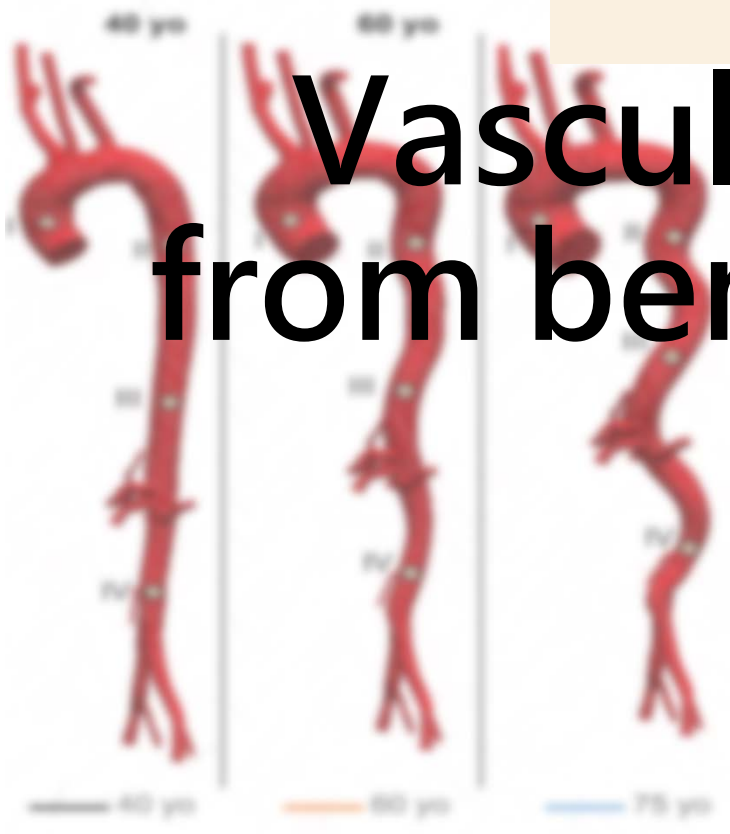
سُورَةُ المُزَّمِّلِ

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

فَكَيْفَ تَتَّقُونَ إِن كَفَرْتُمْ يَوْمًا يَجْعَلُ الْوِلْدَانَ شِيبًا ﴿١٧﴾



Vascular ageing: moving from bench towards bedside

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Tehran University of Medical Sciences

May 2023

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Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness:

A Scientific Statement from the American Heart Association

Raymond R. Townsend, MD, FAHA [Chair], Ian B. Wilkinson, MD, DM, FRCP, FAHA [Vice-Chair], Ernesto L. Schiffrin, MD, PhD, FAHA [Vice-Chair], Alberto P. Avolio, BE, PhD, Julio A. Chirinos, MD, PhD, John R. Cockcroft, FRCP, FESC, Kevin S. Heffernan, PhD, Edward G. Lakatta, MD, Carmel McEniery, PhD, Gary F. Mitchell, MD, Samer S. Najjar, MD, Wilmer W. Nichols, PhD, Elaine M. Urbina, MD, MS, FAHA, and Thomas Weber, MD, FESC on behalf of the American Heart Association Council on Hypertension

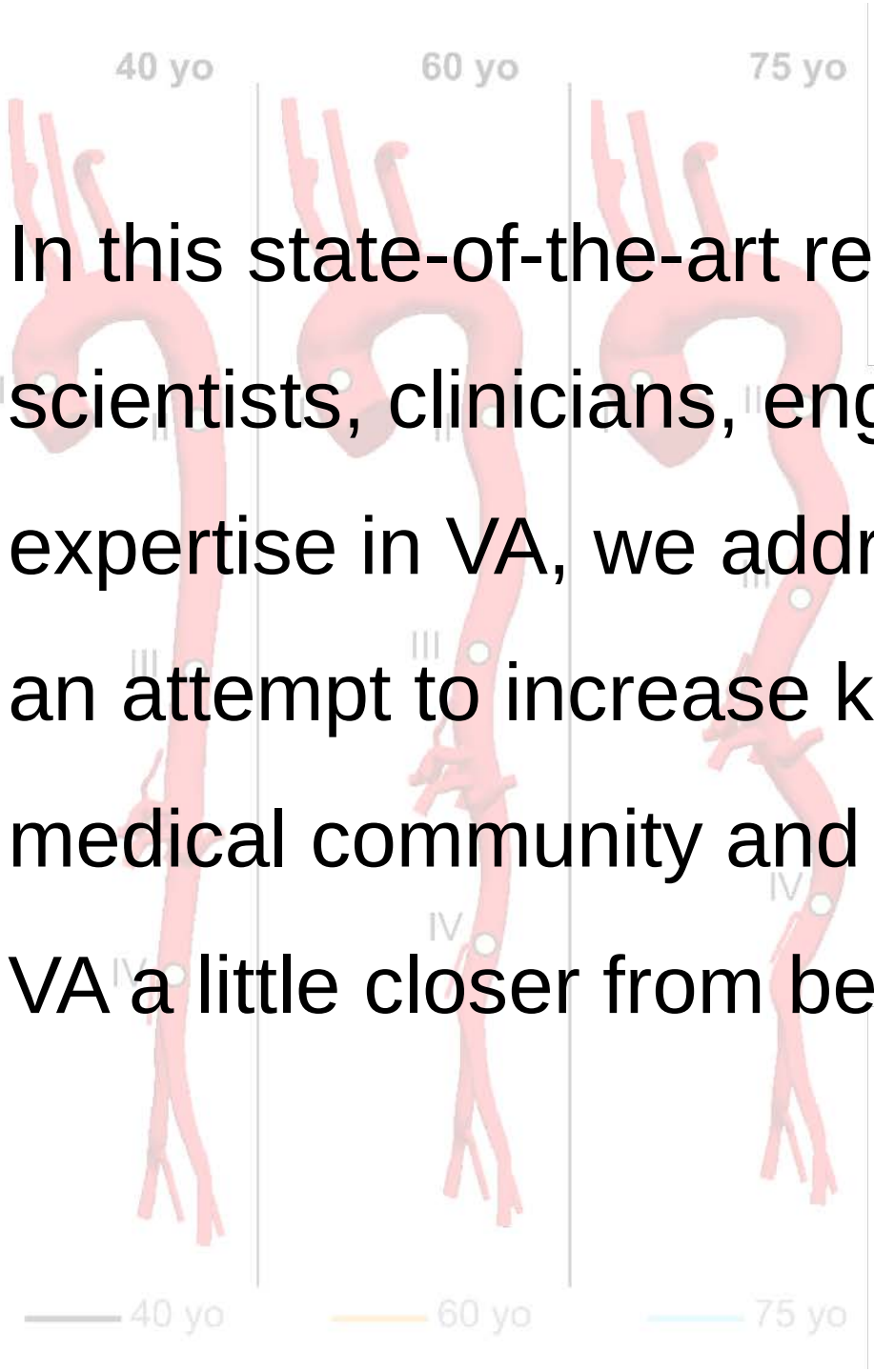
ESC European Society of Cardiology

European Journal of Preventive Cardiology (2023) **00**, 1–17
https://doi.org/10.1093/eurjpc/zwad028

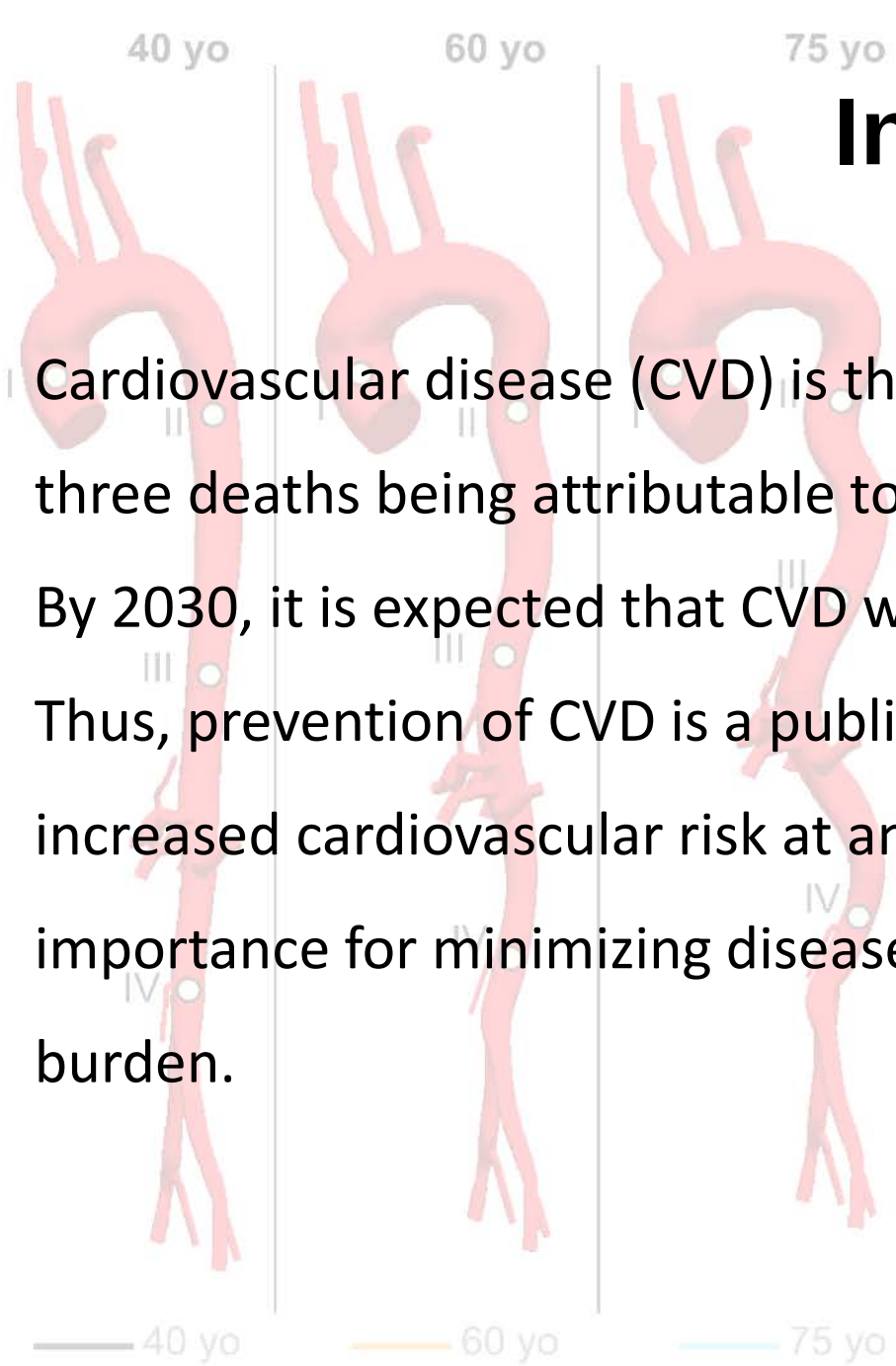
REVIEW
Cardiovascular disease

Vascular ageing: moving from bench towards bedside

Rachel E. Climie [1,2,3]*, Jordi Alastruey[4], Christopher C. Mayer [5], Achim Schwarz[6], Agne Laucyte-Cibulskiene[7,8], Julija Voicehovska[9,10], Elisabetta Bianchini[11], Rosa-Maria Bruno[3], Peter H. Charlton [12], Andrea Grillo[13], Andrea Guala[14], Magid Hallab[15], Bernhard Hametner [5], Piotr Jankowski[16], Karsten Königstein[17], Anna Lebedeva[18], Ioana Mozos[19], Giacomo Pucci[20], Houry Puzantian[21], Dimitrios Terentes-Printzios [22], Gunay Yetik-Anacak[23], Chloe Park[24], Peter M. Nilsson[7], and Thomas Weber[25], on behalf of the VascAgeNet Education and Dissemination Working Group



In this state-of-the-art review and as a network of scientists, clinicians, engineers, and industry partners with expertise in VA, we address six questions related to VA in an attempt to increase knowledge among the broader medical community and move the routine measurement of VA a little closer from bench towards bedside.



Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, with one in three deaths being attributable to CVD.

By 2030, it is expected that CVD will cost US$1044 billion globally.

Thus, prevention of CVD is a public health priority and identifying individuals at increased cardiovascular risk at an asymptomatic, sub-clinical stage is of paramount importance for minimizing disease progression as well as health and economic burden.

