Arterial Stiffness: A Novel Cardiovascular Biomarker

From Physiology to Clinical Practice

Stella Daskalopoulou, MD, MSc, DIC, PhD

Associate Professor, FRSQ Chercheur-Boursier Clinicien
Department of Medicine
Divisions of Internal Medicine and Experimental Medicine
Director, Vascular Health Unit, MUHC
McGill University

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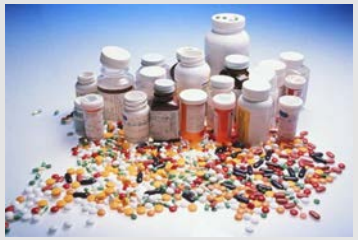
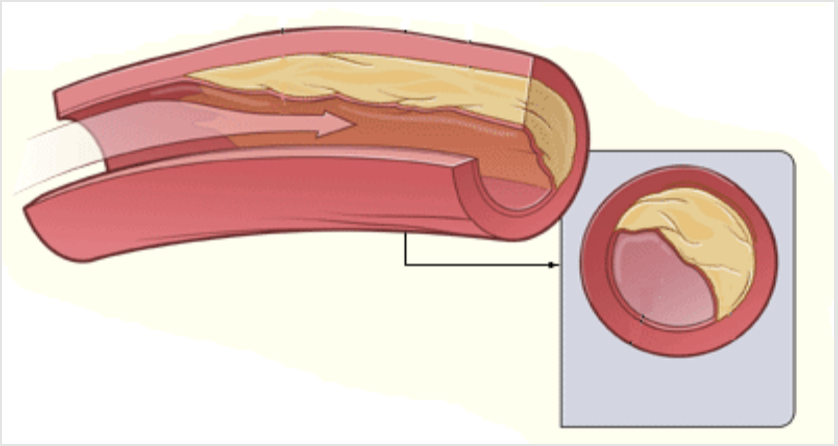
Consulting fees:	N/A
Other:	N/A

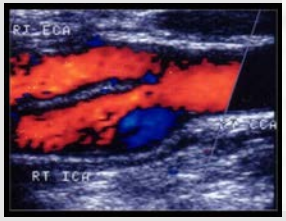
Theme

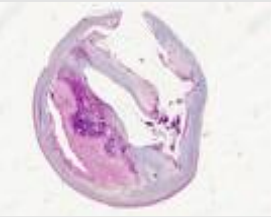
Treatment



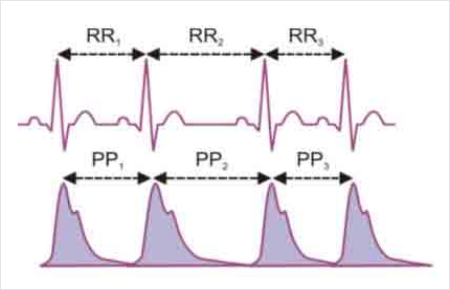


Morphology



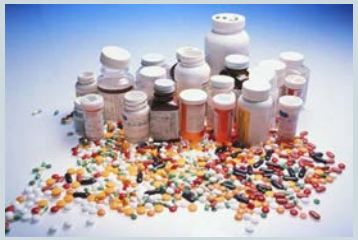


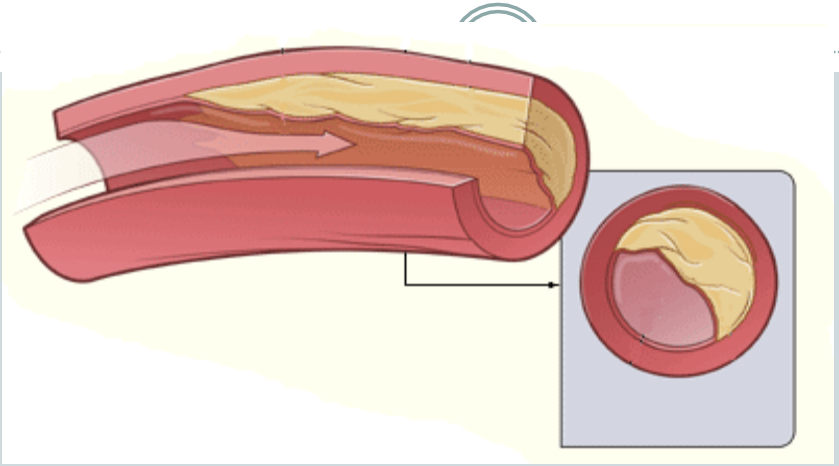
Function - Vessel Hemodynamics



Theme

Treatment





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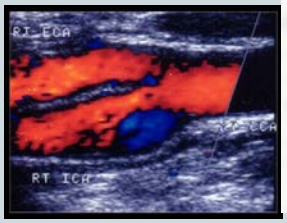

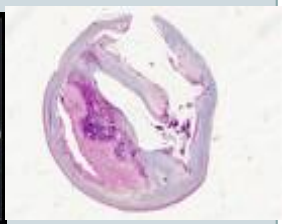

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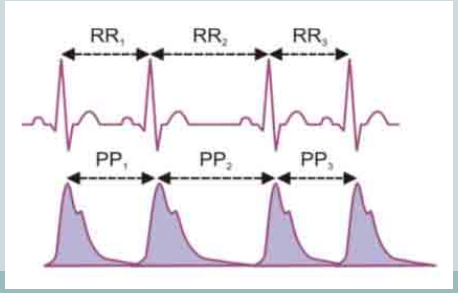
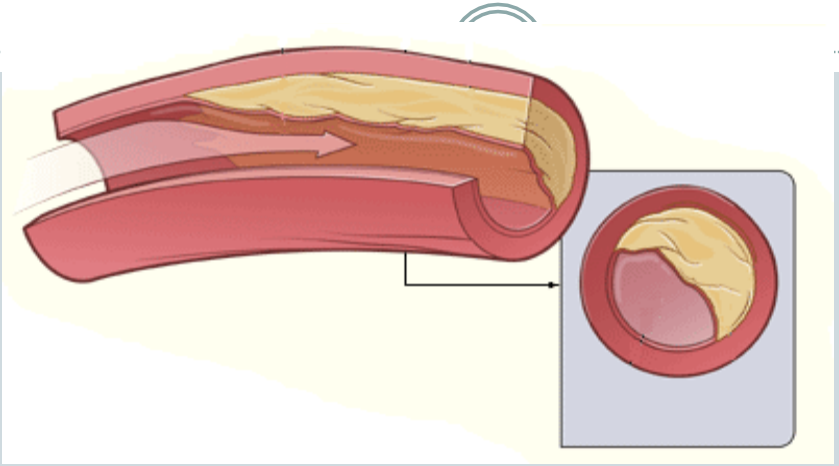
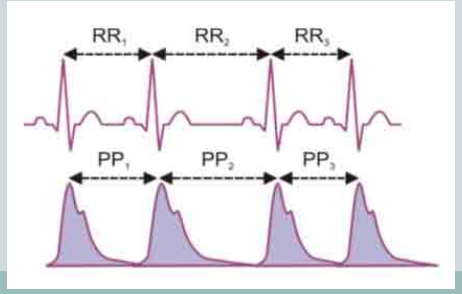




Function - Vessel Hemodynamics



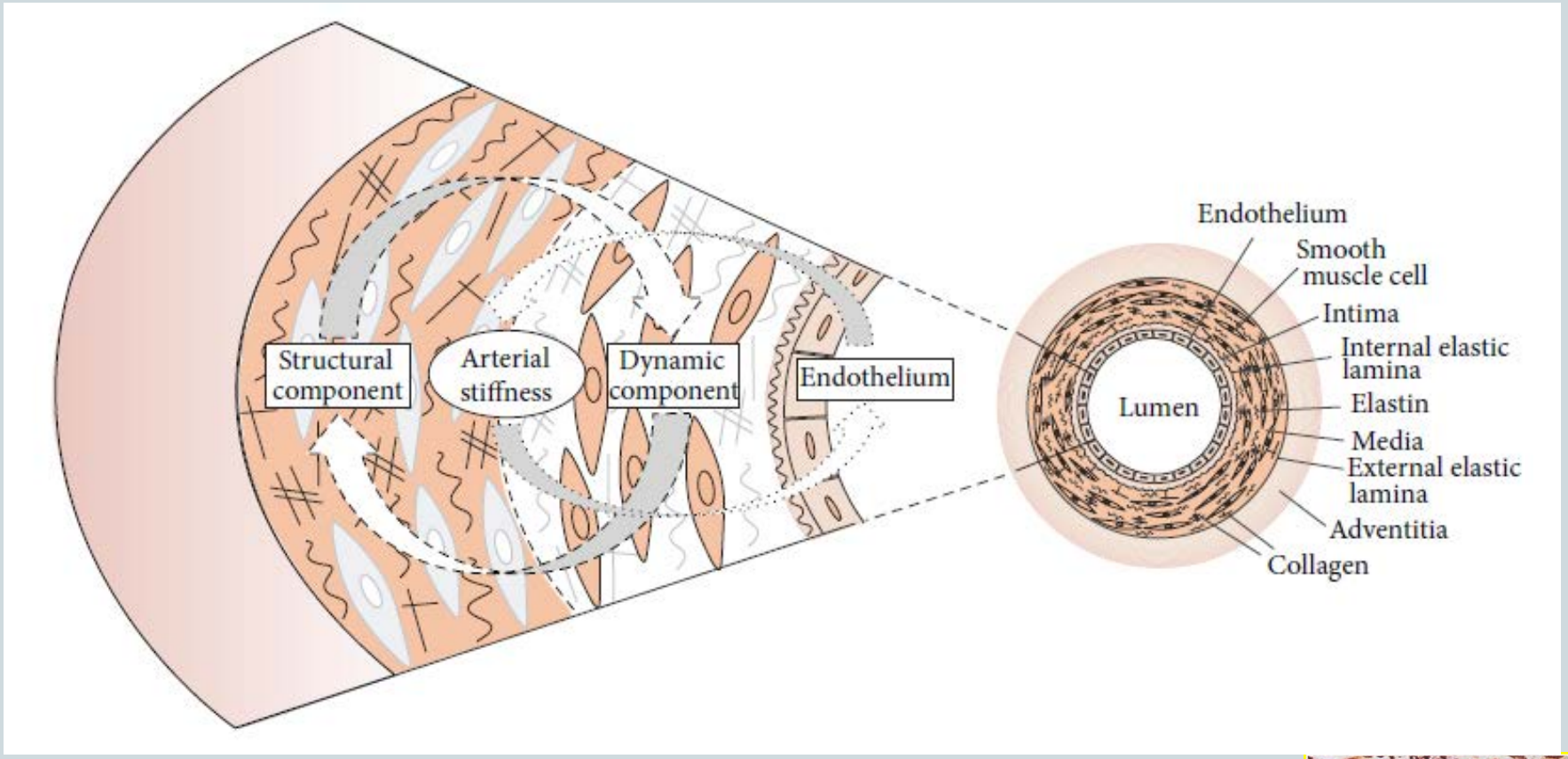
Learning objectives

- What is arterial stiffness - pathophysiology
- Measurement of arterial stiffness
- Clinical implications of arterial stiffness
- Arterial stiffness as a therapeutic target

