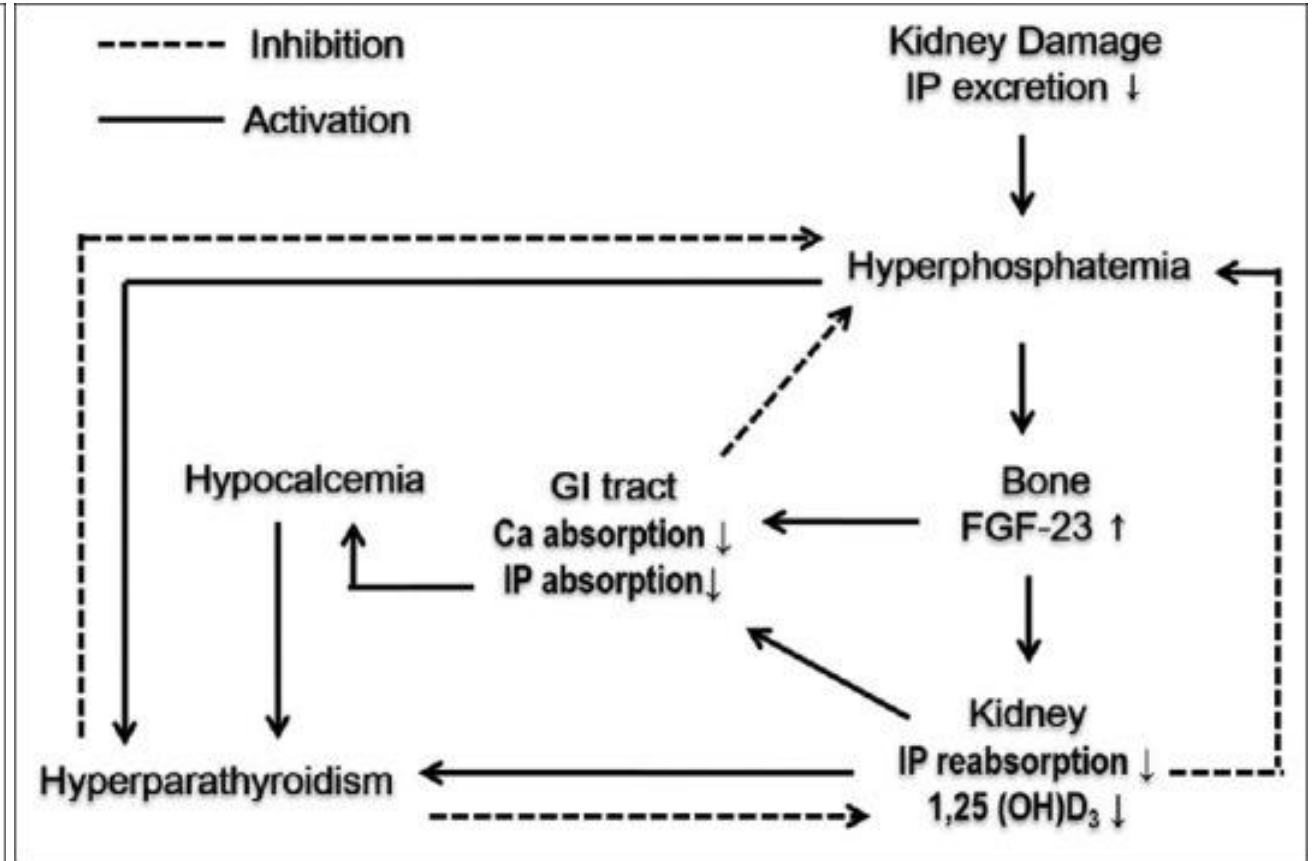
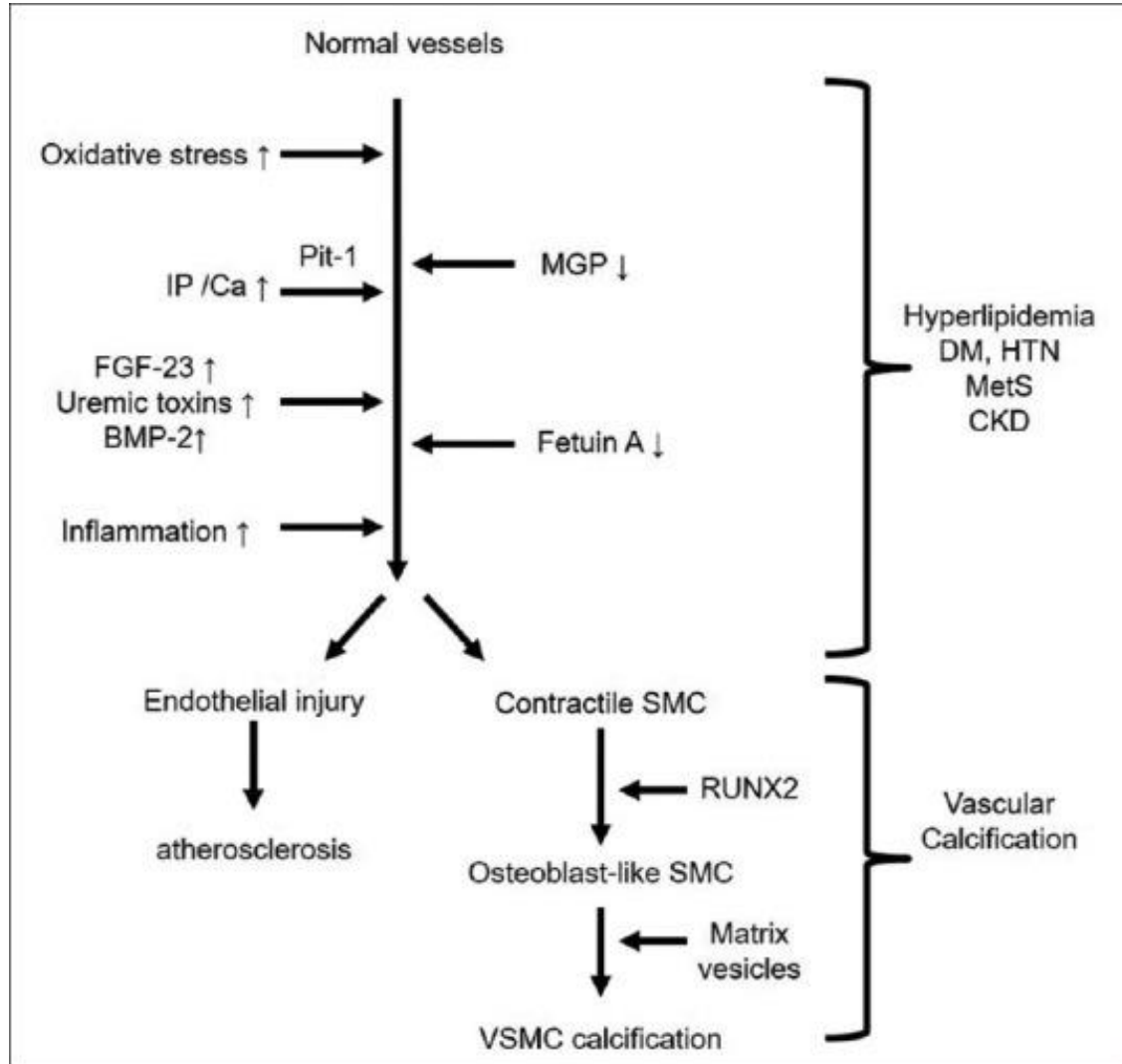
Diastolic phase