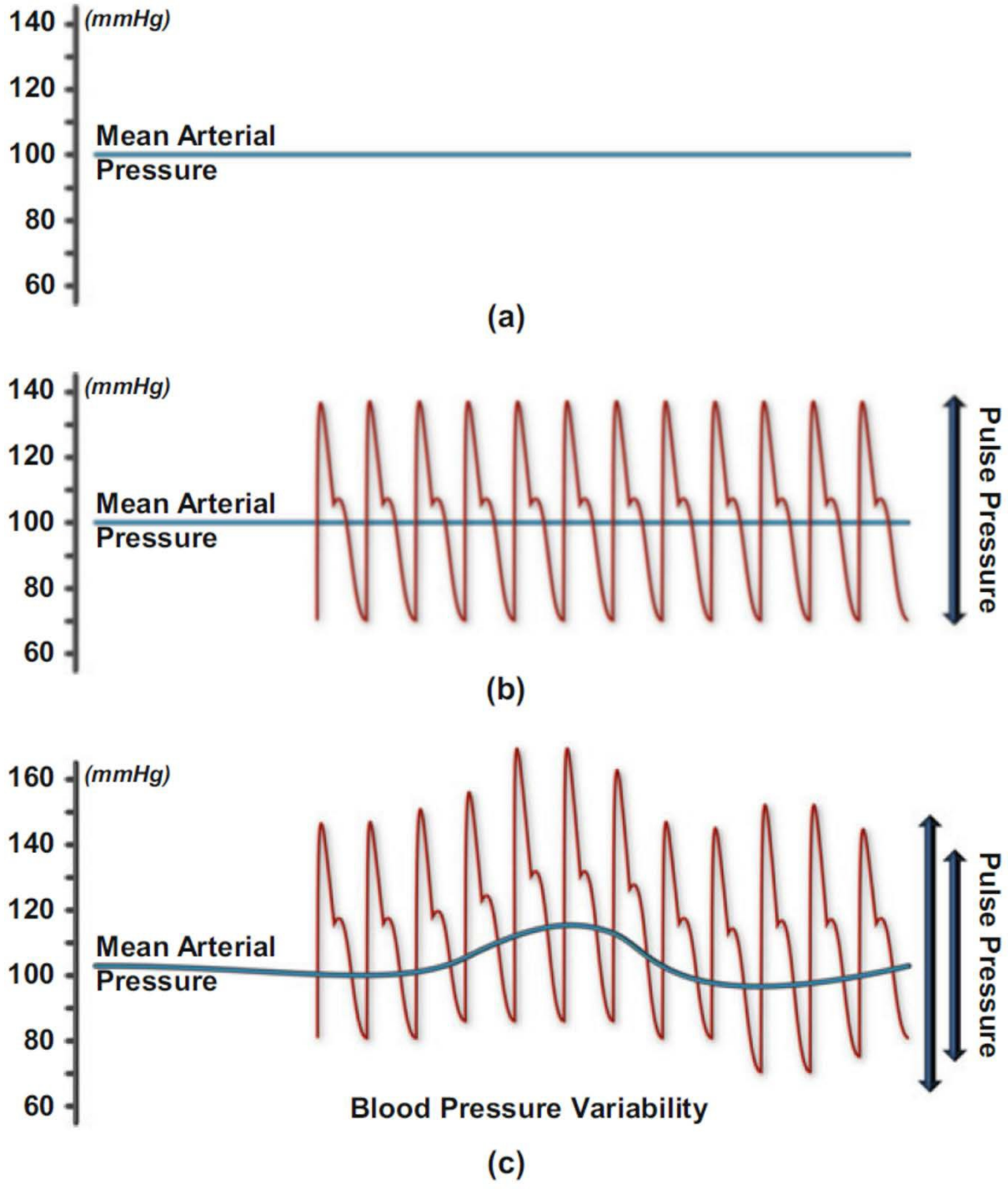
Concept of systolic blood pressure and diastolic blood pressure in the 1970s, in the judgment of most authoritative cardiologists and most authoritative medical textbooks

"Systolic hypertension in the presence of normal or reduced diastolic pressure is rarely considered to be responsible for organ damage"

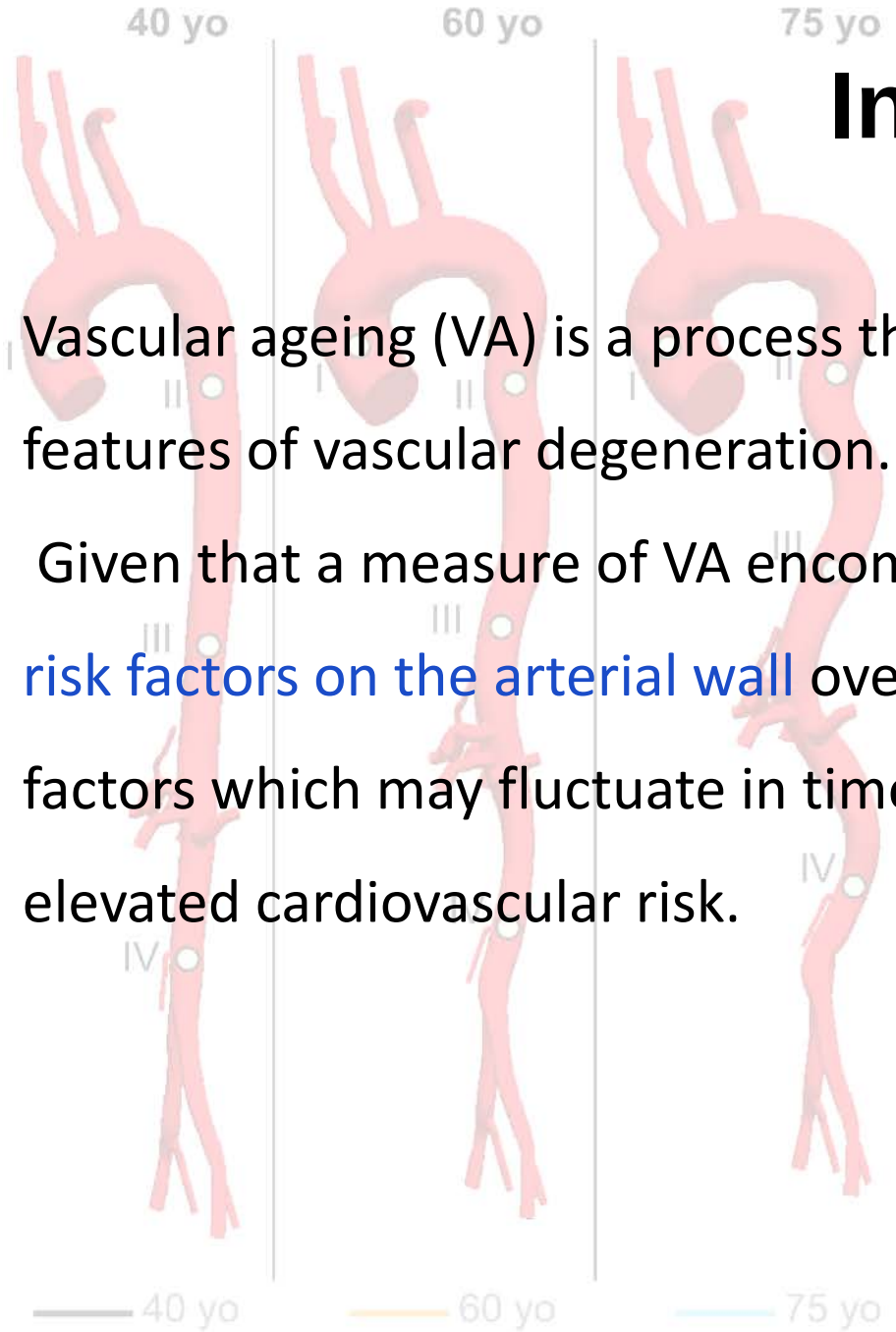
K. Engelman & E. Bramwald
"Elevation of Arterial Blood Pressure"
Harrison's Principles of Internal Medicine
Sixth Edition, 1970; chapter 37

Salvi, P. *Pulse Waves*. *Pulse Waves* (Springer Milan, 2017).

The three components characterizing blood pressure properties. (a) Mean arterial pressure, the steady component. (b) Pulse pressure represents the fluctuation in pressure values around the mean value of blood pressure. (c) Blood pressure variability represents spontaneous oscillations of mean arterial pressure and pulse pressures over short-term and long-term periods



Salvi, P. *Pulse Waves*. *Pulse Waves* (Springer Milan, 2012).

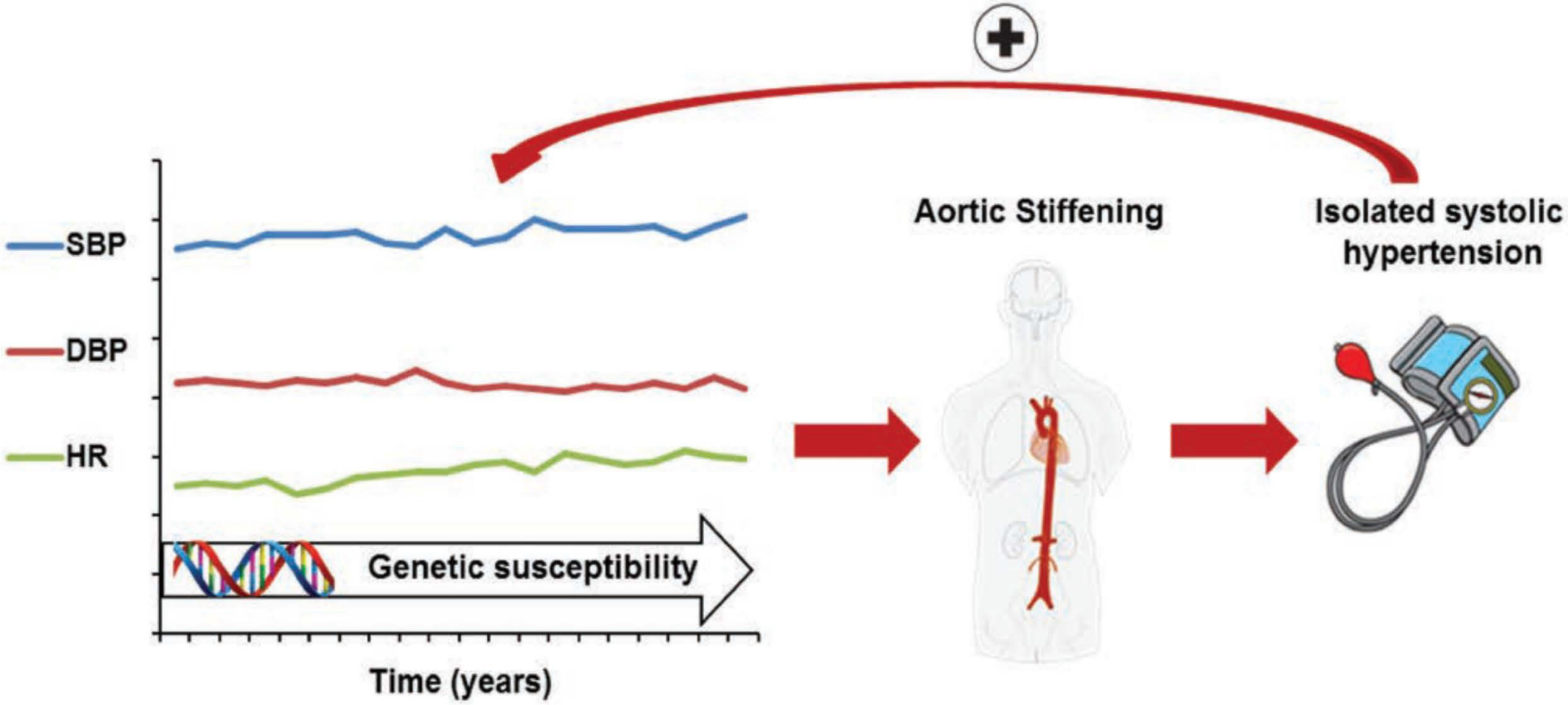


Introduction

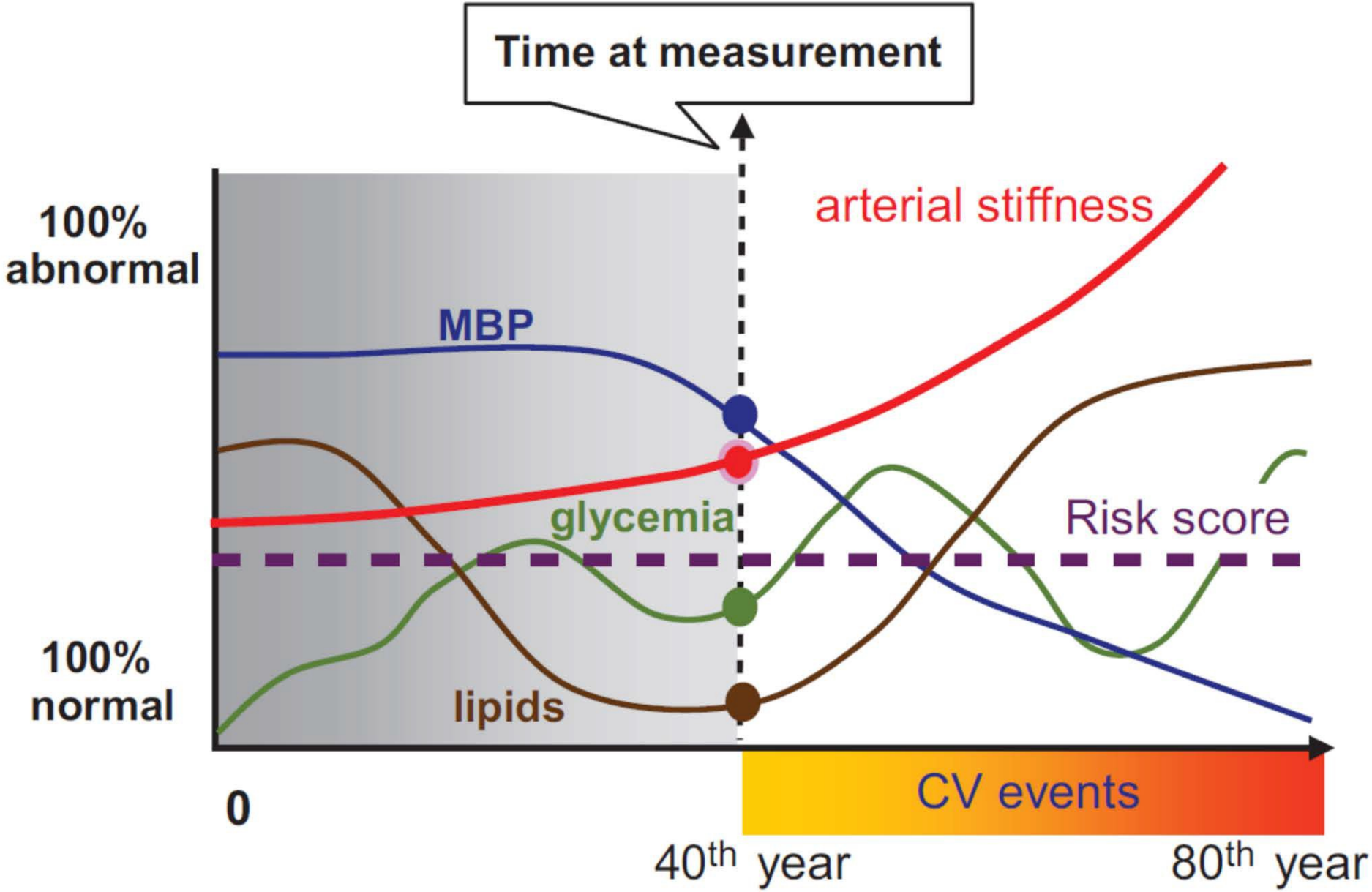
Vascular ageing (VA) is a process that can capture the early (generally asymptomatic) features of vascular degeneration.

Given that a measure of VA encompasses the cumulative effect of all cardiovascular risk factors on the arterial wall over the life course, compared to more traditional risk factors which may fluctuate in time, a measure of VA may help identify those at elevated cardiovascular risk.