Objectives

- *What is arterial stiffness*
- *Arterial stiffness and cardiovascular risk*
- *Arterial stiffness and specific conditions*

Arterial stiffness



Stefanadis C, et al. Circulation 1995;91669-78

Palombo C. and Kozakova M. Vascul Pharmacol 2016;77:1-7

Arterial stiffness

- Caused by structural changes, including fibrosis, medial smooth muscle necrosis, breaks in elastin fibers, calcifications, and diffusion of macromolecules into the arterial wall

- Reflects global arterial endothelial dysfunction

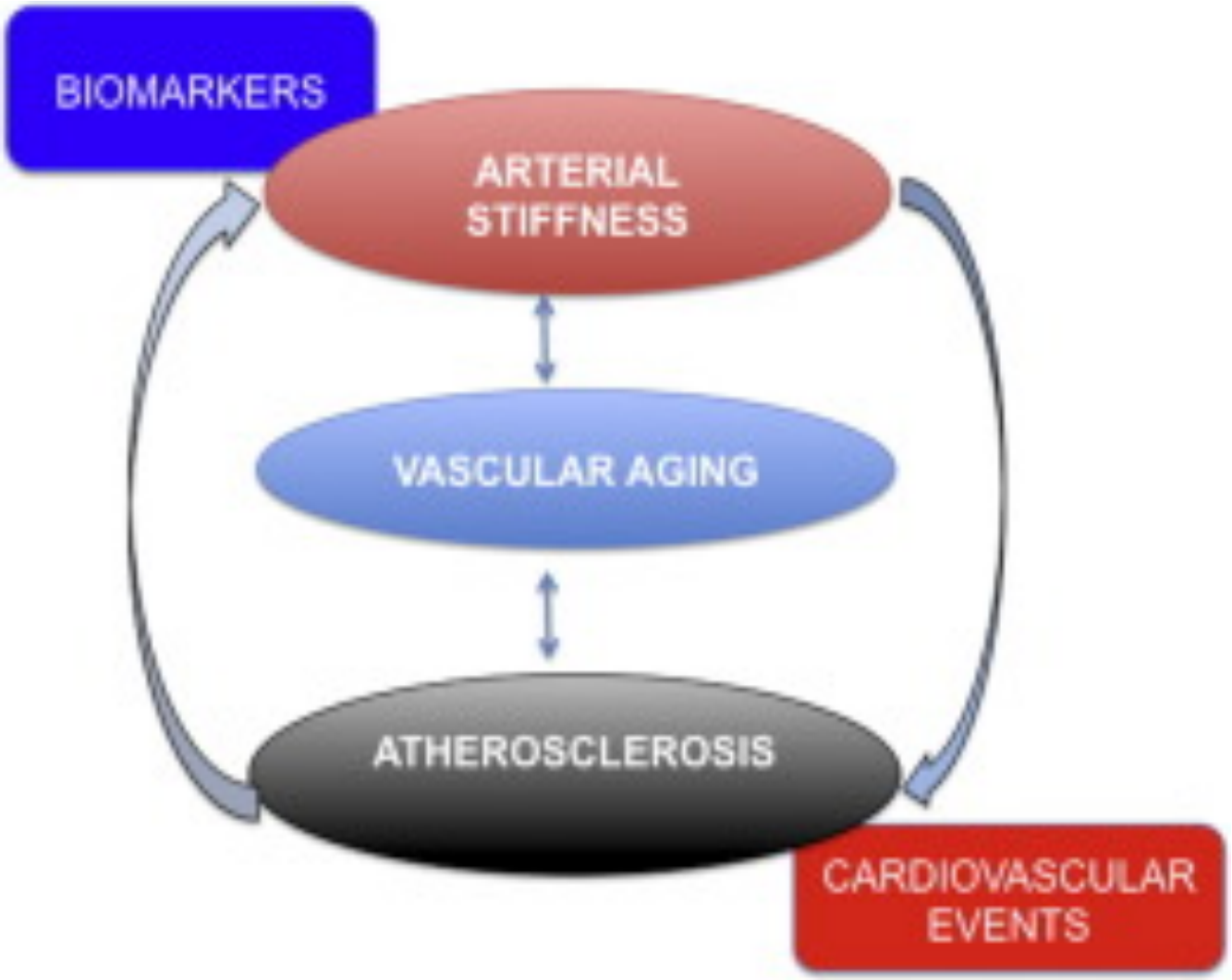
Stefanadis C, et al. Circulation 1995;91669-78
Palombo C. and Kozakova M. Vascul Pharmacol 2016;77:1-7

Arterial stiffness

- A strong relationship between arterial stiffness and the development of atherosclerosis at various sites in the arterial tree has been noted

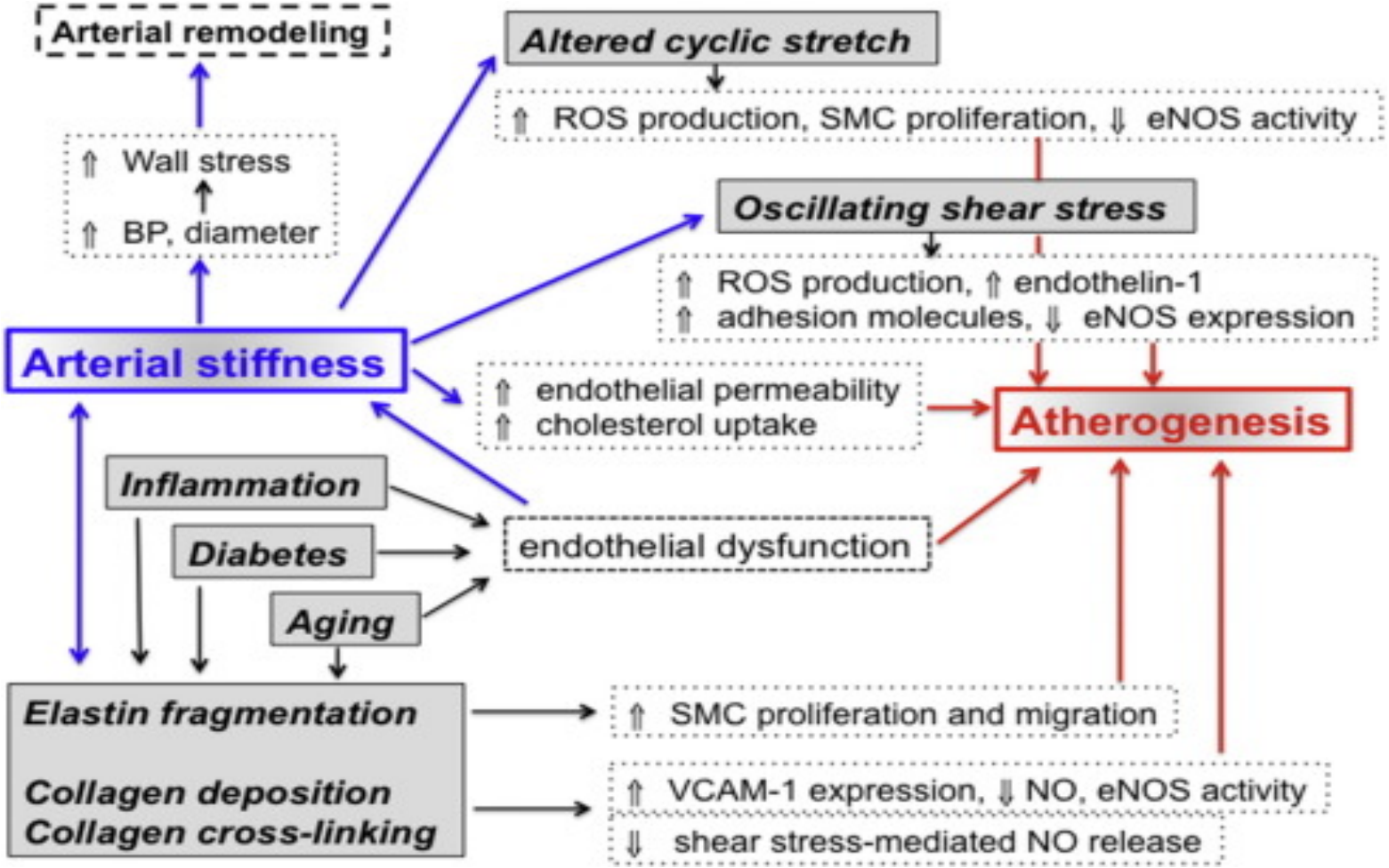
- Early marker of atherosclerosis, as it is affected to a greater extent when compared with IMT in patients with vascular disease

Migrino RQ, et al. Ultrasound Med Biol 2008;34:208-14
Maarek B, et al. Am. J. Cardiol 1987;59:414-7
Wada T, et al. Arterioscler Thromb 1994;14:479-82
Claridge MW, et al. Atherosclerosis 2009;205:477-80



Palombo C. and Kozakova M. Vascul Pharmacol 2016;77:1-7

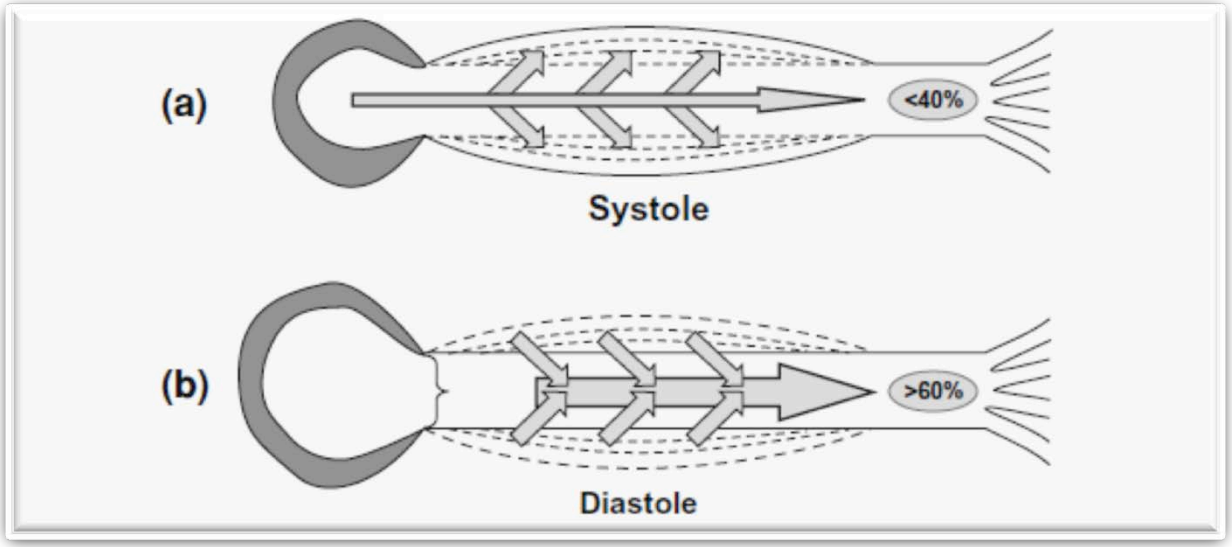
Biological and biomechanical mechanisms relating arterial stiffness and atherosclerosis