**Stiffness parameter  $\beta = \ln (P_s/P_d) \times D/\Delta D$**

$\beta$  represents arterial **distensibility**

$P_s$ : systolic blood pressure,  $P_d$ : diastolic blood pressure,  $D$ : diameter of the artery,  $\Delta D$ : change in diameter.

# Vascular calcification of chronic kidney disease: A brief review





## Odds ratio of brachial-ankle PWV for presence of high or very-high CKD stage

Variables, unit of increase	Crude			Multivariate-adjusted		
	OR	CI	p	OR	CI	p
Aortic PWV, 1 SD						
24-Hour (i.e., 241 cm/s for male, 242 cm/s for female)	3.24	2.12–5.03	<0.001	2.75b	0.43–16.95	0.28
Daytime (i.e., 241 cm/s for male, 243 cm/s for female)	3.14	2.06–5.09	<0.001	1.90c	0.30–11.46	0.49
Nighttime (i.e., 246 cm/s for male, 242 cm/s for female)	3.50	2.26–5.81	<0.001	4.80d	1.02–24.20	<0.05

Variables	N	Risk stratification of CKD categories				P <sub>trend</sub>
		Total	Low	Moderate	High or very-high	N/A
Brachial-ankle PWV, 1 SD (i.e., 442 cm/s)						
eGFR, ml/min/1.73 m <sup>2</sup>	184	65	58	61		<0.001
Variable, unit of increase						
Nighttime aortic SBP, 15 mm Hg for female	21.5 (7.5, 101.6)	7.5 (4.2, 13.7)§	27.6 (8.6, 59.8)†	513.7 (72.7, 1,904.4)†§		<0.001
Nighttime aortic PWV, 242 cm/s for female	24-Hour aortic SBP, mm Hg	116 ± 13	116 ± 13	115 ± 12	118 ± 13	0.38
	24-Hour aortic PP, mm Hg	36 ± 8	34 ± 7	35 ± 8	39 ± 8†‡	<0.01
	24-Hour aortic PWV, cm/s	982 ± 241	855 ± 243§	976 ± 229†	1,123 ± 163†§	<0.001
	24-Hour Alx@75, %	25.6 ± 8.4	24.0 ± 8.8	25.2 ± 7.4	27.7 ± 8.7*	<0.05
	Brachial-ankle PWV, cm/s	1,811 ± 439	1,612 ± 412‡	1,794 ± 412*	2,040 ± 385†§	<0.001