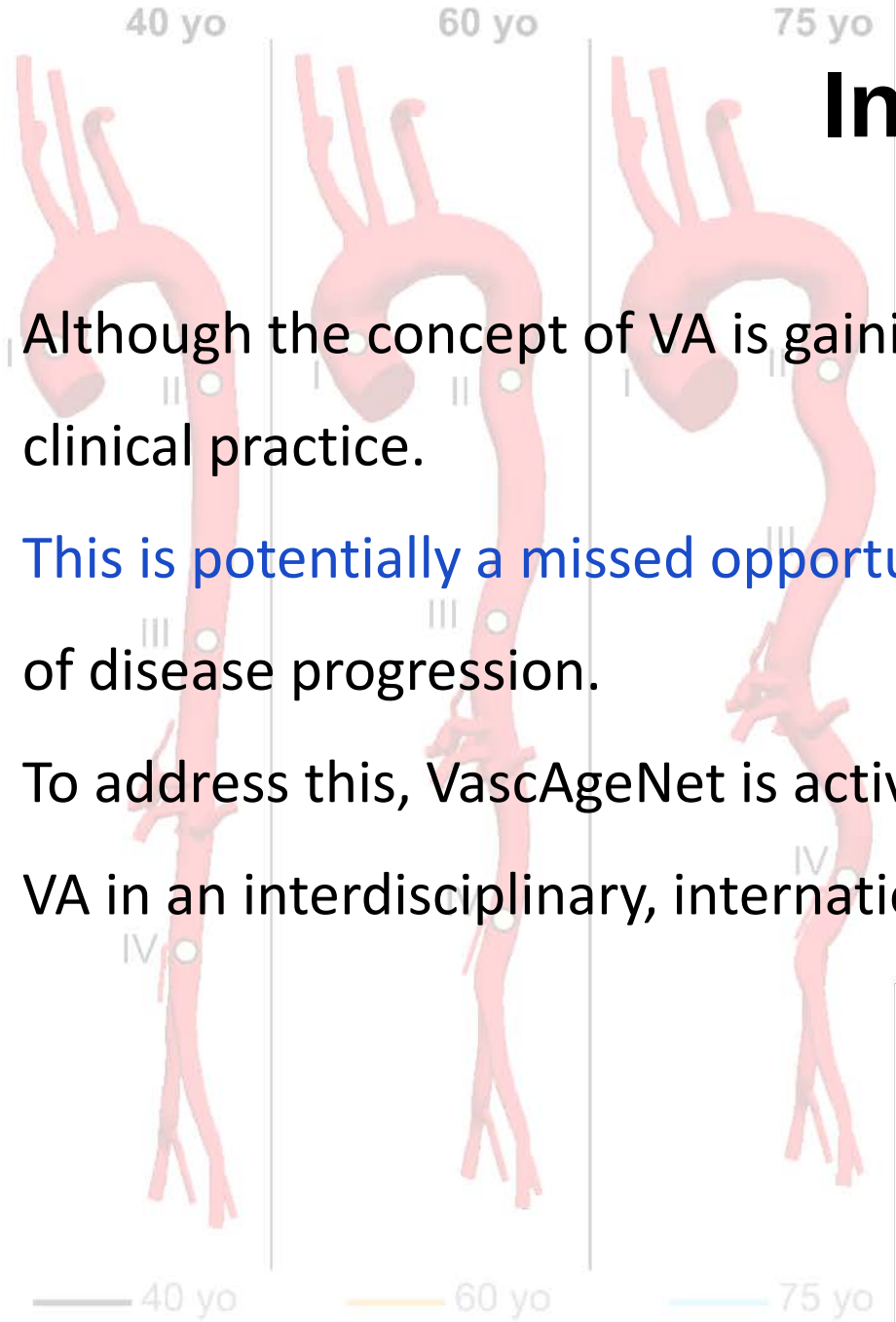
Assessment of arterial stiffness provides information about the long-term effects of blood pressure and heart rate.



Wilkinson, I. B., Mäki-Petäjä, K. M. & Mitchell, G. F. Uses of Arterial Stiffness in Clinical Practice. *Arterioscler. Thromb. Vasc. Biol.* 1063–1067 (2020). doi:10.1161/ATVBAHA.120.313130



Hypertension **54**, 3–10 (2009).



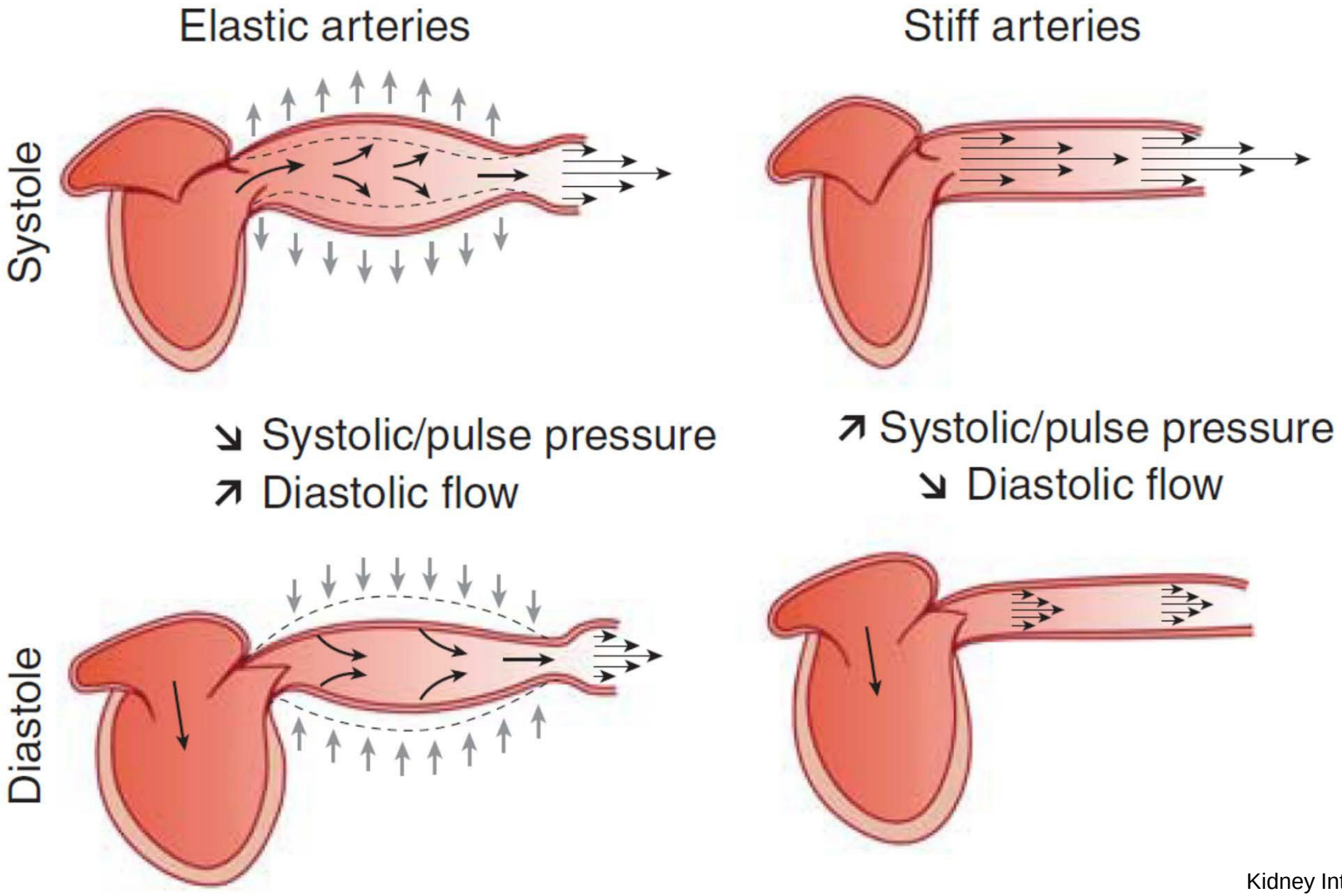
Introduction

Although the concept of VA is gaining interest, it is seldom measured in routine clinical practice.

This is potentially a missed opportunity to identify at-risk individuals at an early stage of disease progression.

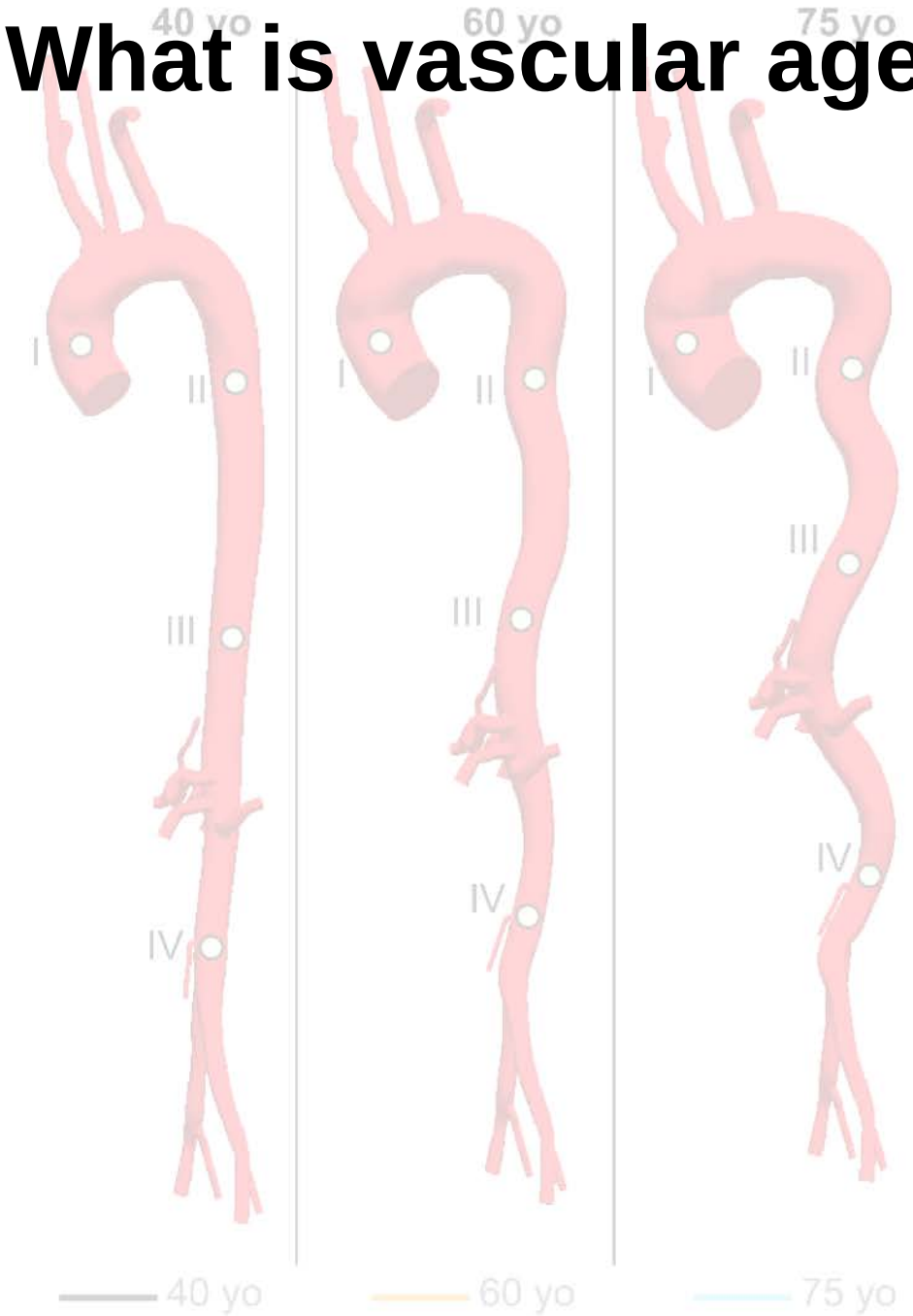
To address this, VascAgeNet is actively working to refine and harmonize measures of VA in an interdisciplinary, international, and inter-sectorial approach.

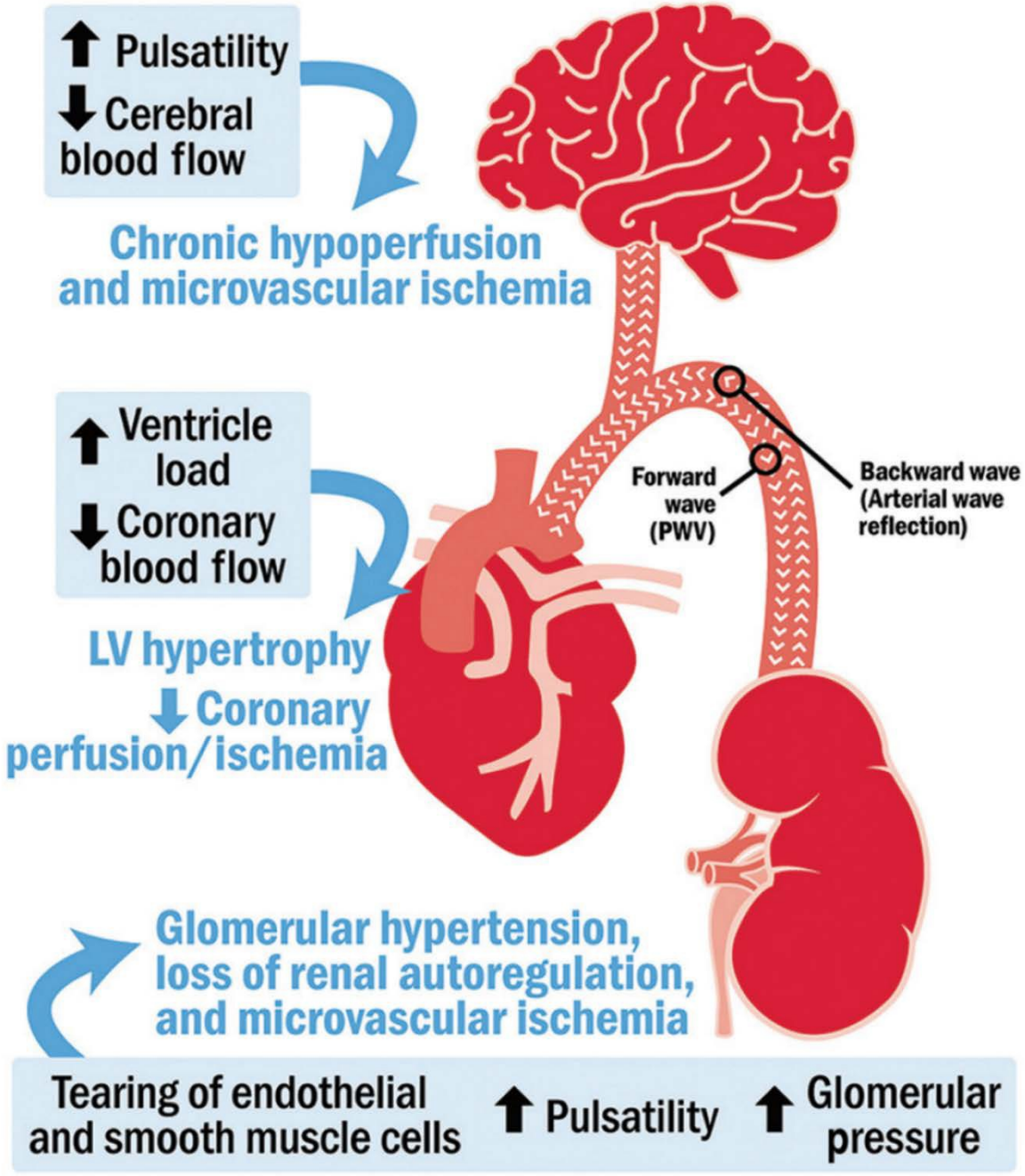
Schematic representation of the role of arterial stiffness in assuring blood flow through the peripheral circulation.