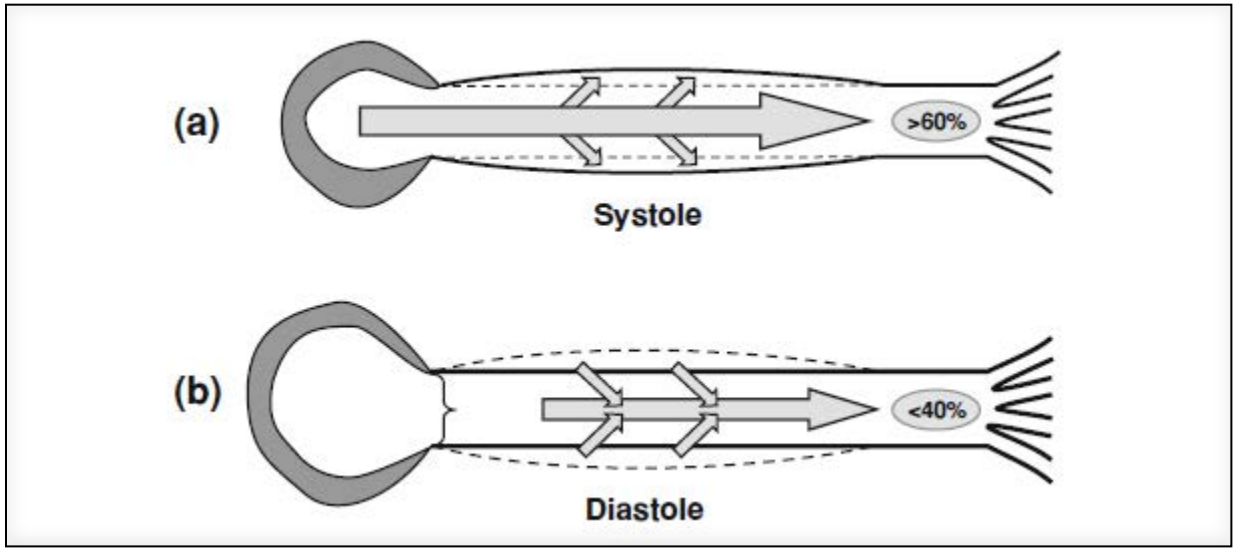
Palombo C. and Kozakova M. Vascul Pharmacol 2016;77:1-7

Good vascular distensibility

AORTIC BUFFERING

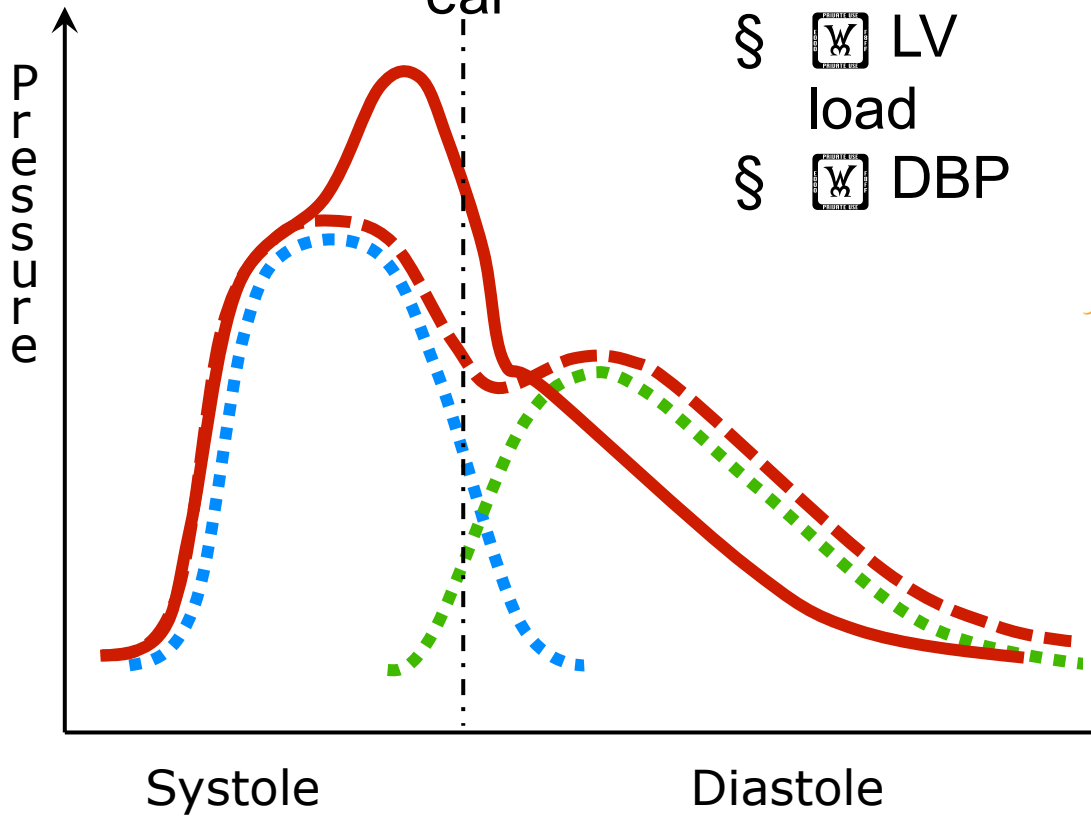


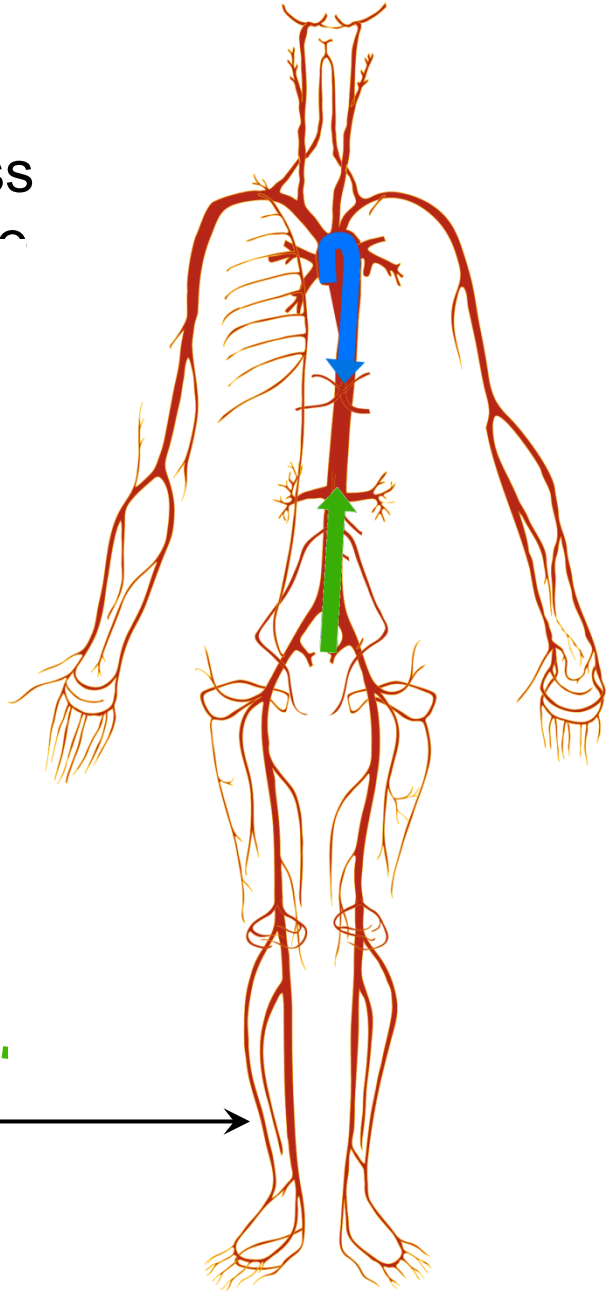
Reduced vascular distensibility



Windkessel phenomenon in left ventricular/aorta ratio

1. Reflected wave is
pr 2. Increased arterial stiffness
wi caus
to t
ear
3. Leads to:
   - § SBP
   - § LV load
   - § DBP





Consequences

1. Central systolic pressure and central pulse pressure increases
2. Increased ventricular load
3. Decreased myocardial perfusion during diastole

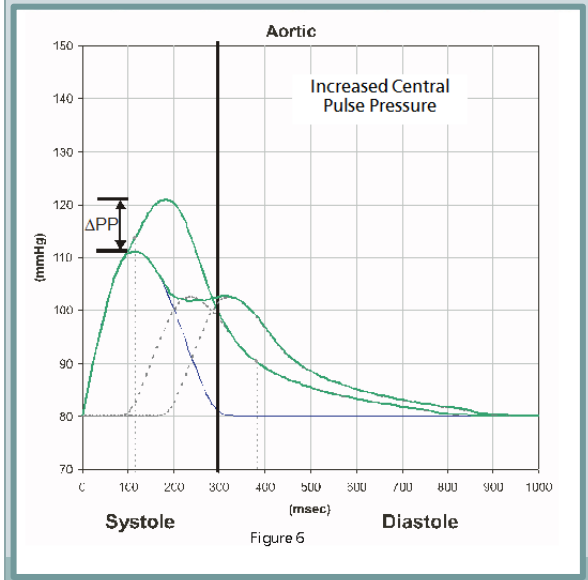


Figure 6

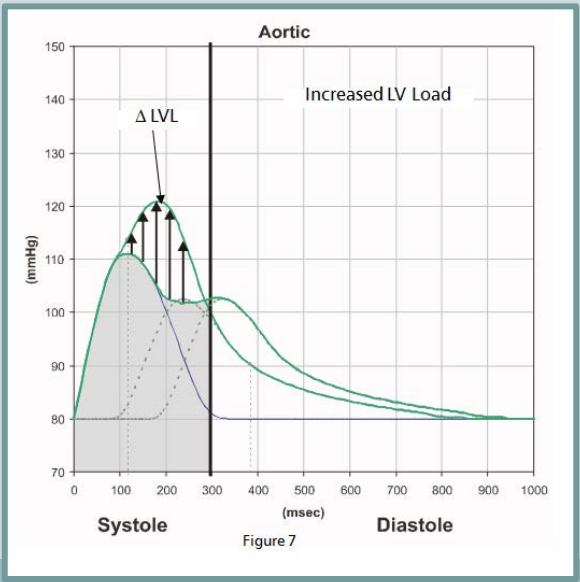


Figure 7

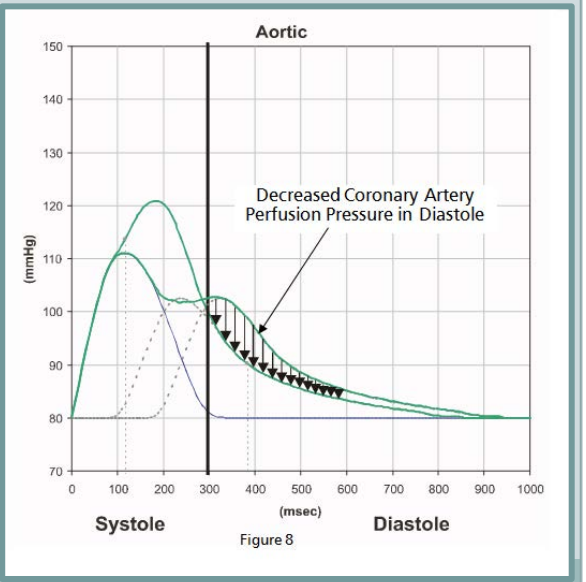
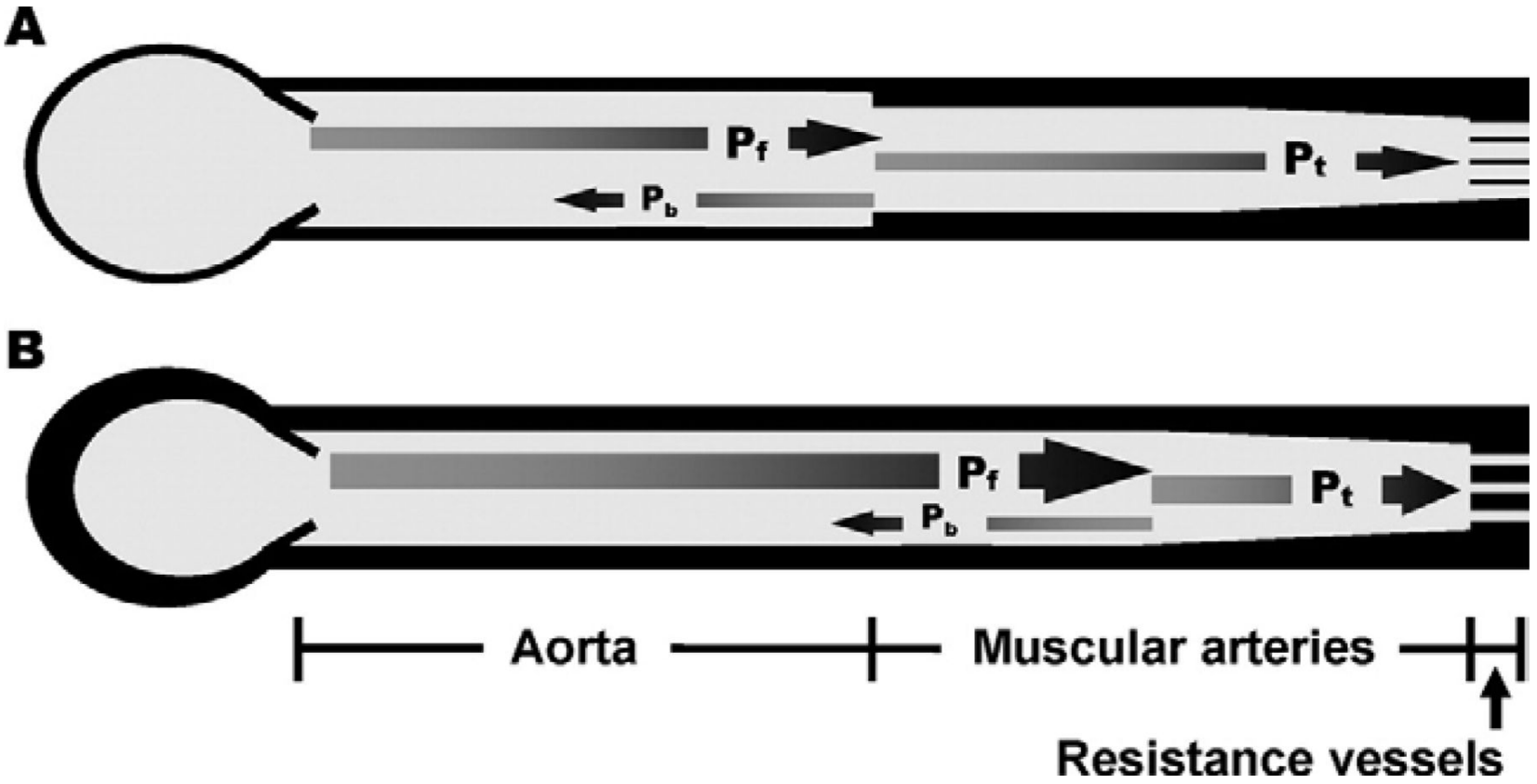


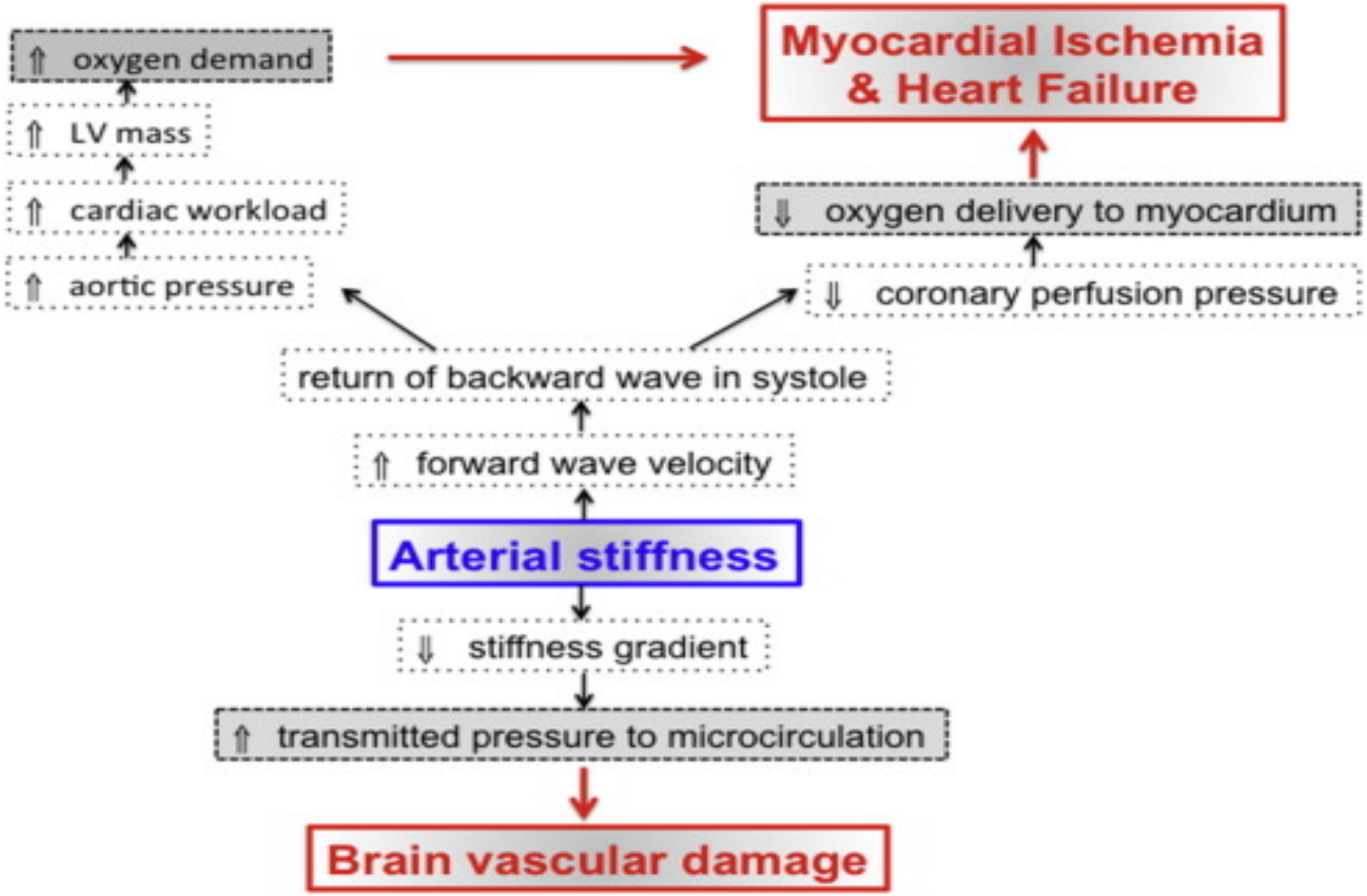
Figure 8

Model showing the effects of impedance matching on the forward (Pf), backward (Pb), and transmitted (Pt) pressure waves



Mitul Vyas et al. Am J Hypertens 2007;20:642-647

Hemodynamic links between arterial stiffness and target organ damage



Palombo C. and Kozakova M. Vascul Pharmacol 2016;77:1-7

Arterial Stiffness

- *Cumulative indicator of arterial health*
- *Associated with CVD and events*
- *Recommended by international guidelines*

Mancia G et al. 2007 Guidelines for the management of arterial hypertension. Eur Heart J 2007;28:1462-536
Laurent S et al. Eur Heart J 2006;27:2588-605

Measurements of arterial stiffness

- applanation tonometry
- echotracking
- Doppler
- Ultrasound

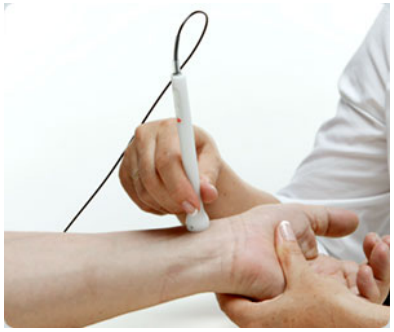
- The simplest and most reproducible non-invasive technique to date is the measurement of arterial waveforms obtained by applanation tonometry

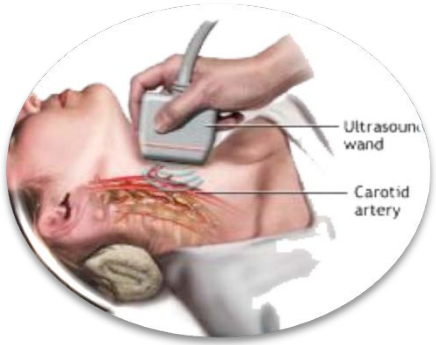
Applanation tonometry

- central blood pressure
- augmentation index *(systemic)*
- carotid-radial pulse wave velocity *(peripheral, muscular)*
- carotid-femoral pulse wave velocity *(central, elastic)*