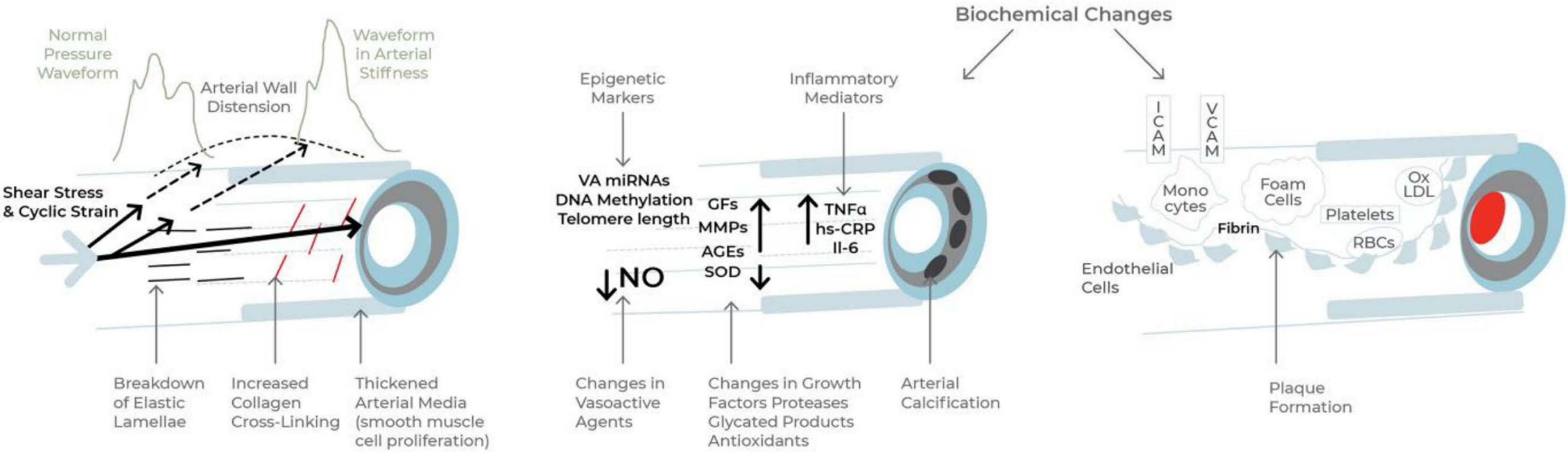
Kidney International (2012) 82, 388–400

1- What is vascular ageing?



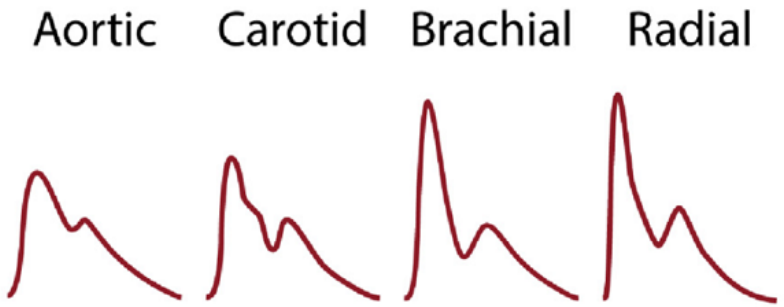


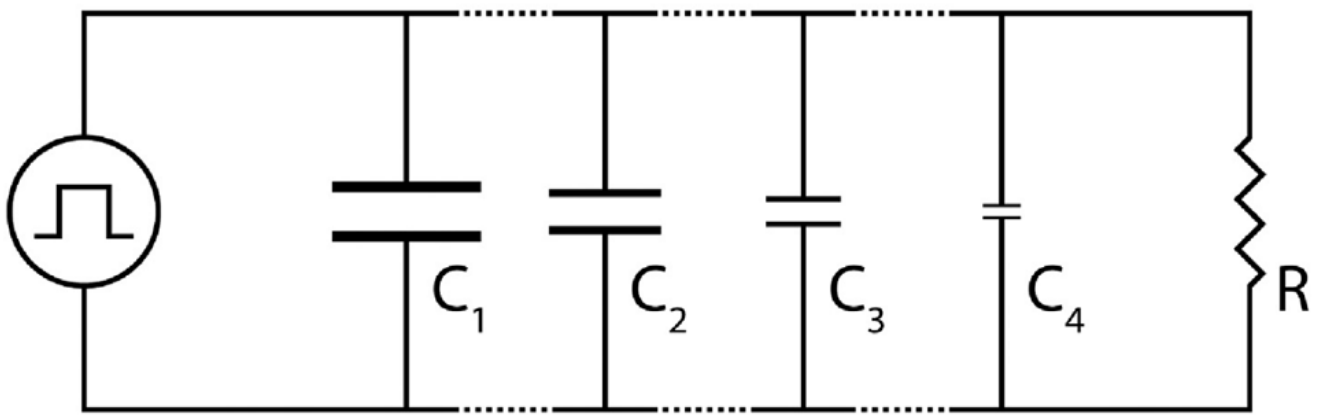
1- What is vascular ageing?



Mechanisms of vascular ageing comprising of arteriosclerotic and atherosclerotic processes. The figure depicts structural and mechanical changes, as well as major biochemical derangements contributing to vascular ageing processes. VA miRNAs, micro-ribonucleic acids of vascular ageing; NO, nitric oxide; GF, growth factors; MMP, matrix metalloproteinase; AGEs, advanced glycation end-products; SOD, superoxide dismutase; TNF-α, tumour necrosis factor-alpha; hs-CRP, high-sensitivity C-reactive protein; Il-6, interleukin-6; ICAM, intercellular adhesion molecule; RBCs, red blood cells; Ox LDL, oxidized low-density lipoprotein.

2- How can vascular ageing be estimated and what does vascular ageing add to the established biomarkers in the clinic?





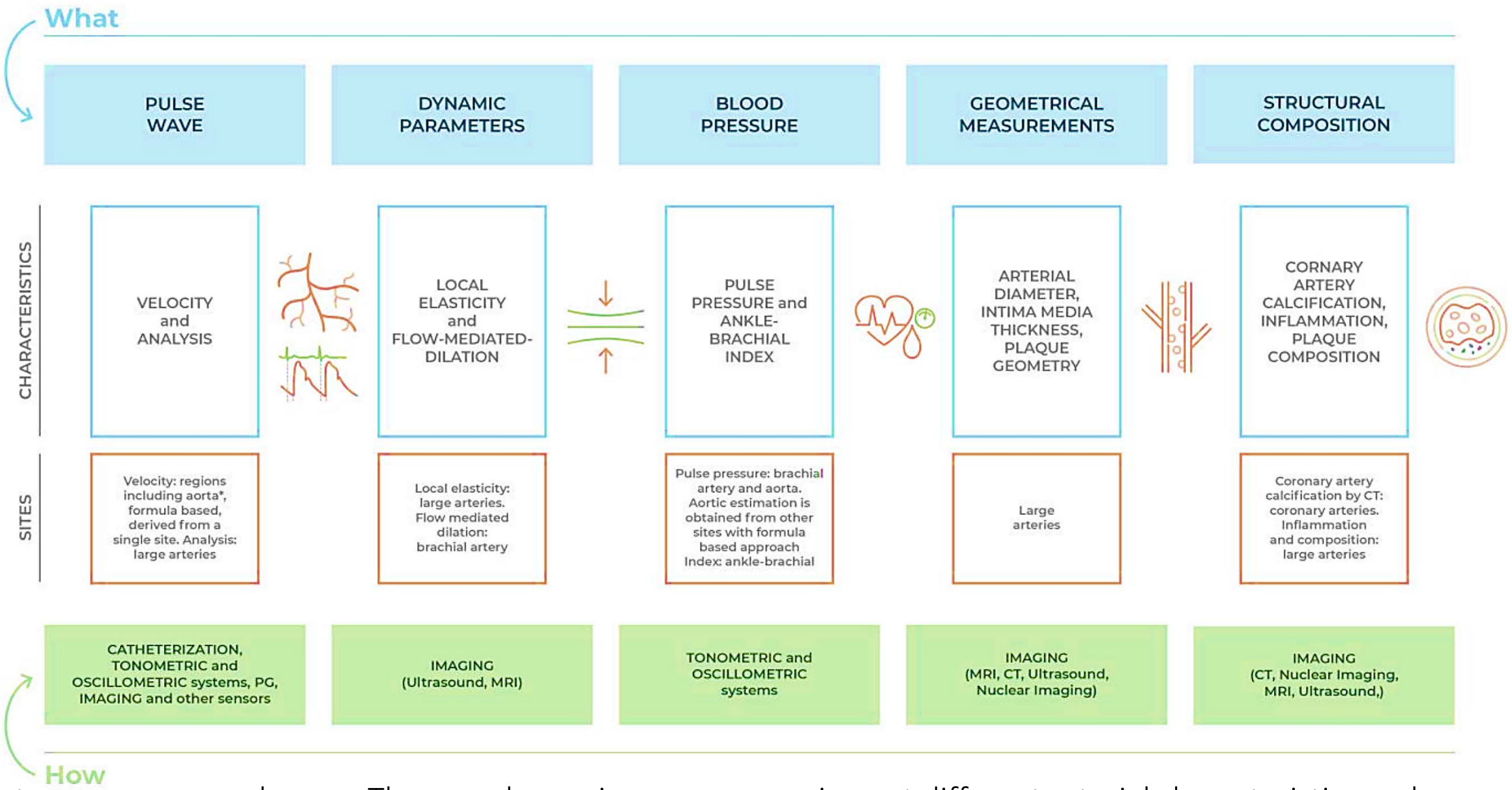
Ageing biomarker	Method of measurement	Added value
Aortic pulse wave velocity	Regional measure by phase-contrast MRI; measured using time-resolved 2D or 3D MRI. Better quantification achieved in the frequency domain, pairing flow waveforms via Fourier or wavelet analysis.	Significant independent predictor of CVD events in middle-aged individuals.[26]
Carotid–femoral pulse wave velocity	Ratio of travelled distance between the carotid and femoral pulse sites and transit time between common carotid and common femoral artery; based on tonometers, piezoelectric sensors, cuffs, or Doppler ultrasound, either simultaneously or sequentially, using ECG for gating; travel distance measured at body surface.	Independent predictive value for cardiovascular events and mortality[27]; potential for re-classification of patients beyond commonly recommended risk scores[28]; current gold standard of arterial stiffness assessment.[29]
Brachial–ankle pulse wave velocity	Transit time calculated with occlusive cuffs placed at brachial artery and ankle.	Prognostic value for all-cause mortality and cardiovascular events, independent of traditional risk factors.[30]
Cardio–ankle vascular index	Cardio-ankle vascular index is a variation of brachial-ankle pulse wave velocity and measured with occlusive cuffs and phonocardiogram. It is a marker of arterial stiffness based on the stiffness parameter β and reflects arterial stiffness from origin of the ascending aorta to the ankle.	Prognostic value for all-cause mortality, cardiovascular mortality, and cardiovascular events. May improve risk classification.[31]

Ageing biomarker	Method of measurement	Added value
Aorto–femoral volume wave velocity	Segmental impedance plethysmography with dedicated electrodes placed at regular ECG leads plus at the right side of the neck used to derive an arterial plethysmogram for the four extremities.	Independent associations with cardiovascular risk factors and development of hypertension shown in young adults.[32]
Carotid–brachial/radial pulse wave velocity	Similar to carotid-to-femoral PWV measured as transit time and travel distance between the two measuring sites (common carotid artery in the neck and brachial/radial artery at the arm).	Aortic–brachial arterial stiffness mis-match, defined as carotid–femoral pulse wave velocity divided by carotid–radial pulse wave velocity, was an independent predictor for mortality in dialysis patients.[33]
Finger–toe pulse wave velocity	Involves photoplethysmographic probes placed at the pulpar artery of the finger and the toe.	Easy-to-use measurement device, investigator independent, a good correlation with the reference method has been published, detection algorithm has been improved and validated in adults.[34]
Estimated and formula-based pulse wave velocity	Estimation of pulse wave velocity using formulas, e.g. from the Reference Value population project based on age, systolic BP, and pulse waveform characteristics.	Independent prognostic value including significant re-classification in secondary analysis of the SPRINT trial[35]; prospective data from the MORGAM project; and in patients undergoing coronary angiography.[36]
Pulse wave velocity derived with bathroom scales	Dedicated bathroom scales measure the time delay between ventricular ejection and pulse arrival at the foot.	Estimation of the aortic pulse wave velocity is feasible with a bathroom scale, but this measure lacks formal invasive validation studies.[37]