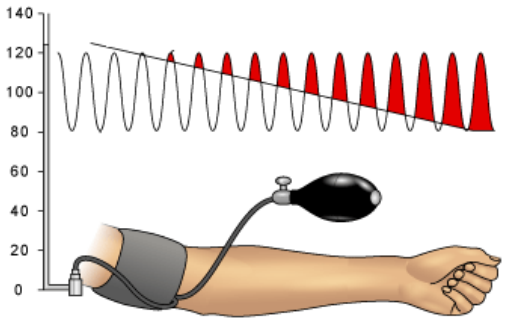
Mancia G et al. 2007 Guidelines for the management of arterial hypertension. Eur Heart J 2007;28:1462-536
Laurent S et al. Eur Heart J 2006;27:2588-605

Measurements of arterial stiffness



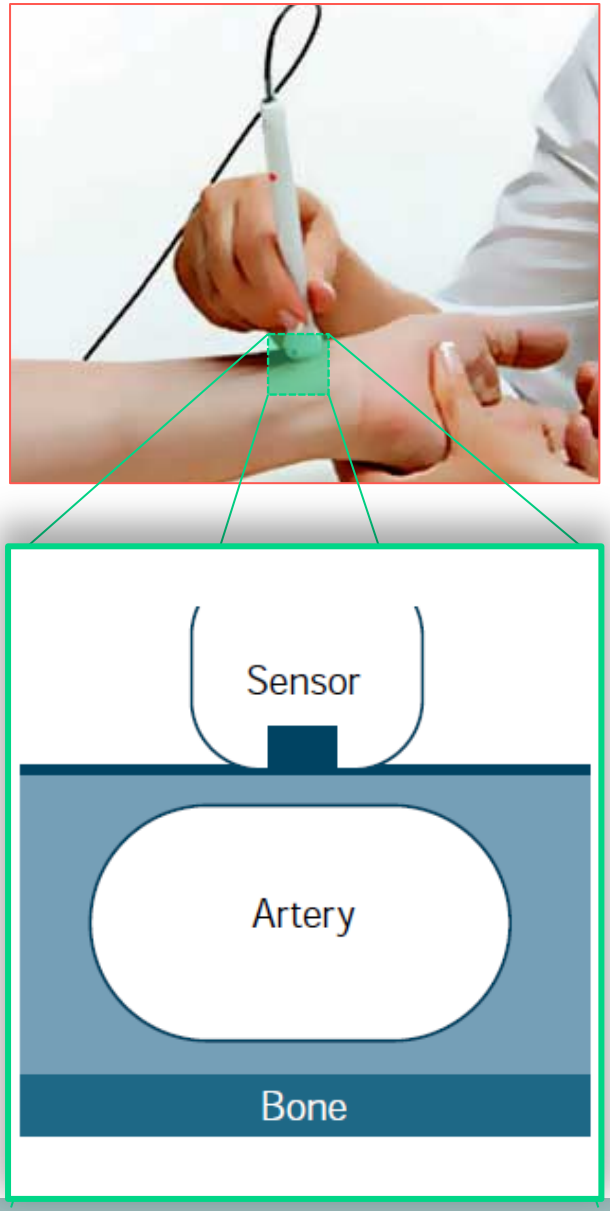


Sphygmocor (transfer functions)
Pulse pen Carotid tonometry
Arteriograph
Echo-tracking
Complior
Omron
Mobilograph / Arcsolver
A-PULSE CASPro®



Applanation tonometry
Echotracking
Doppler
Ultrasound

Measuring Arterial Stiffness



APPLANATION TONOMETRY

Pen-like instrument is placed over the pulse

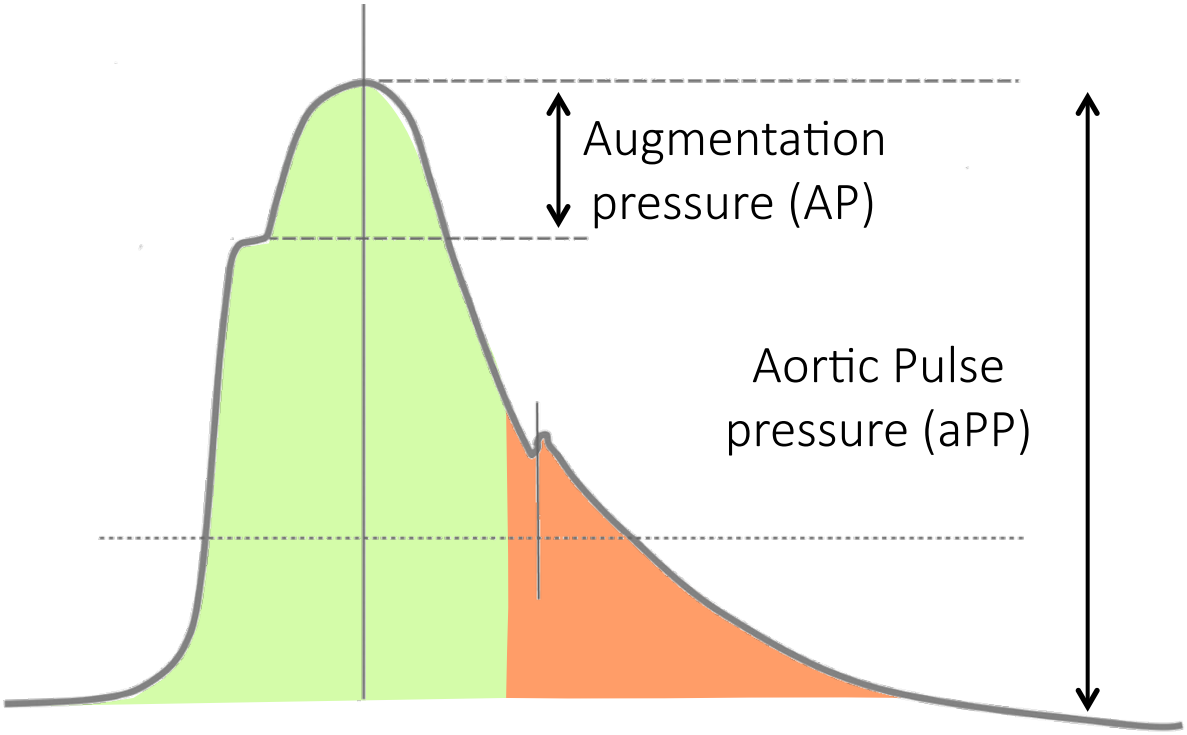
High-fidelity arterial waveform is captured

PWA
Pulse Wave Analysis

PWV
Pulse Wave Velocity

PWA

provides indicators of arterial stiffness

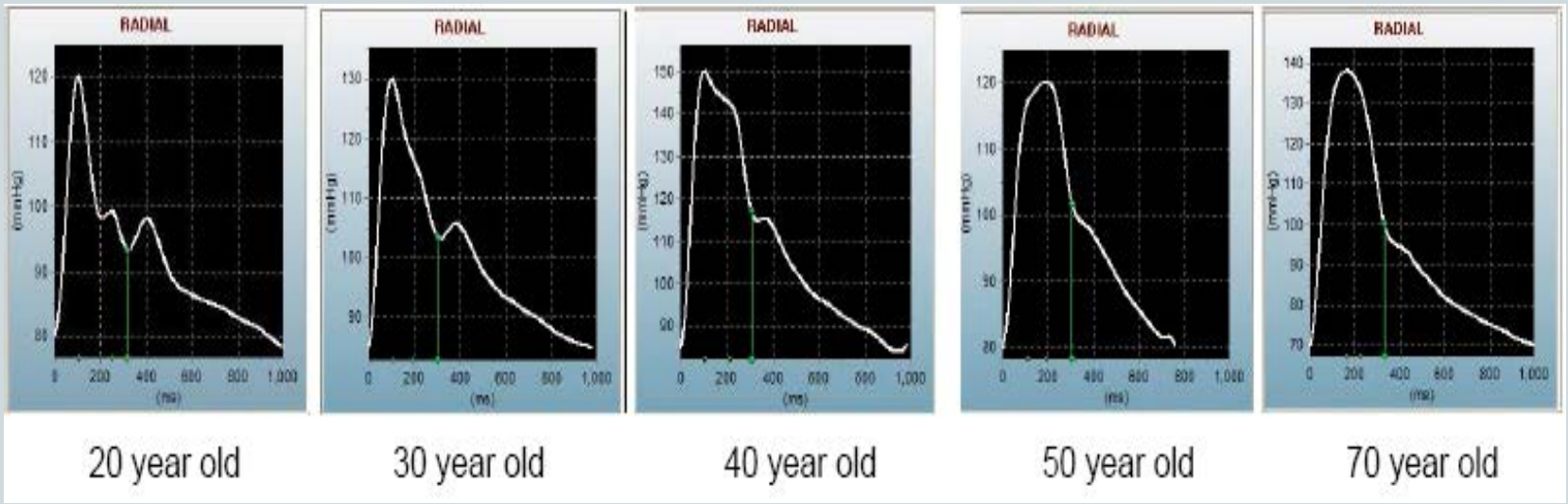


$$\text{Augmentation index} = \frac{AP}{aPP}$$

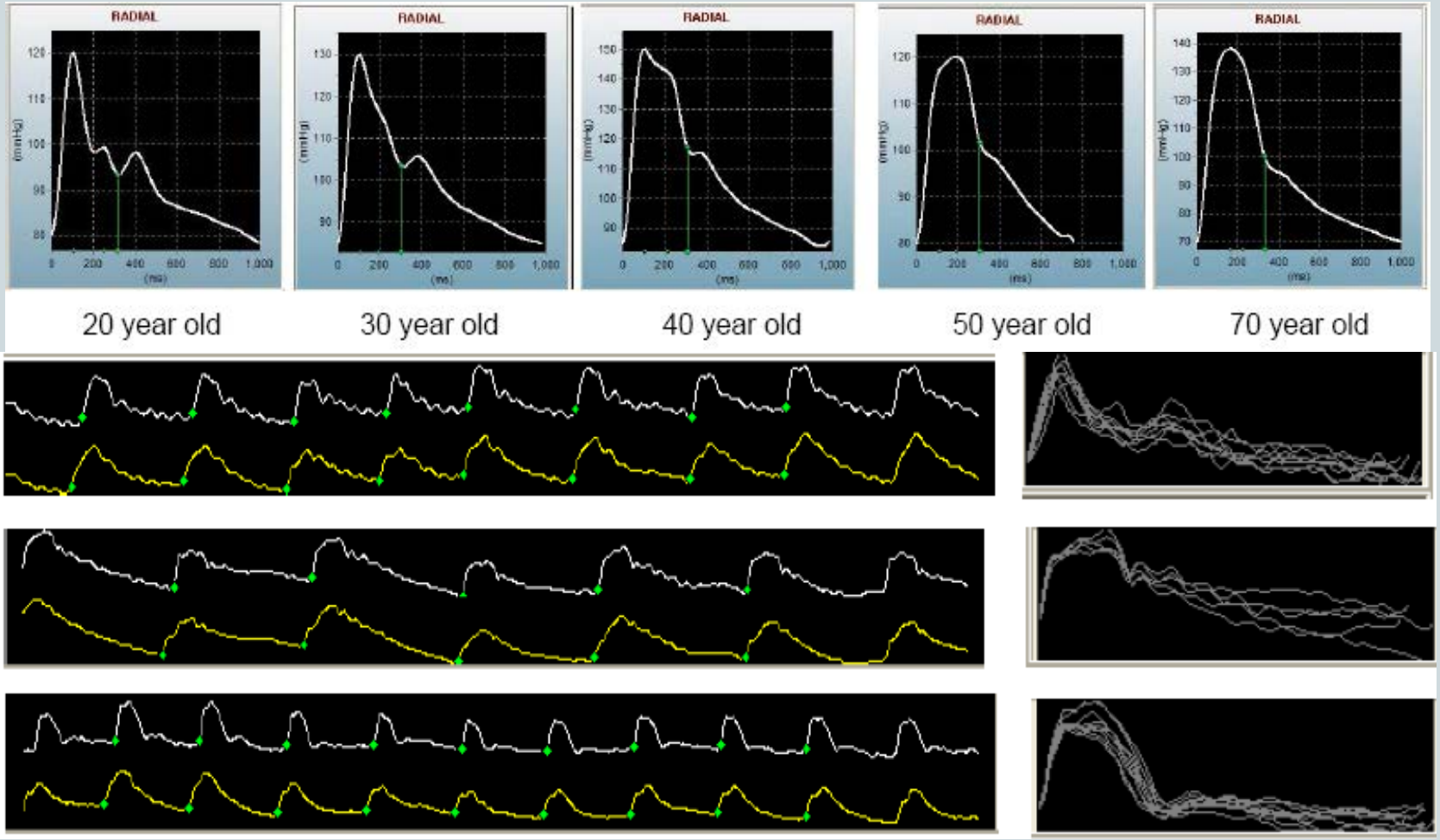
$$\text{Subendocardial Viability Ratio (SEVR)} = \frac{O_2 \text{ supply}}{O_2 \text{ demand}}$$

Mills, et al. Thorax 2008;63:306-11

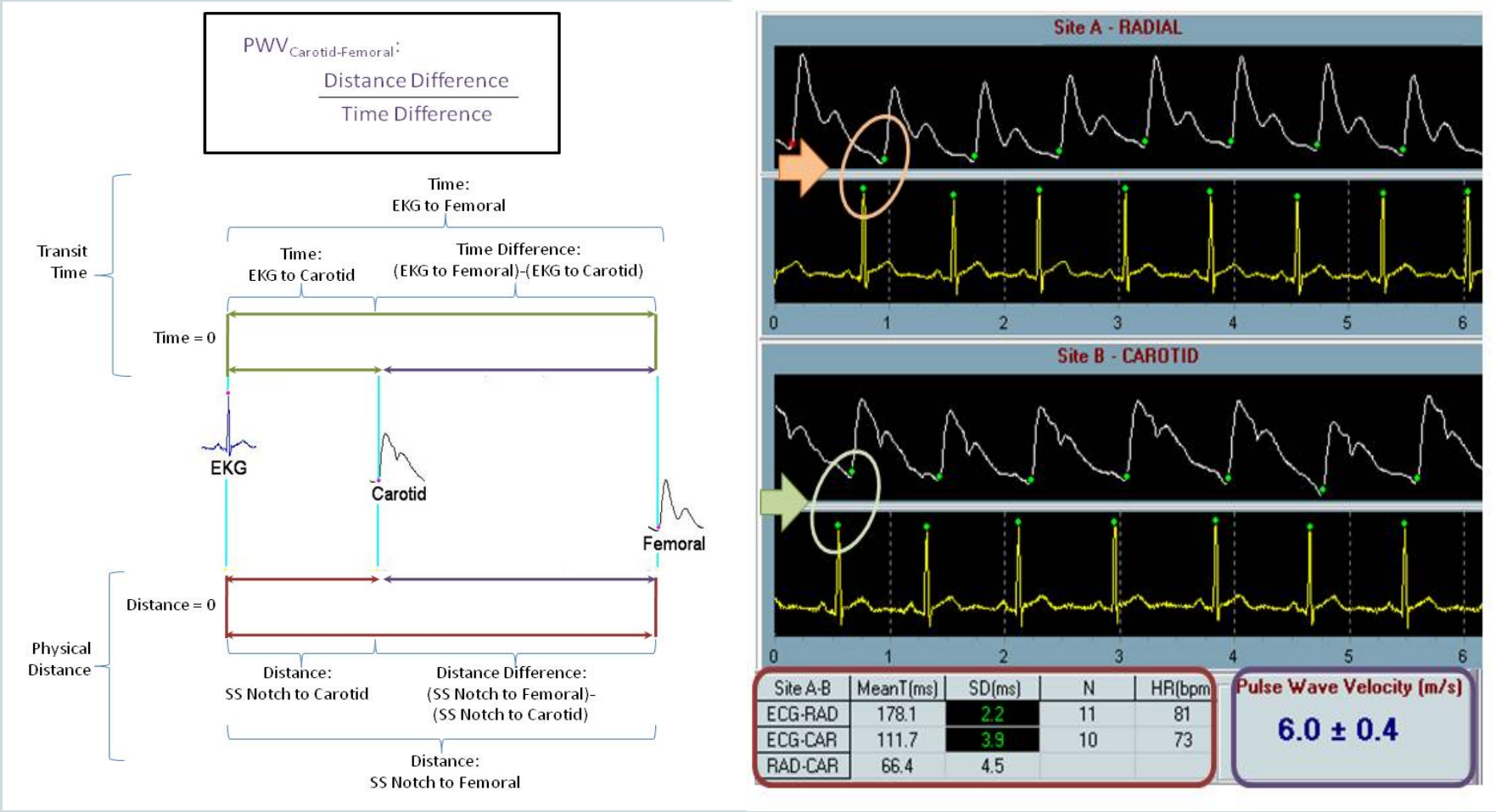
Typical Arterial Waveforms



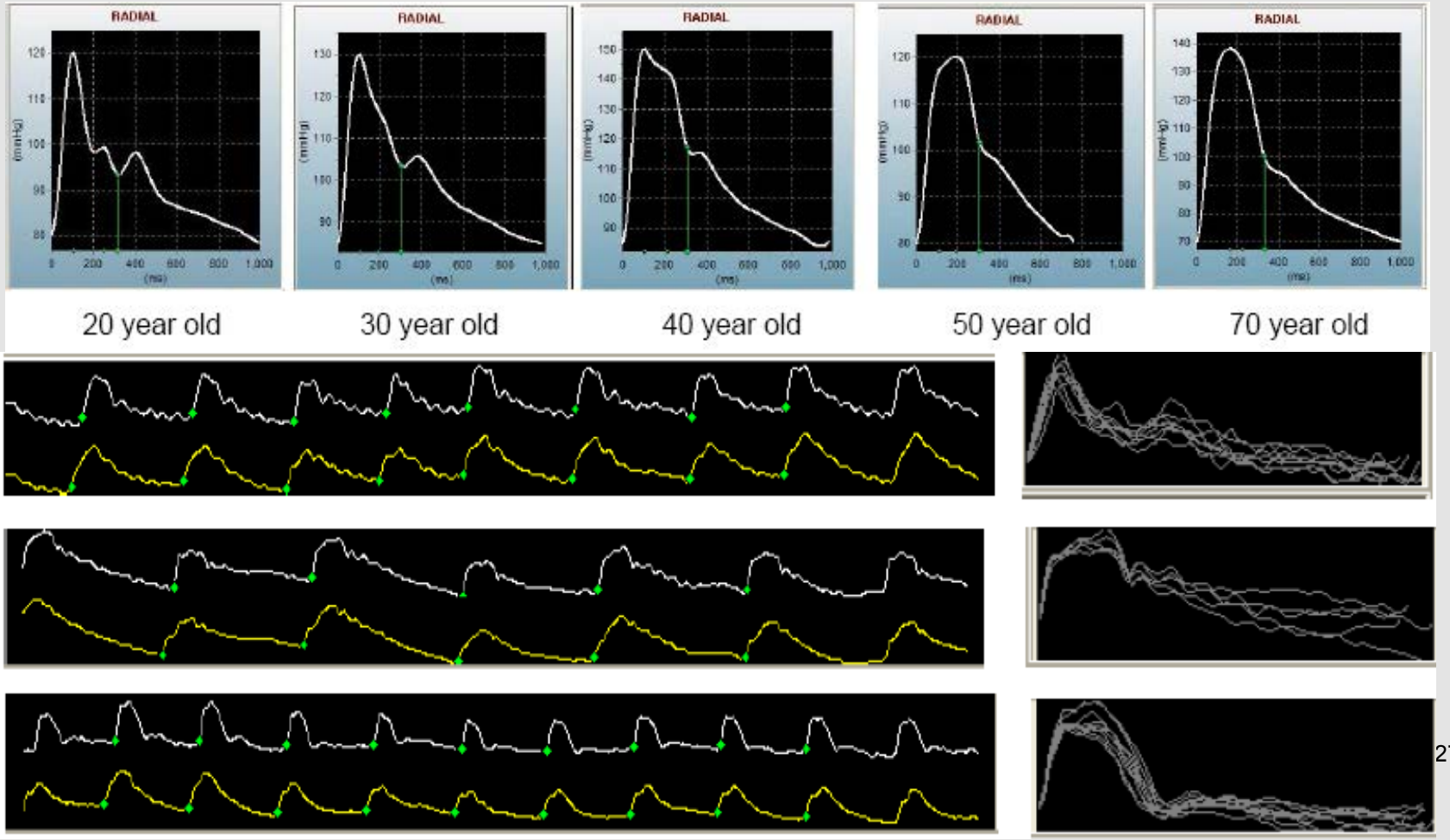
Typical Arterial Waveforms



PWV = distance (m)/transit time (s)