Ageing biomarker	Method of measurement	Added value
Brachial pulse pressure	Measured using validated sphygmomanometers; brachial pulse pressure defined as systolic minus diastolic BP.	Significant predictor of heart failure and all-cause mortality in middle-aged and elderly individuals.[38]
Central pulse pressure	Central pulse pressure based on waveforms recorded at the radial, brachial, or carotid artery, mainly using tonometers or cuffs; waveforms are calibrated with brachial BP and processed with dedicated formulas (e.g. transfer functions or regression models) leading to central systolic BP and pulse pressure.	Central hypertension increased cardiovascular and cerebrovascular risk irrespective of brachial BP status in a person-level meta-analysis.[39]
Waveform features related to wave reflections	Information on wave reflection derived by pulse waveform analysis based on central waveforms, e.g. augmentation index or parameters of wave separation analyses using (measure or model-based) flow waveforms.	Indices of wave reflections are independent predictors of cardiovascular events and of heart failure, with significant risk re-classification.[40]
Photoplethysmographic assessment	Photoplethysmogram used to derive an arterial pulse wave signal and several parameters. It can be assessed at various locations such as at the finger, by pulse oximeters for example.	Association of some of the derived indices with carotid-to-femoral pulse wave velocity and the presence of peripheral arterial disease.[41]

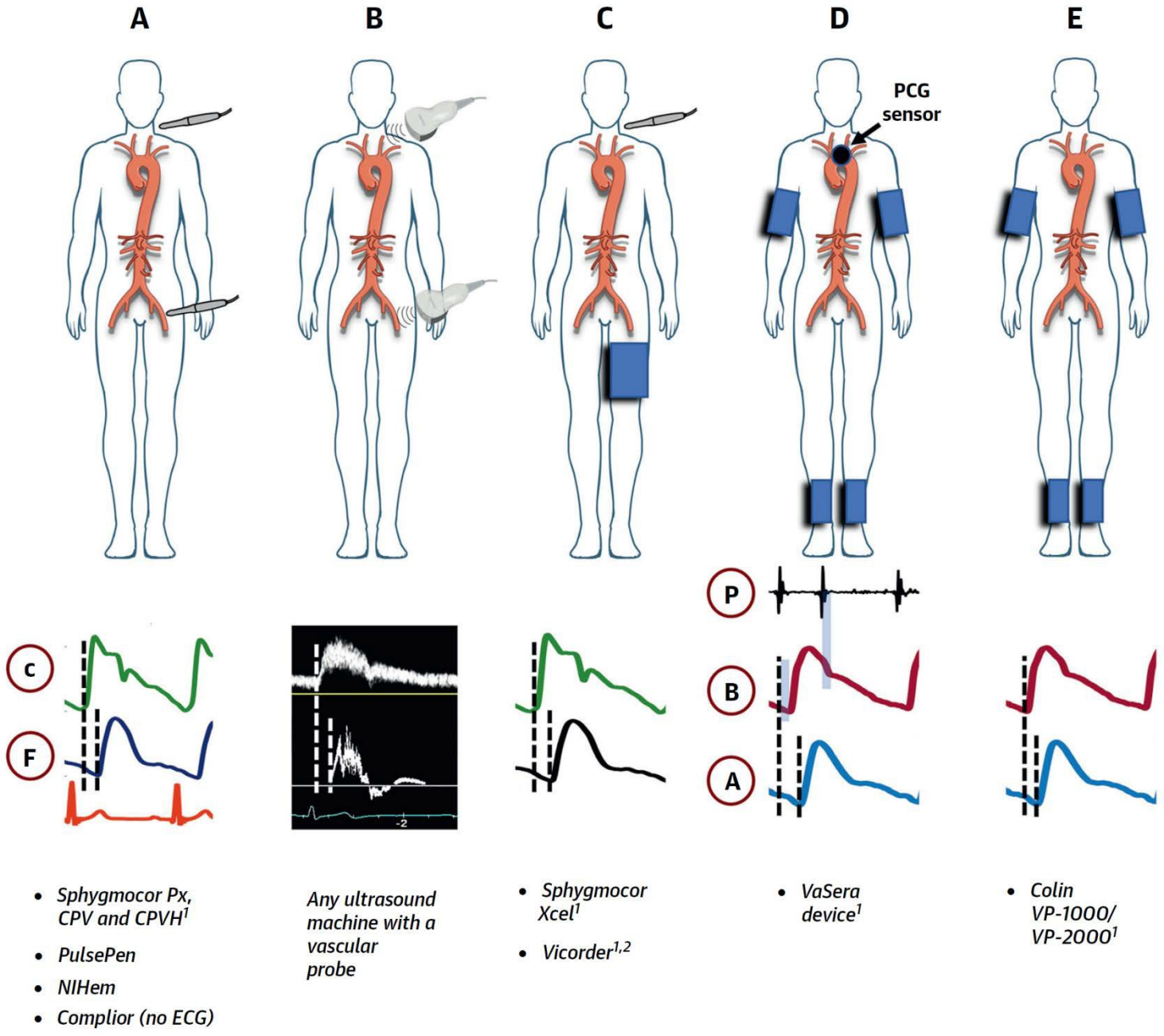
Ageing biomarker	Method of measurement	Added value
Distensibility of large arteries	Distensibility can be estimated by a relative change in diameter, area, or volume divided by the pulse pressure generating this change; often measured as change in diameter by ultrasound or area by MRI using peripheral pressure.	Aortic distensibility predicts all-cause mortality and cardiovascular events among individuals without overt cardiovascular disease[42]; carotid distensibility is an independent predictor of cardiovascular events.[43]
Carotid intima–media thickness	Assessed as the distance between the lumen–intima interface and the media–adventitia interface at different carotid segments using computerized systems based on ultrasound data processing or echo-tracking.	Association with future CVD events in individuals at high risk; whether a change in carotid intima–media thickness relates to future event risk is controversial.[44,45]
Carotid plaque	Defined as the presence of a focal wall thickening at least 50% greater than the surrounding vessel wall or as a focal region with an intima–media thickness ≥1.5 mm protruding into the lumen; obtained by ultrasound data or computerized tomography, MRI, and nuclear imaging; contrast-enhanced ultrasound imaging to assess plaque instability.	Presence of carotid plaque and carotid plaque burden are independent predictors of cardiovascular events, and significantly improve risk re-classification.[46]
Coronary artery calcification	Measured with electron-beam computed tomography or multi-slice computed tomography, and quantified semi-automatically as Agatston score.	Coronary artery calcification is a sign of sub-clinical coronary atherosclerosis; improves accuracy of risk prediction based on the Framingham risk score.[47]

Ageing biomarker	Method of measurement	Added value
Ankle–brachial index	Ratio of ankle systolic blood BP to brachial systolic BP; assessment with cuff-based systems, or with hand-held tonometers (recommended).[a]	Measure of asymptomatic hypertension-mediated organ damage; associated with an increased risk of cardiovascular and all-cause mortality; improvement beyond Framingham risk score in general population.[48,49]
Brachial artery flow-mediated dilation	Flow-mediated dilation induces the release of nitric oxide, resulting in vasodilation that can be assessed as an index of vasomotor function; ischaemia is caused by arterial occlusion using a cuff and released after 5 min leading to reactive hyperaemia; meanwhile, the brachial artery is imaged above the antecubital fossa in the longitudinal plane, and the diameter of the artery and the vasodilatation is assessed by ultrasound.	Related to the risk of cardiovascular events; a 1% increase in flow-mediated dilation is related to a 12% reduction in cardiovascular events.[25,50–53]
Aortic diameter	Leading measure of large artery size; can be measured by ultrasound, MRI, or computed tomography.	Independent prognostic value in the general population, even at values lower than those used for clinical definition of aneurysm.[54]
Large artery inflammation (positron emission tomography)	Combined with computed tomography or magnetic resonance, positron emission tomography imaging has been applied successfully in the assessment of large arteries inflammation mainly by evaluating ^{18}F-fluorodeoxyglucose (^{18}F-FDG) standardized uptake values.	^{18}F-FDG SUV is independently related to the occurrence of cardiovascular events[55,56]; is a promising therapeutic target.[57]



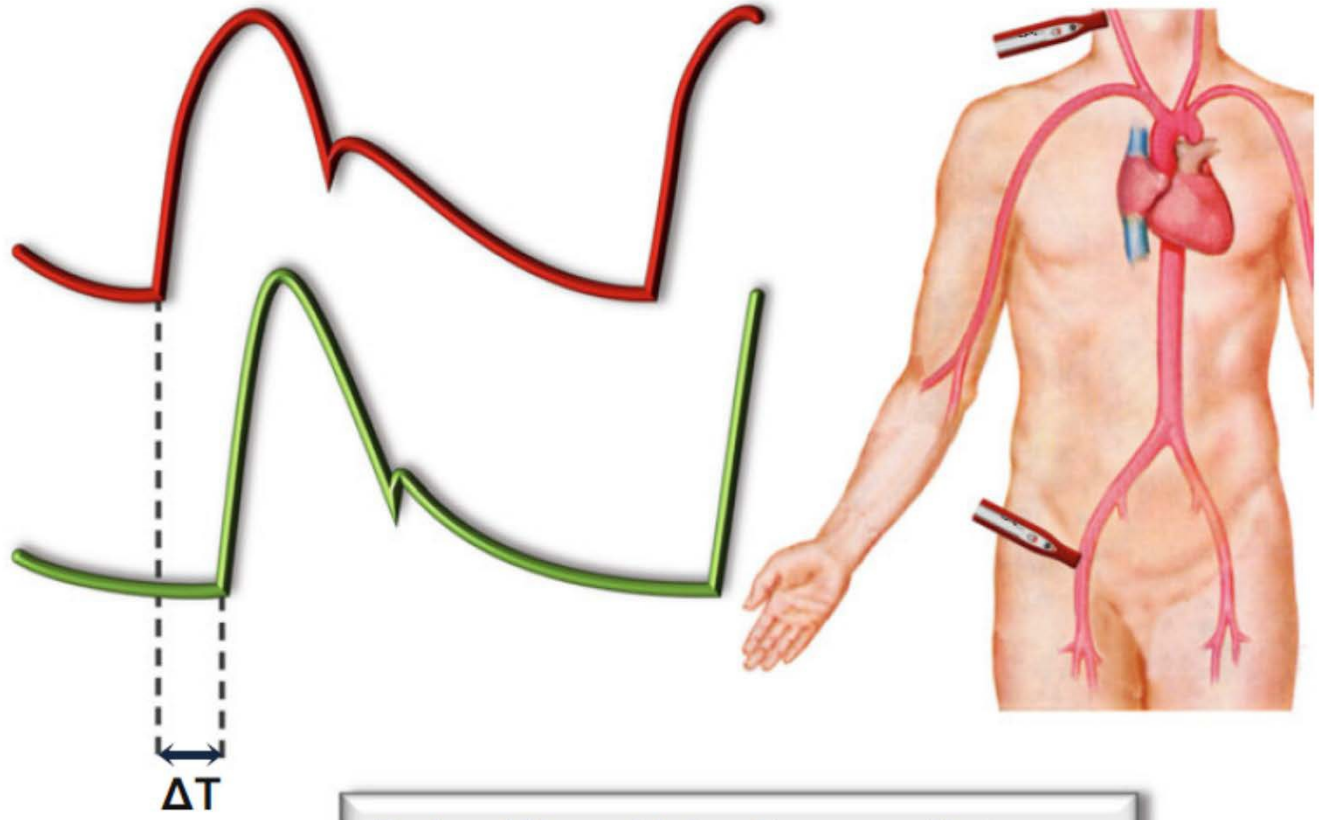
How to measure vascular age. The vascular ageing process can impact different arterial characteristics: pulse wave velocity and features, arterial dynamic or geometrical parameters, pulse pressure, and vessel structural composition. Alterations of these properties can be assessed by processing images or signals obtained using various technologies.

Methods of Measurement of Carotid–Femoral PWV, CAVI, and ba–PWV by Various Devices



Chirinos, J. A., Segers, P., Hughes, T. & Townsend, R. Large-Artery Stiffness in Health and Disease: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **74**, 1237–1263 (2019).

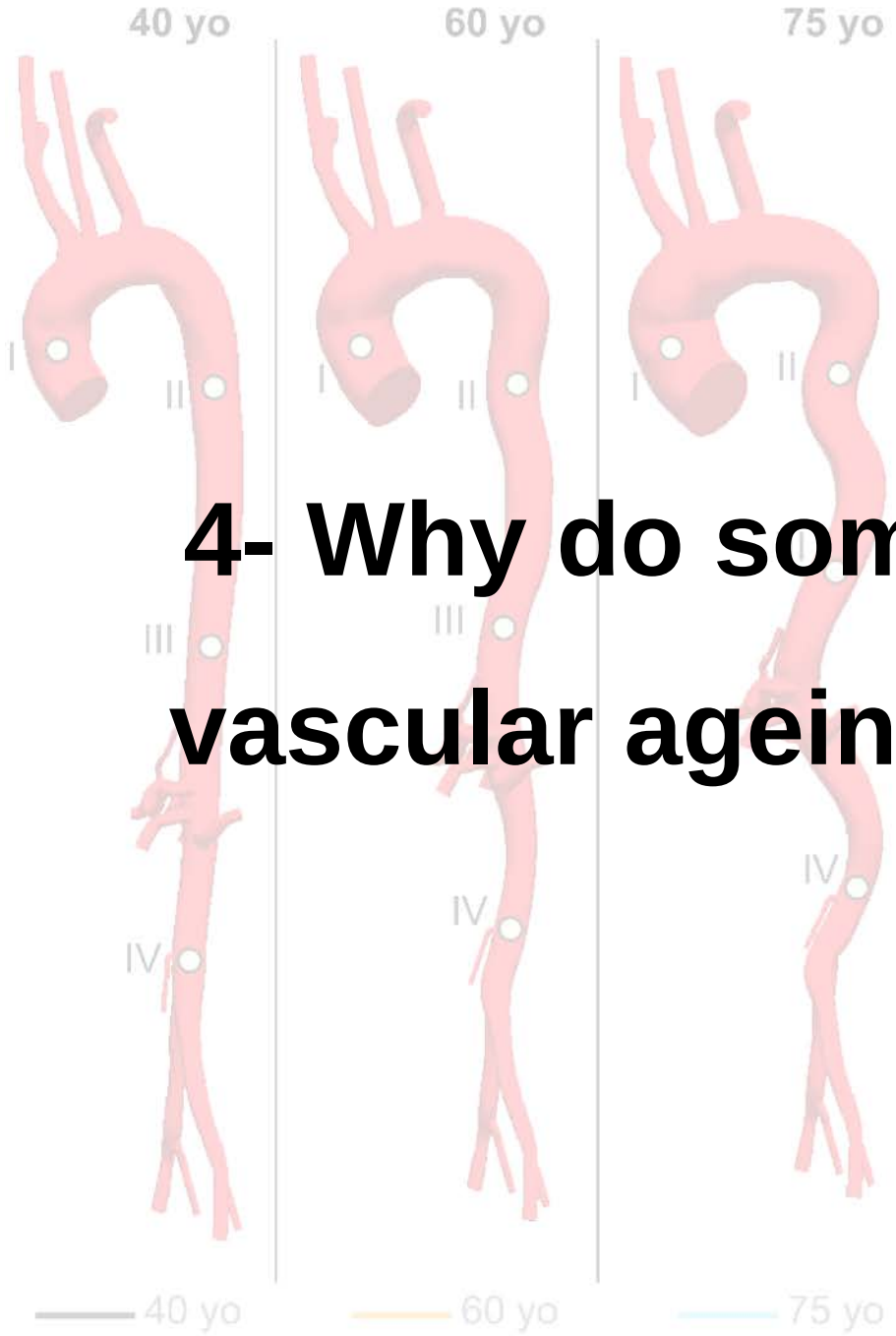
Carotid–femoral pulse wave velocity assessed all at once: carotid and femoral pressure waveforms are recorded simultaneously



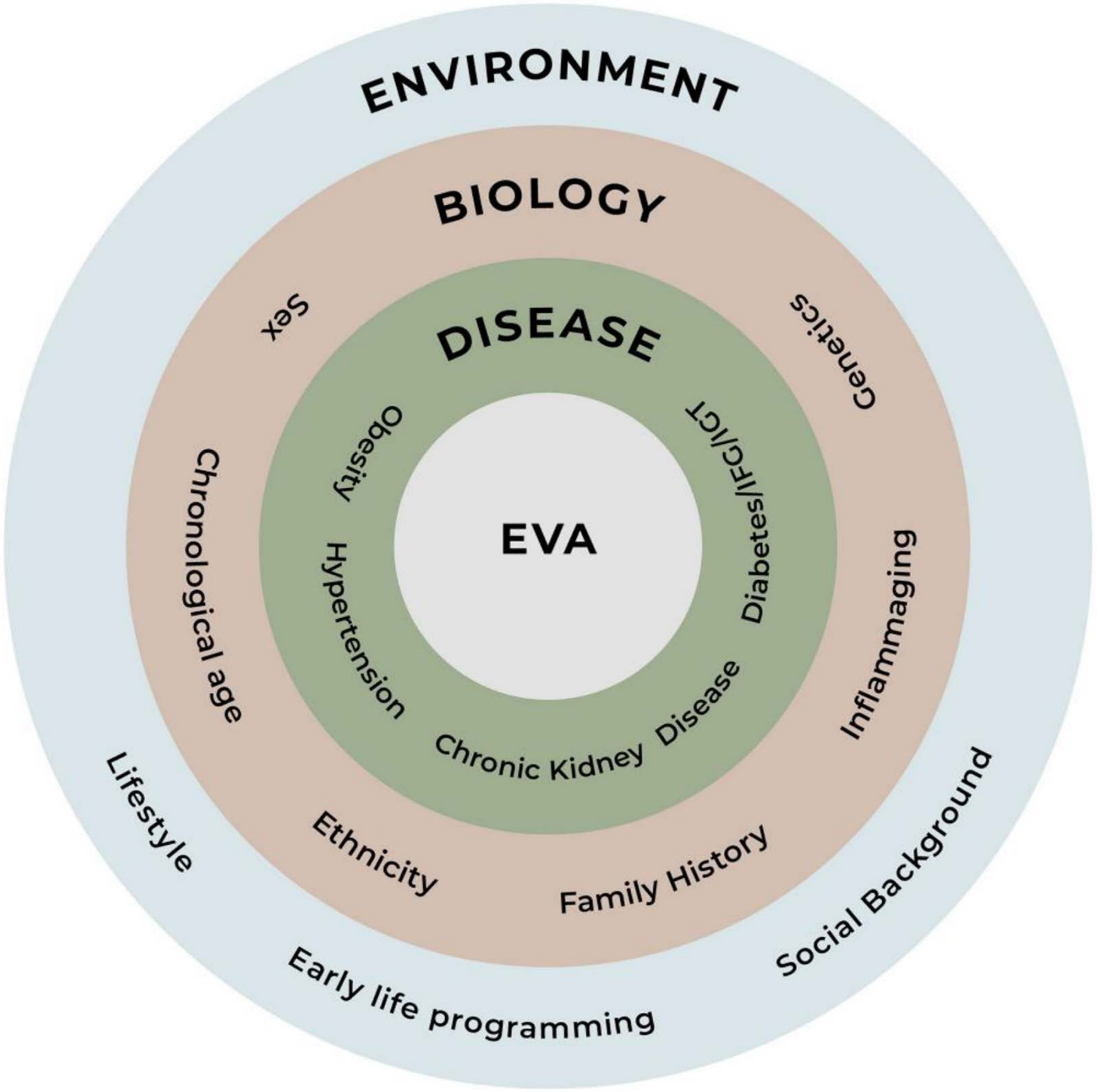
Salvi, P. *Pulse Waves*. *Pulse Waves* (Springer Milan, 2012).

3- How do vascular ageing measures relate to chronological ageing?

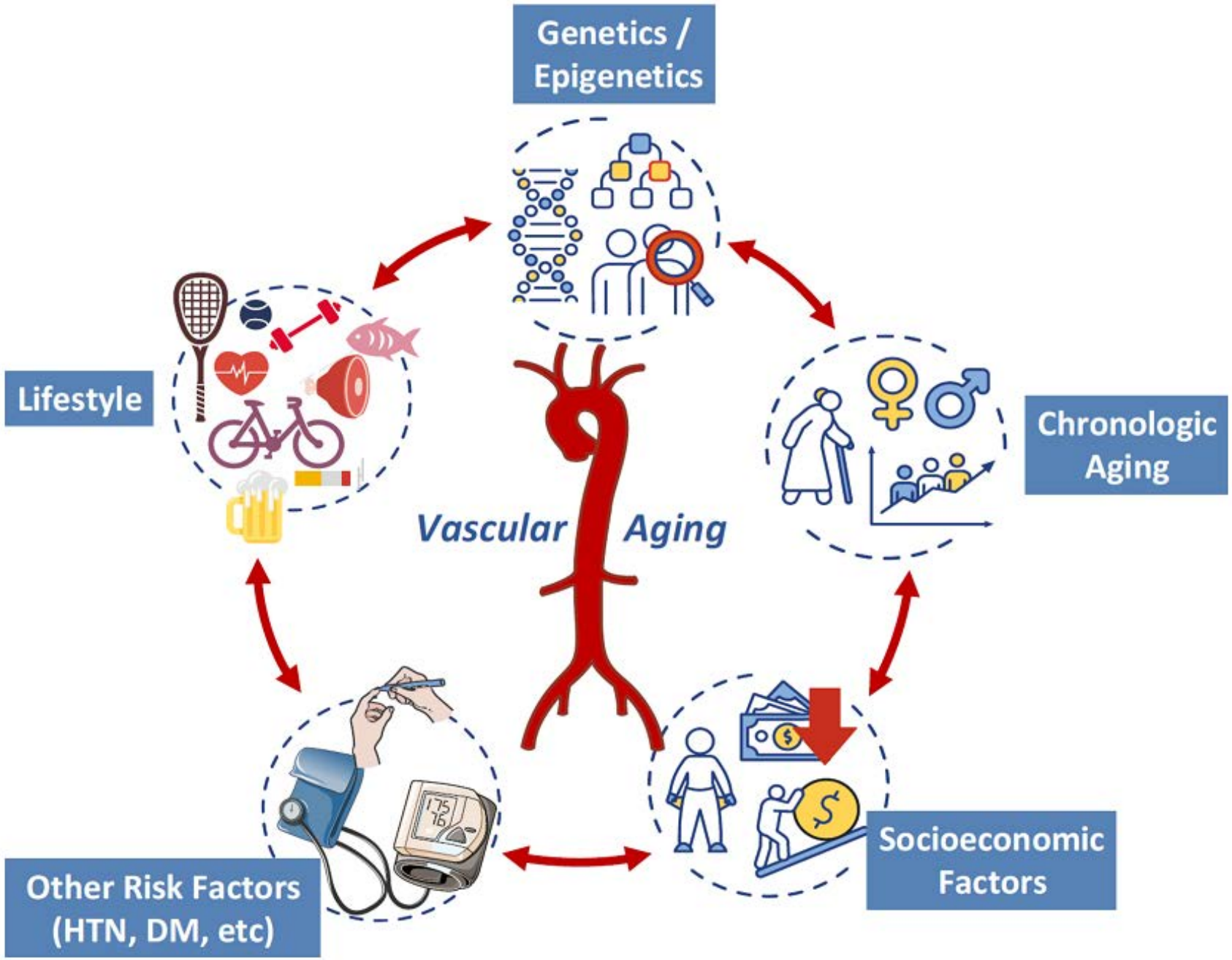
- Pulse wave velocity
- Pulse pressure
- Waveform features related to wave reflection
- Carotid intima–media thickness
- Carotid plaque
- Coronary artery calcification
- Endothelial function

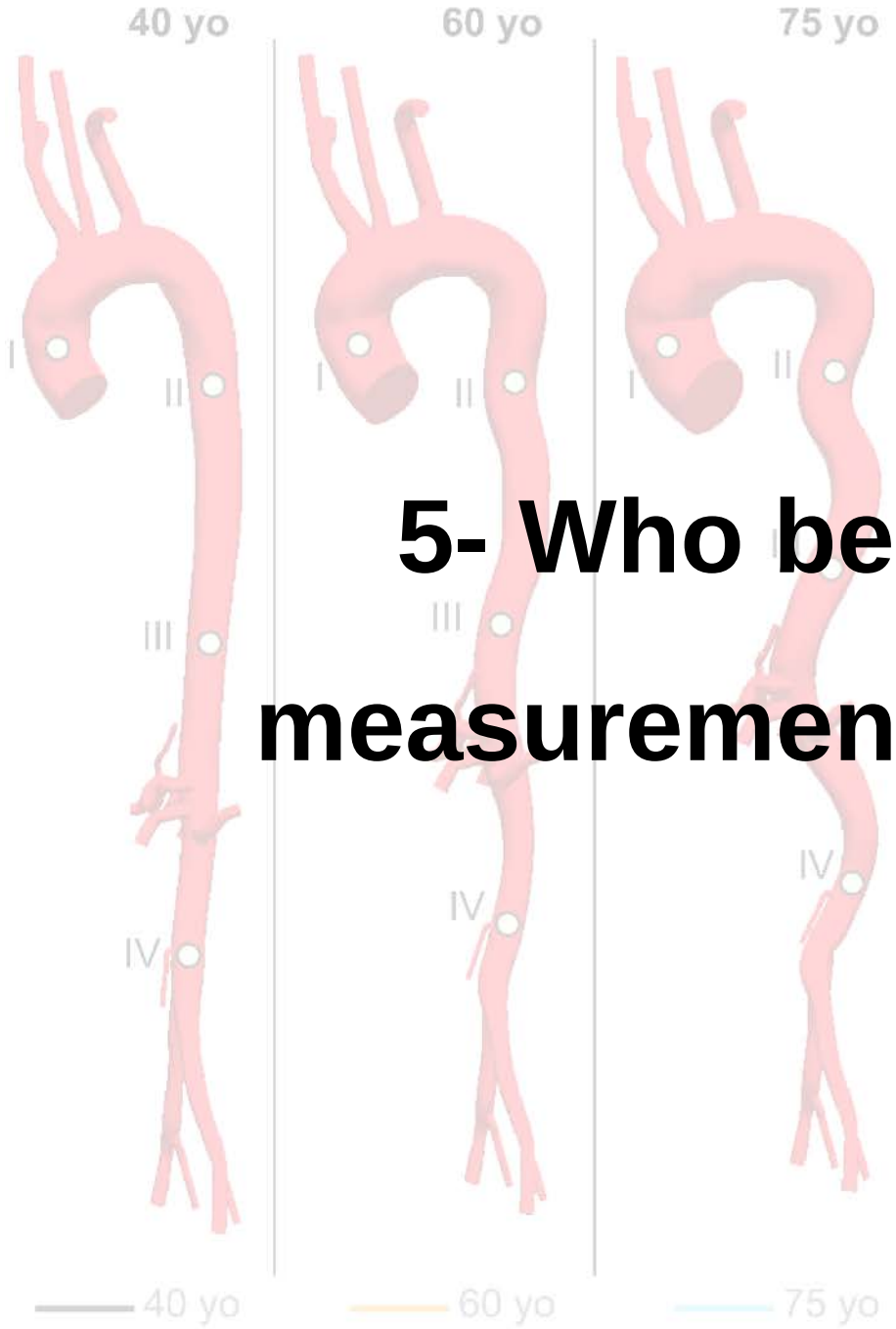


4- Why do some people display early vascular ageing compared to others?



Factors contributing to why some people display early vascular ageing (EVA) compared to others. IFG, impaired fasting glucose; IGT, impaired glucose tolerance.