Typical Arterial Waveforms



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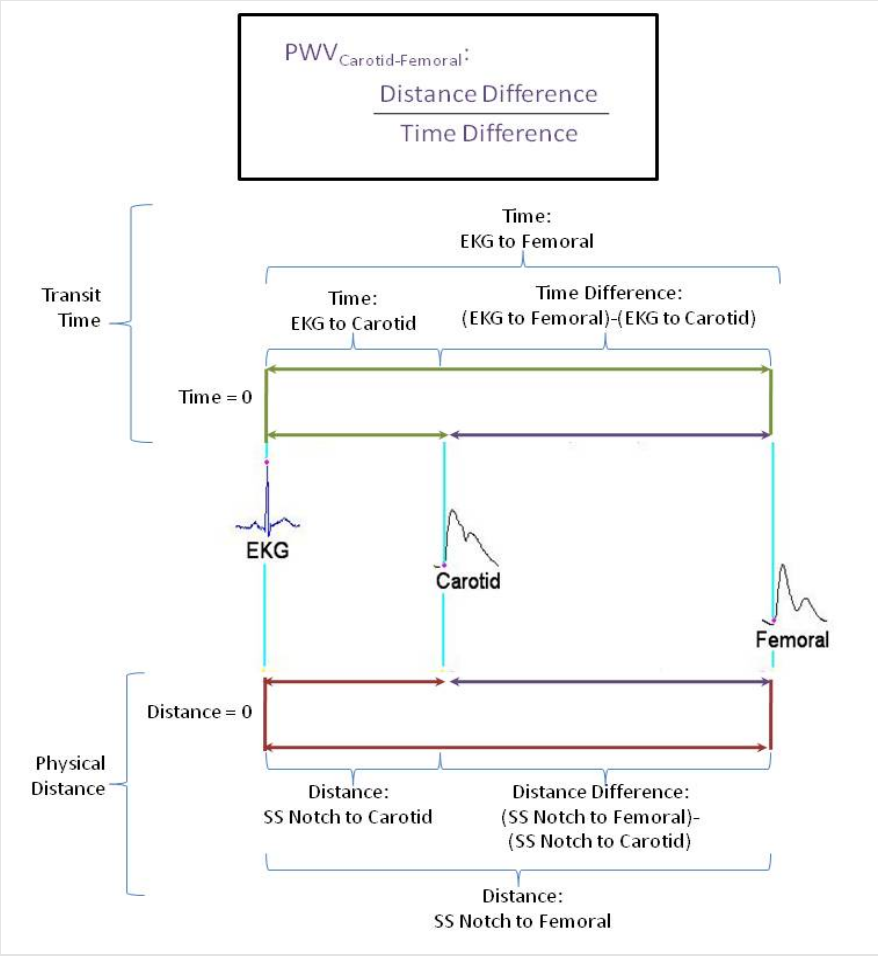
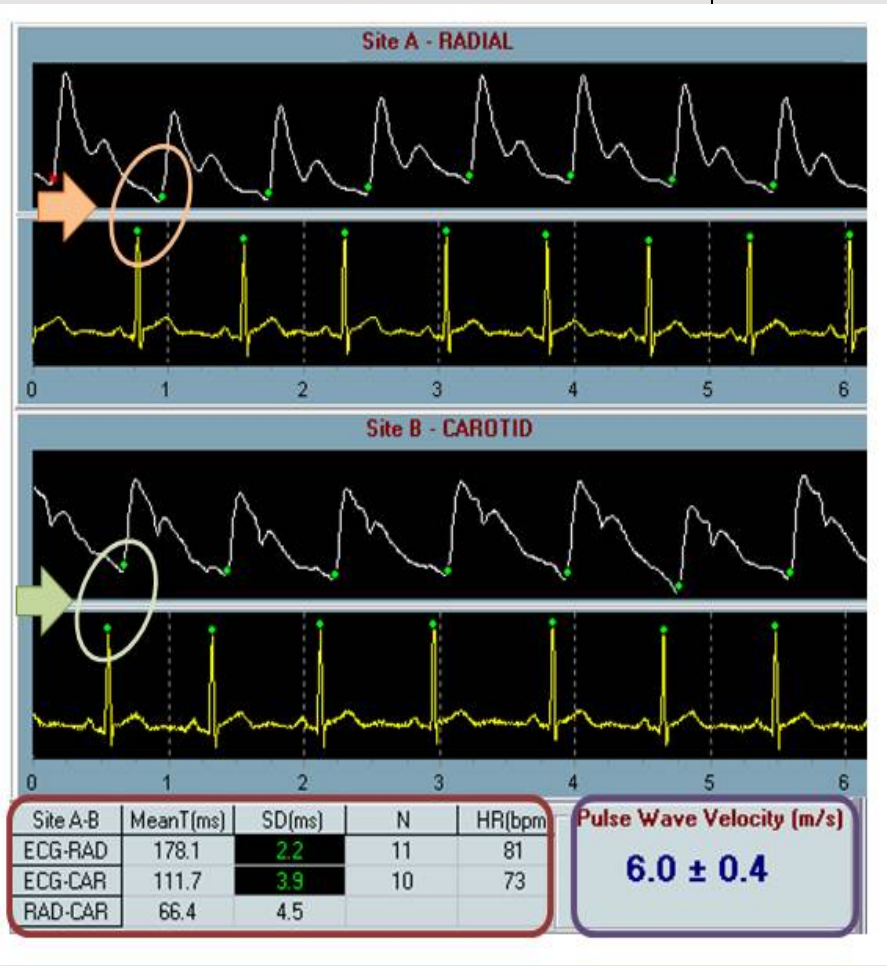


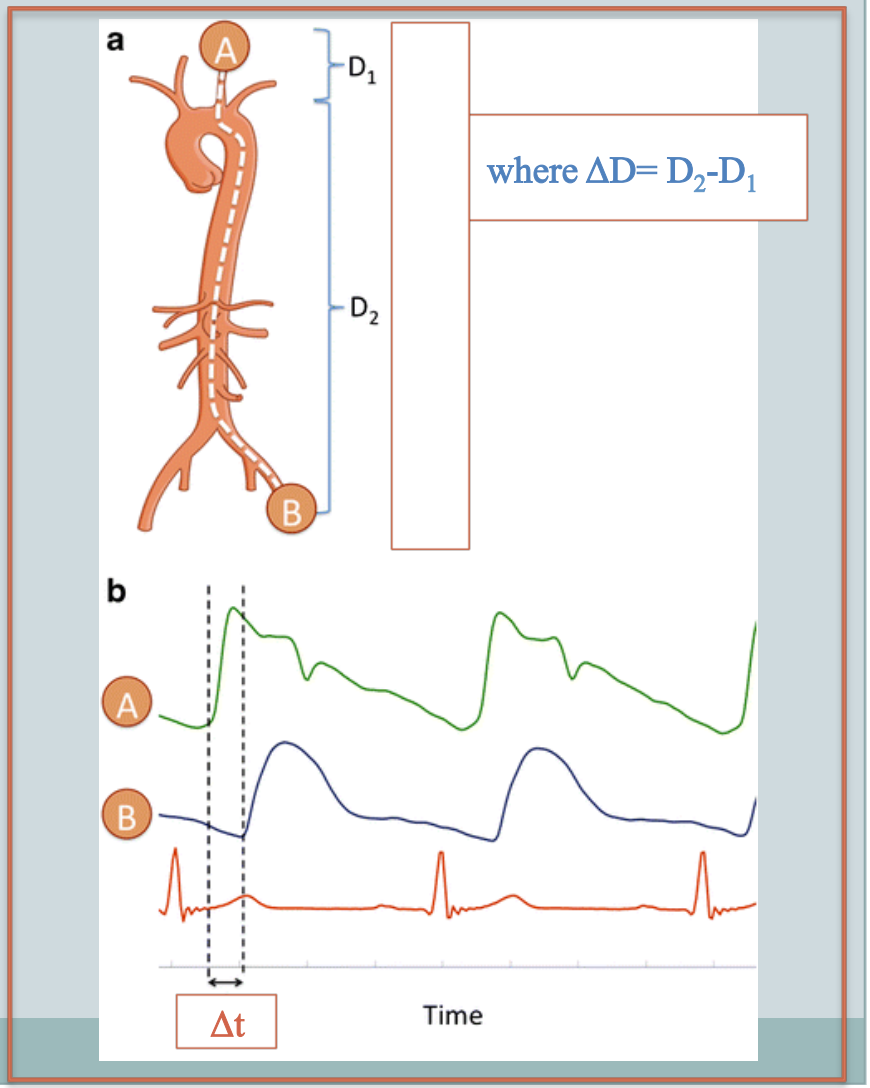


Pulse Wave Velocity (PWV)

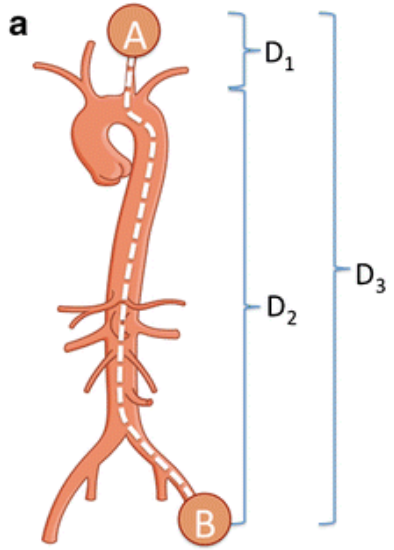
- Speed of pulse wave

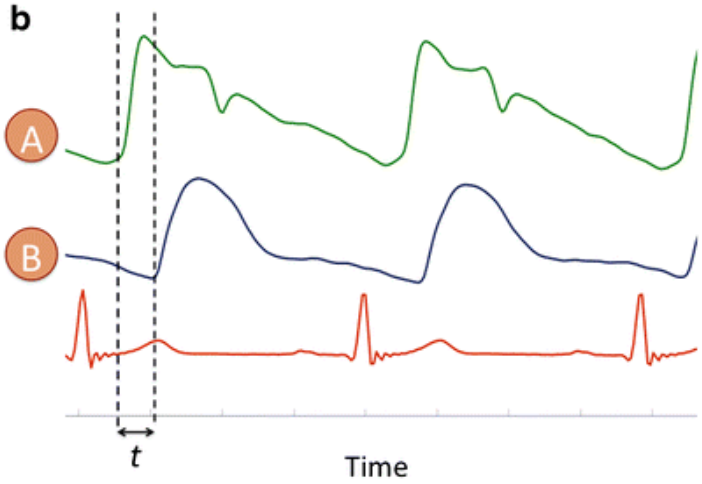
$$\frac{\text{distance difference } (\Delta D)}{\text{time difference } (\Delta t)}$$