Genetics / Epigenetics
Lifestyle
Chronologic Aging
Vascular Aging
Other Risk Factors (HTN, DM, etc)
Socioeconomic Factors

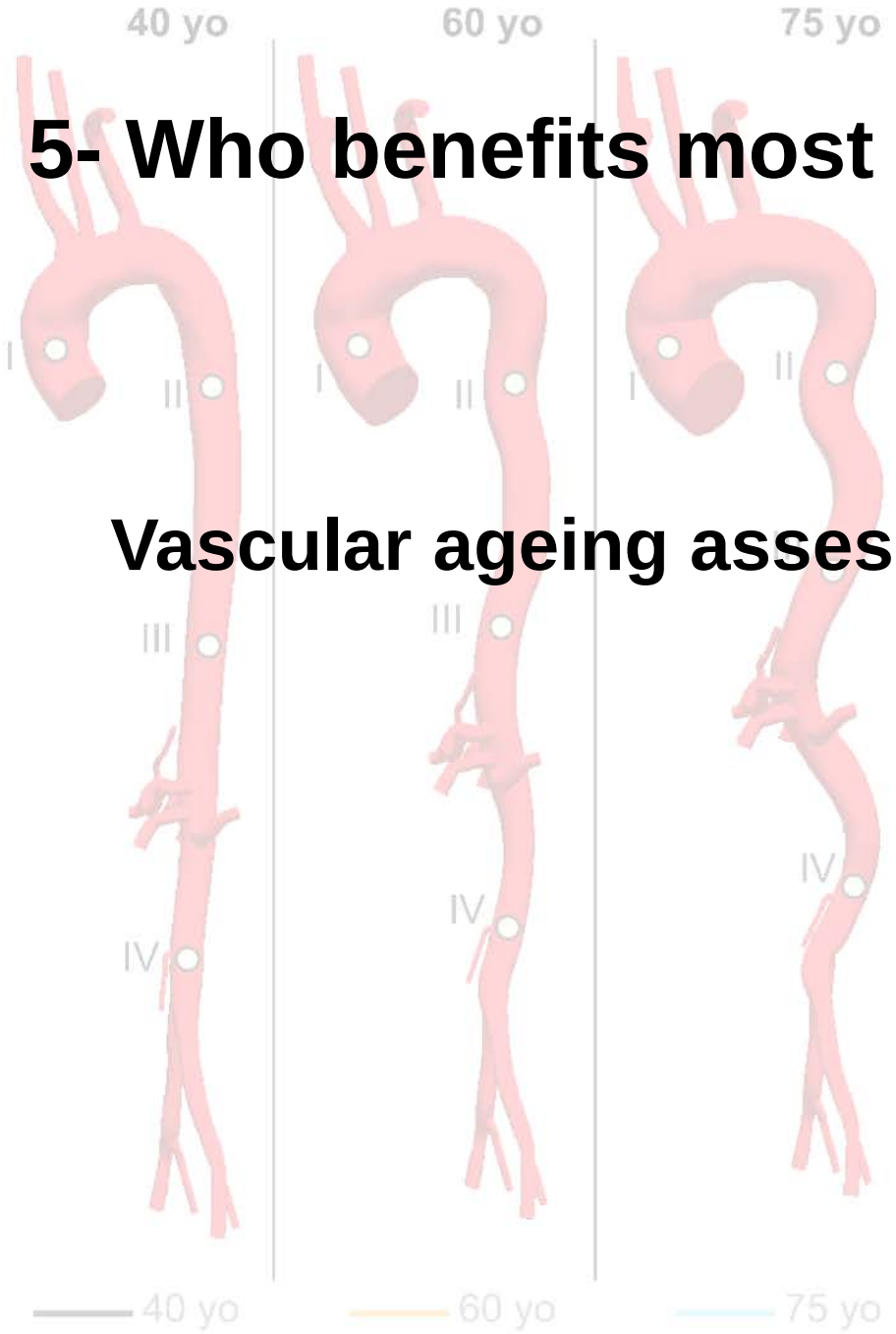


5- Who benefits most from a measurement of vascular ageing?

Clinical Scenario	Rationale	Impact on Clinical Management
Hypertension		
ACC/AHA Stage 1 Hypertension (130-139/80-89 mm Hg) with PCE-calculated 10-yr ASCVD risk ~10% without diabetes or CKD	LAS can be useful to refine risk stratification when PCE-calculated 10-year ASCVD risk is close to the threshold for treatment, after an informed clinician-patient discussion.	• Initiation of pharmacologic antihypertensive therapy
Stage 2 isolated systolic hypertension (>140 mm Hg) in very young adults with paucity of other cardiovascular risk factors	The combination of high pulse pressure amplification (with normal central systolic pressure) and low or normal LAS for age support a low CV risk.	• Withholding of pharmacologic antihypertensive therapy
Nonhypertensive adults <40 yrs of age with family histories of ISH	LAS is partially heritable. LAS precedes and predicts the development of ISH, a potentially avoidable threshold in the life course of cardiovascular disease (see **Figure 14B**). A high PWV for age is consistent with early vascular aging.	• Guide clinician-patient risk discussions • Intensification of lifestyle interventions • More frequent assessments of cardiovascular risk before age 40 (<4 to 6 yrs)
Other CV risk-assessment scenarios		
Refinement of cardiovascular risk assessment in nondiabetic adults 40 to 75 yrs of age at intermediate PCE-calculated 10-year ASCVD risk	In this group of patients, risk-based decisions for preventive interventions may be uncertain and LAS measurements can be used to refine risk assessment (particularly if various "risk-enhancing" clinical parameters do not clearly favor a specific course of action).	• Guide clinician-patient risk discussion • Guide decision making regarding initiation of pharmacologic therapy (i.e., statins)
Refinement of cardiovascular risk assessment in middle-aged nondiabetic adults at borderline PCE-calculated 10-yr risk of ASCVD (5% to <7.5%) who also have other factors that increase their ASCVD risk ("risk enhancers")	In this group of patients, LAS measurements may be useful to improve risk-based decisions as an alternative or as a "gate-keeper" for coronary calcium score testing, particularly when concerns about radiation exposure (younger age, overweight/obese) or about cost are present.	• Guide clinician-patient risk discussion • Guide decision making regarding further testing (coronary calcium score) or initiation of therapy (i.e., statins)
Assessment of CV risk in special populations	PCE-calculated 10-year risk estimations can provide notoriously miscalibrated estimates in non-U.S. populations, particularly those at earlier stages of the epidemiologic transition. This may also apply to immigrants from those populations in the U.S.	• Guide clinician-patient risk discussions and various interventions • An abnormal PWV for age indicates subclinical arterial damage and suggests a higher-risk. Expert clinical judgment must guide result interpretation and decision making depending on the specific clinical scenario.

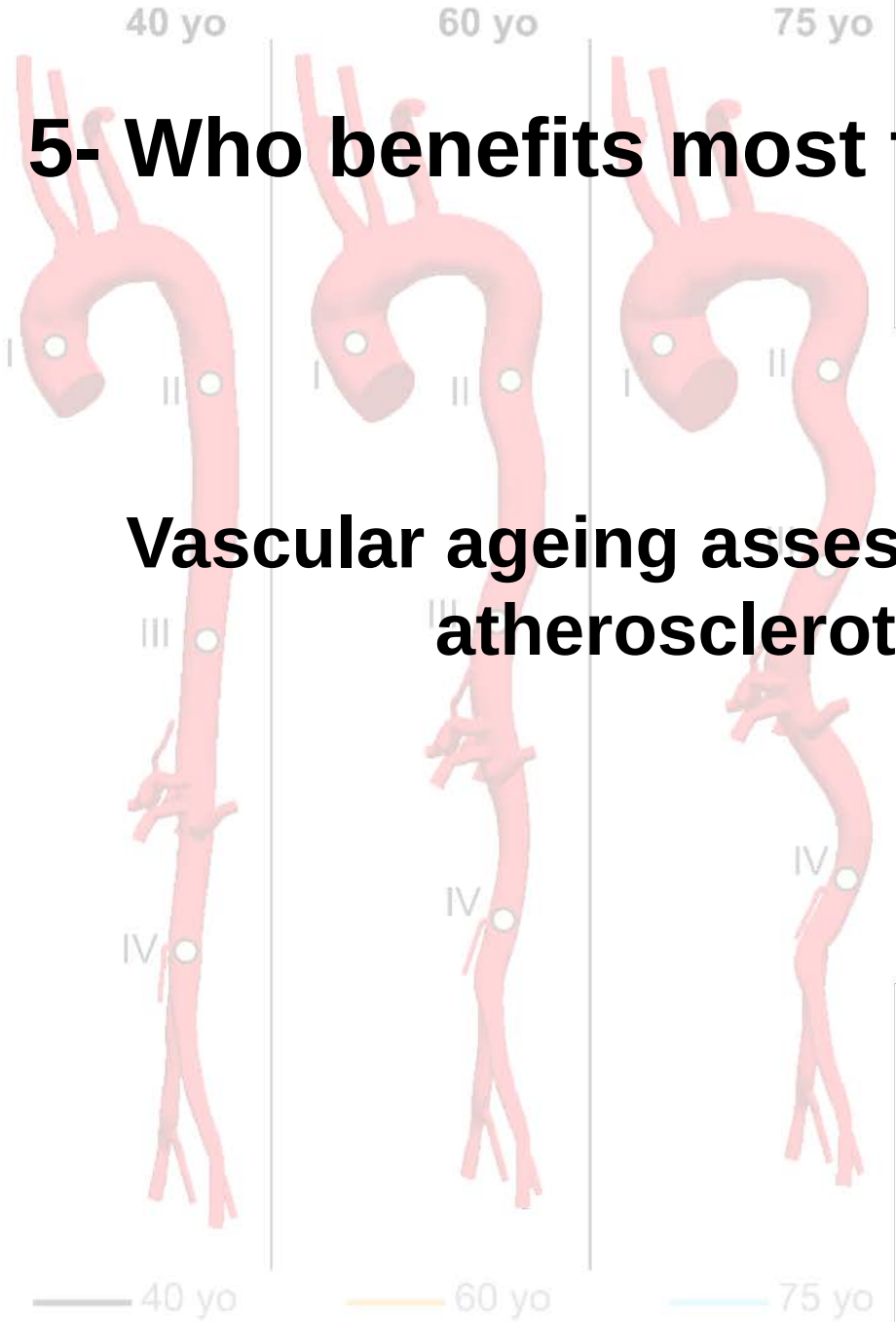
ACC/AHA ¼ American College of Cardiology/American Heart Association; ASCVD ¼ atherosclerotic cardiovascular disease; CV ¼ cardiovascular; PCE ¼ pulled cohort equations.

Chirinos, J. A., Segers, P., Hughes, T. & Townsend, R. Large-Artery Stiffness in Health and Disease: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **74**, 1237–1263 (2019).



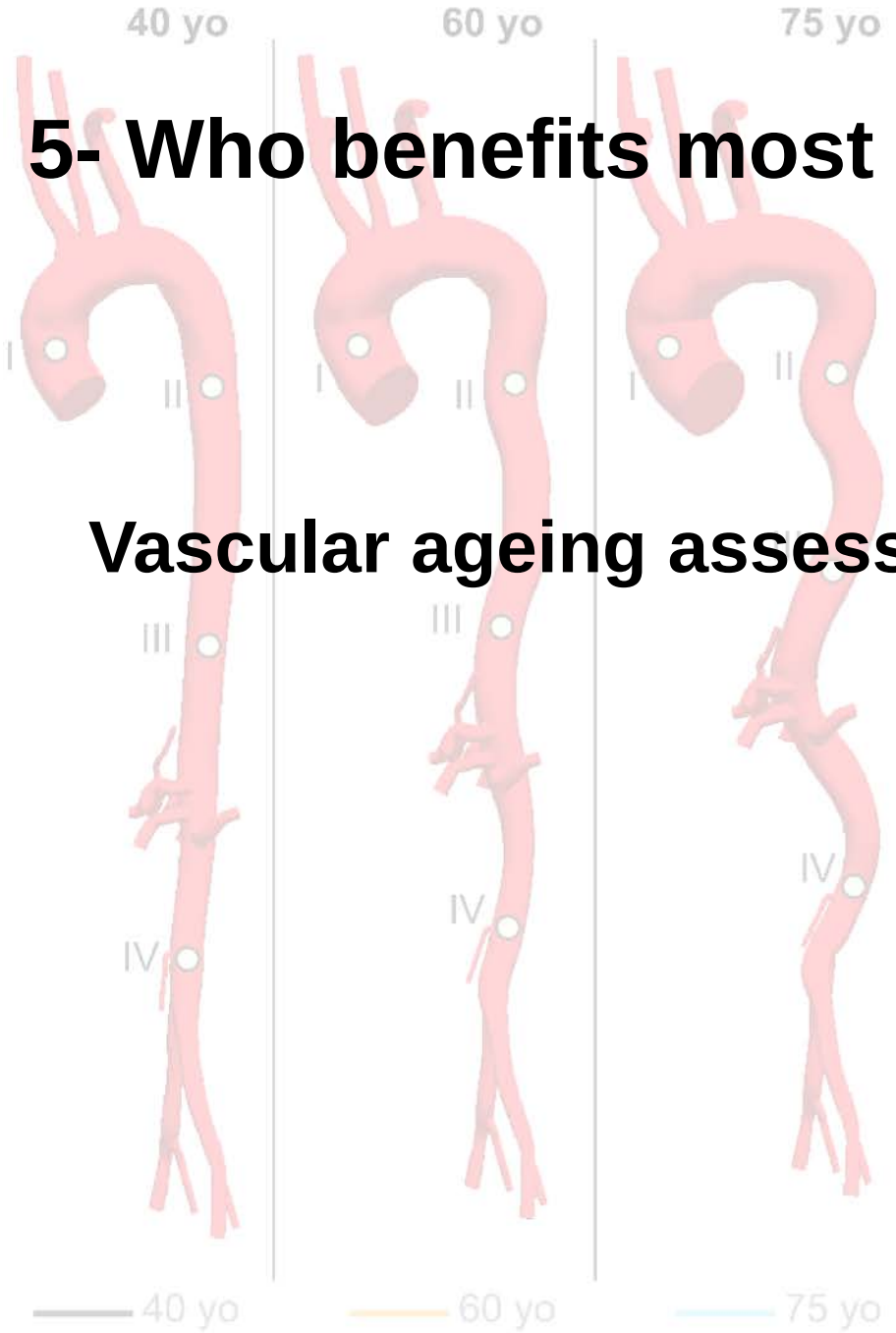
5- Who benefits most from a measurement of vascular ageing?

Vascular ageing assessment in apparently healthy people



5- Who benefits most from a measurement of vascular ageing?

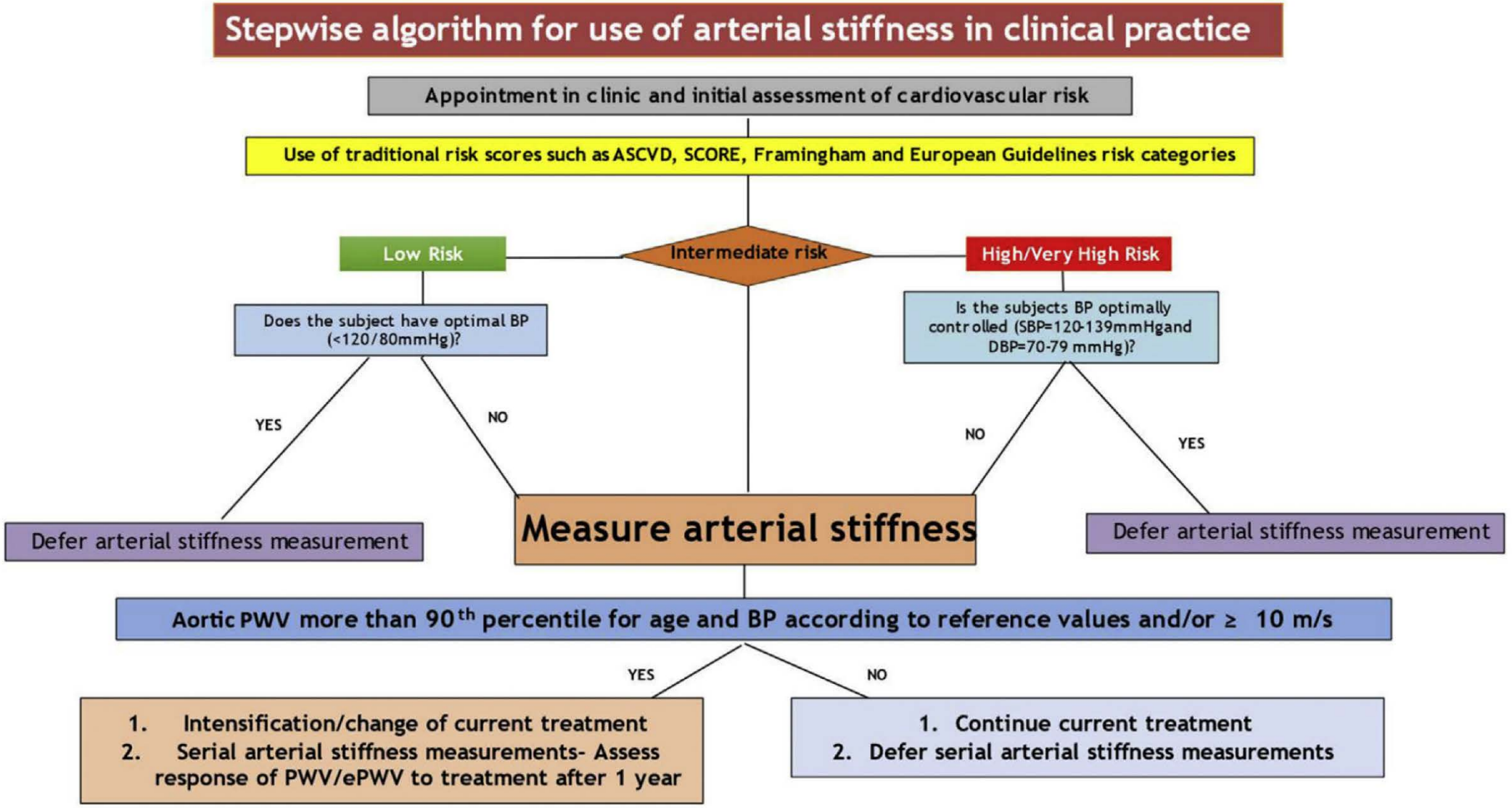
Vascular ageing assessment in patients with established atherosclerotic cardiovascular disease



5- Who benefits most from a measurement of vascular ageing?

Vascular ageing assessment in patients with risk modifiers

Algorithmic approach of the use of measurement of pulse wave velocity in the clinical practice.

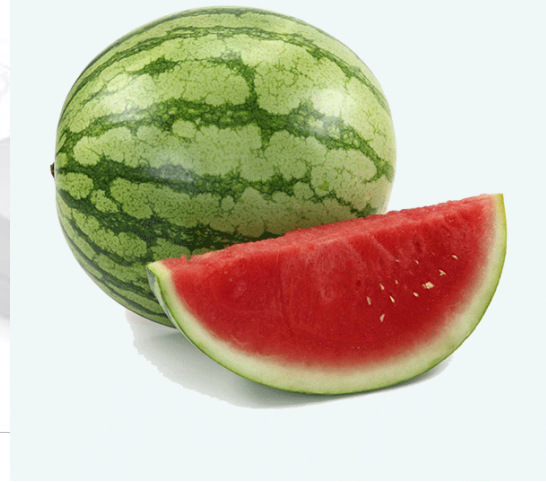


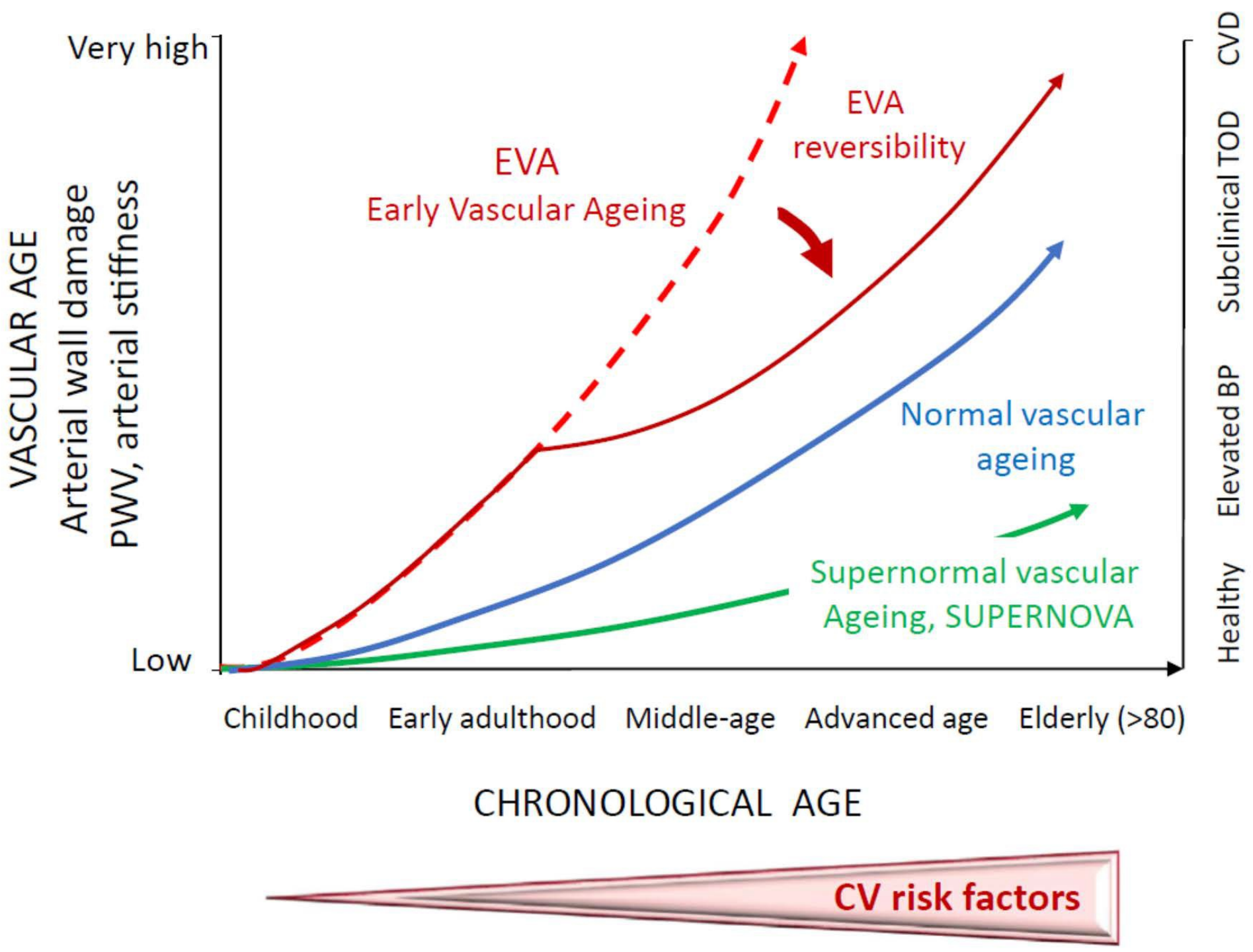
D. Acemoglu, A. Uganda, A. Fund, Textbook of Arterial Stiffness and Pulsatile Hemodynamics in Health and Disease, Elsevier, 2022. Chapter 33,

6- How can vascular ageing be modified?

Lifestyle modifications

- Exercise
- A healthy diet: rich in fruits and vegetables (red-coloured fruits and vegetables, especially tomatoes and watermelon). ***Polyphenol***, found mostly in the skin of red grapes, peanuts, and several types of berries. A healthy vascular diet should also comprise of ***polyunsaturated fatty acids***, cocoa flavonoids, tea catechins, and dairy products, while **limiting** salt, red meats, caffeine, and alcohol consumption.




Very high
Low
VASCULAR AGE
Arterial wall damage
PWV, arterial stiffness
EVA
Early Vascular Ageing
EVA
reversibility
Normal vascular
ageing
Supernormal vascular
Ageing, SUPERNOVA
Healthy
Elevated BP
Subclinical TOD
CVD
Childhood
Early adulthood
Middle-age
Advanced age
Elderly (>80)
CHRONOLOGICAL AGE
CV risk factors

6- How can vascular ageing be modified?

Risk factor modification

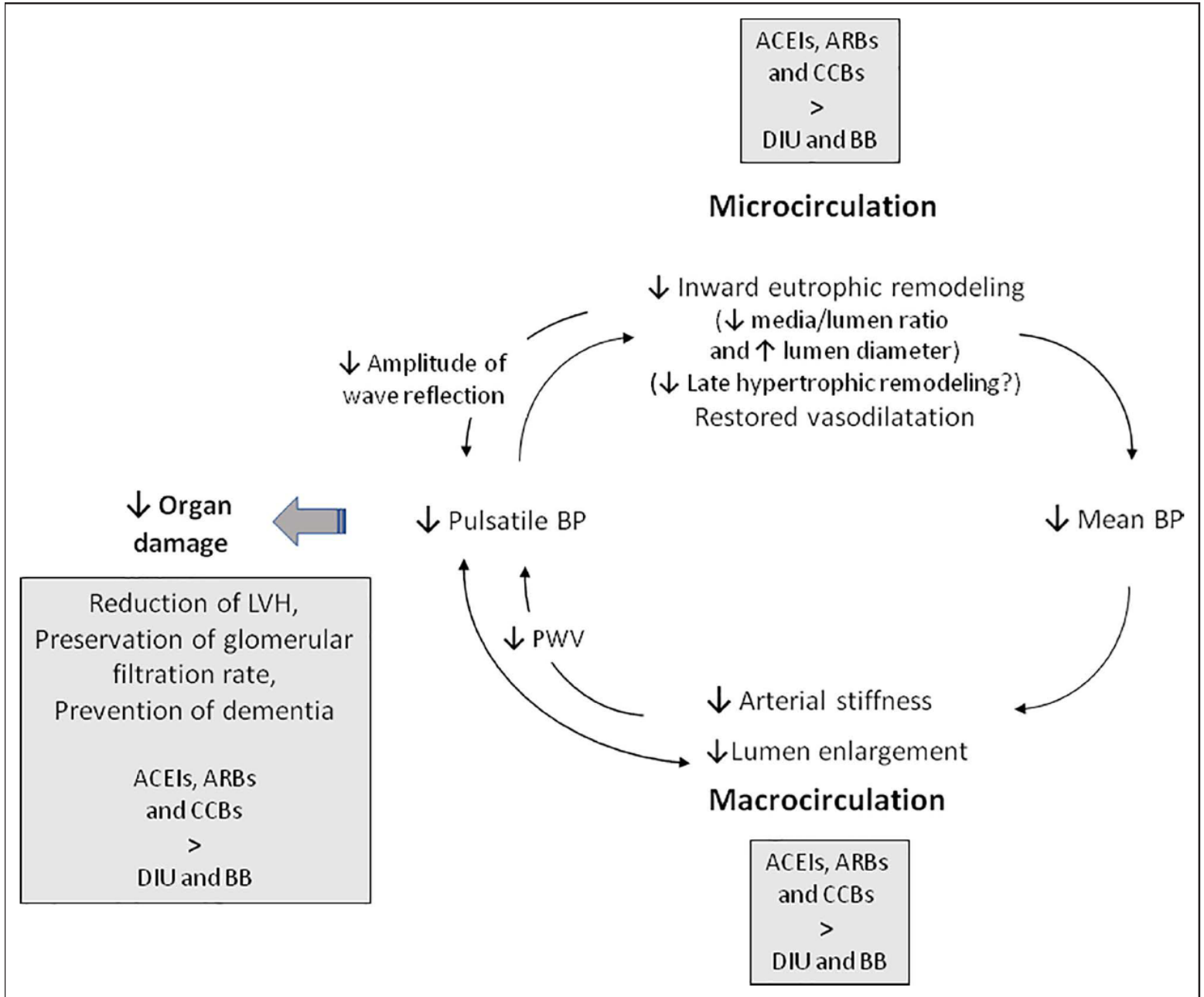
- Smoking cessation, weight loss, and controlling/lowering blood glucose and BP all have beneficial effects on VA.
- Smokers have decreased vascular distensibility, increased arterial stiffness, and increased atherosclerosis (CAC and carotid IMT) compared to never smokers.
- Obesity leads to haemodynamic alterations, chronic inflammation, and endothelial dysfunction that impair vascular structure and function.
- Diabetes and hypertension
- lowering stress and normalizing sleep patterns

6- How can vascular ageing be modified?

Pharmacological interventions

- statins,
- aspirin,
- antidiabetic,
- anti-inflammatory drugs,
- and some antihypertensive drugs such as renin–angiotensin–aldosterone system blockers.

Schematic representation of a virtuous circle of pharmacological improvement of small and large arteries in essential hypertension, leading to regression of organ damage.




Thank you