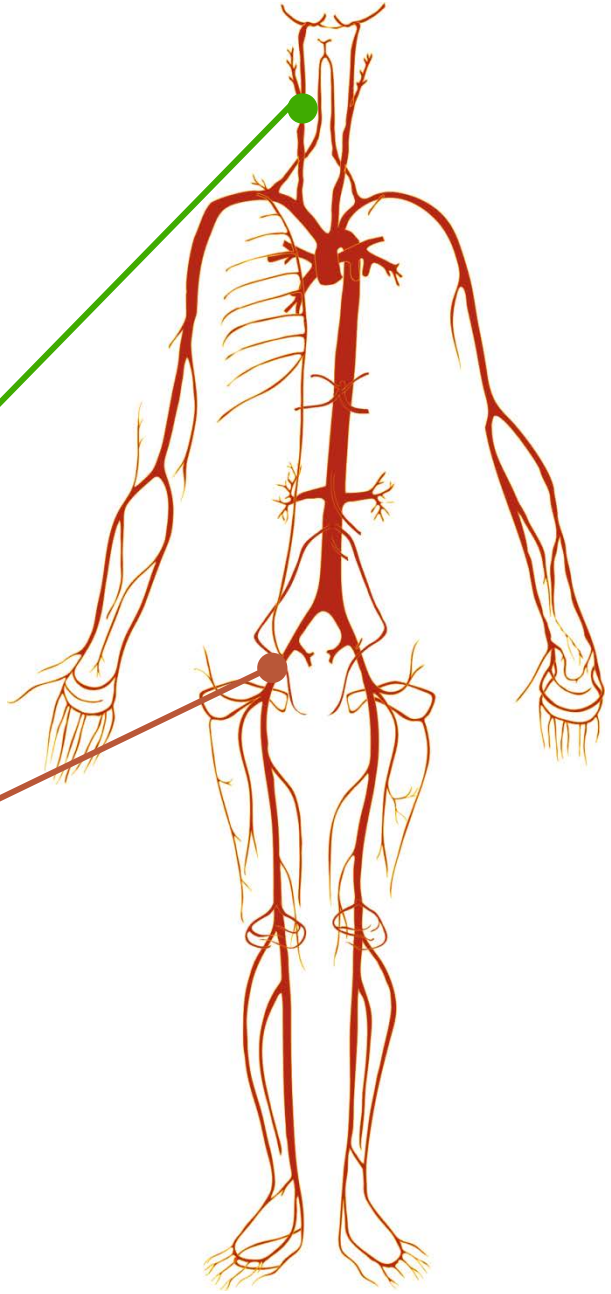
- Higher value = stiffer arteries
- crPWV (carotid radial)
  - Muscular Arteries
- cfPWV (carotid femoral)
  - Elastic arteries
  - "Gold standard"



cfPWV, the "gold standard"

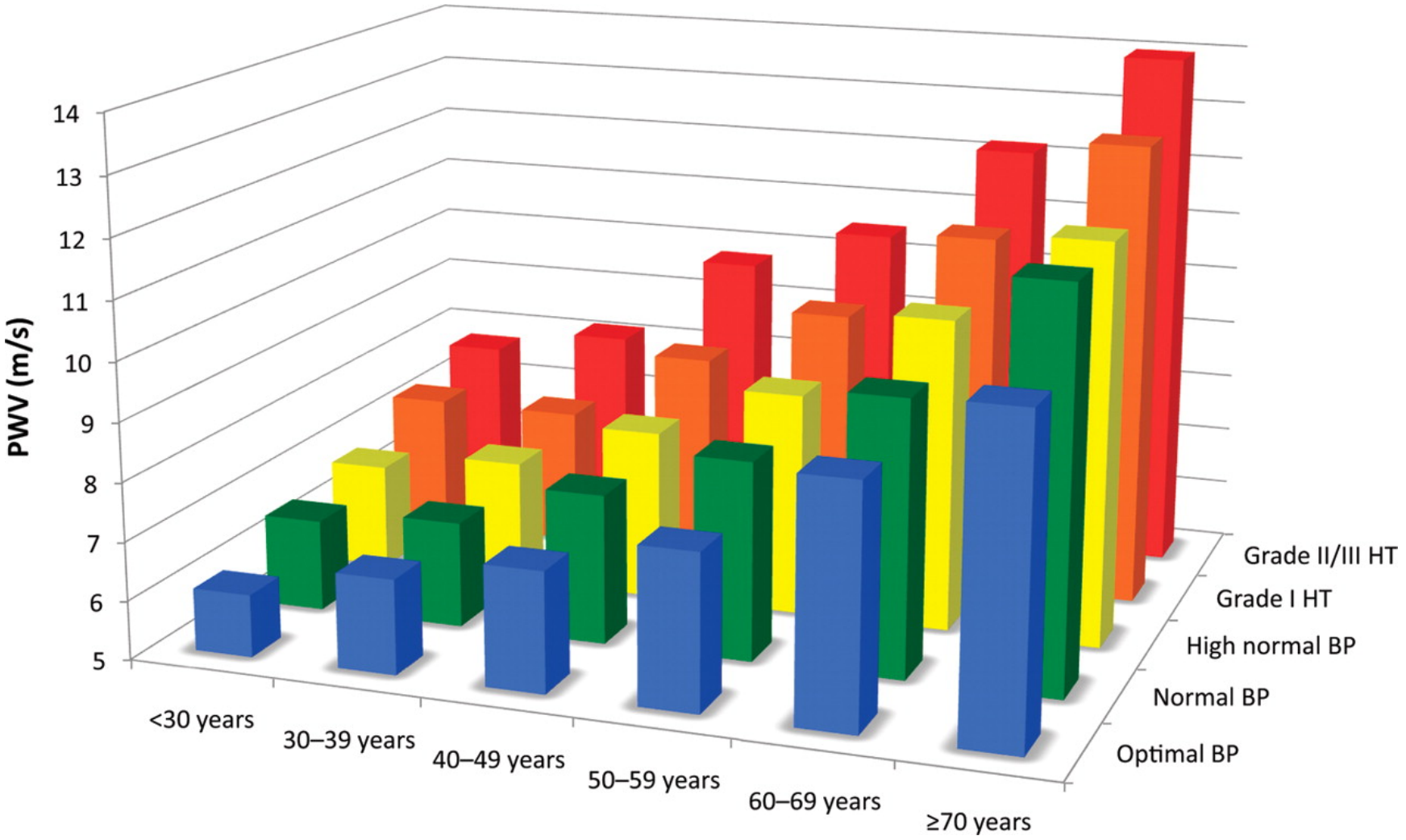






Chirinos J, et al. Cardiovasc Transl Res 2013;5:243-55

Reference values for PWV: mean values according to age & BP categories (11,092 subjects)



Reference Values for Arterial Stiffness' Collaboration. Eur Heart J 2010;31:2338-50

PWV: 'establishing normal and reference values'

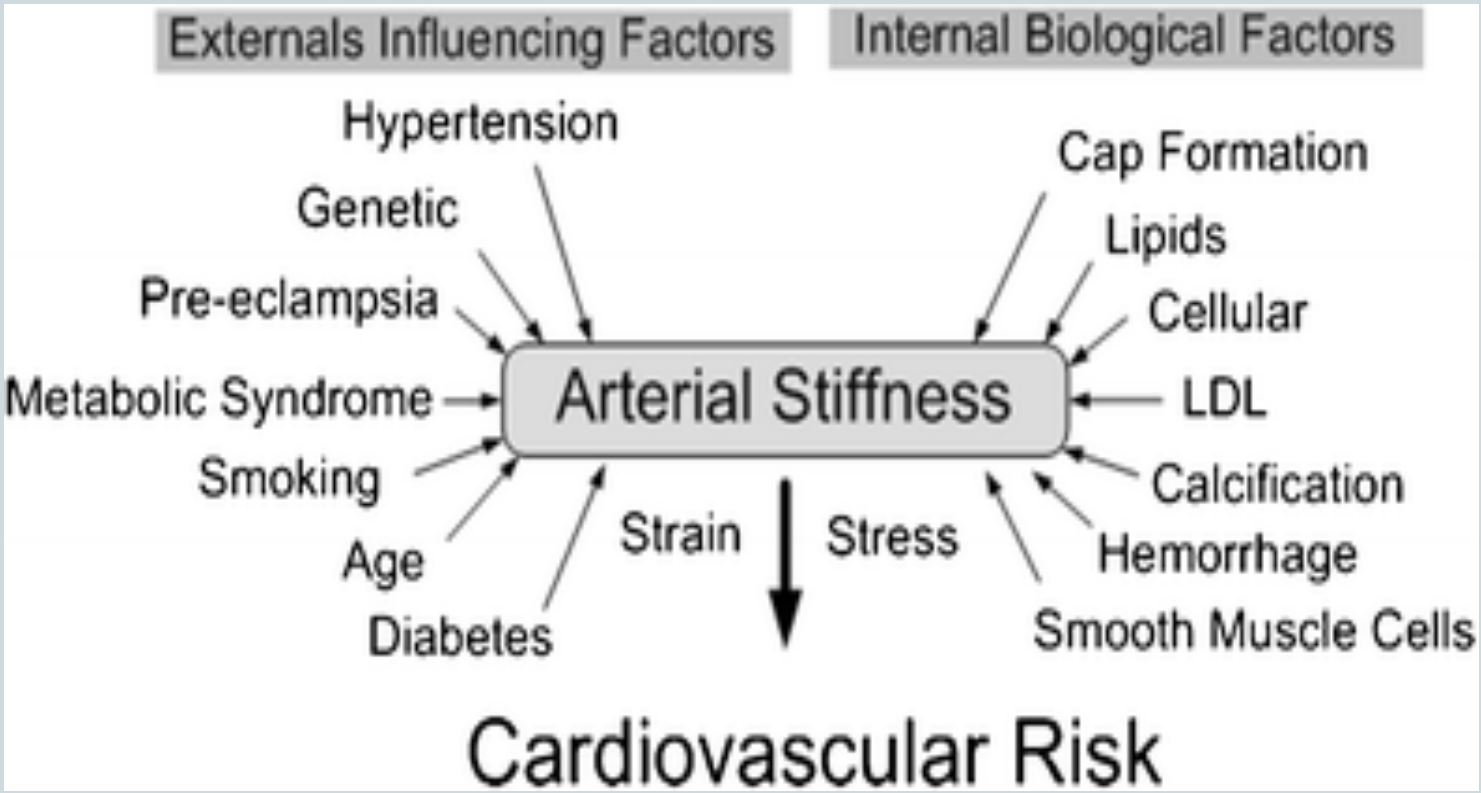
Distribution of pulse wave velocity (PWV) values (m/s) in the reference value population (11 092 subjects) according to age and blood pressure category

Age category (years)	Blood pressure category				
	Optimal	Normal	High normal	Grade I HT	Grade II/III HT
PWV as mean (±2 SD)					
<30	6.1 (4.6–7.5)	6.6 (4.9–8.2)	6.8 (5.1–8.5)	7.4 (4.6–10.1)	7.7 (4.4–11.0)
30–39	6.6 (4.4–8.9)	6.8 (4.2–9.4)	7.1 (4.5–9.7)	7.3 (4.0–10.7)	8.2 (3.3–13.0)
40–49	7.0 (4.5–9.6)	7.5 (5.1–10.0)	7.9 (5.2–10.7)	8.6 (5.1–12.0)	9.8 (3.8–15.7)
50–59	7.6 (4.8–10.5)	8.4 (5.1–11.7)	8.8 (4.8–12.8)	9.6 (4.9–14.3)	10.5 (4.1–16.8)
60–69	9.1 (5.2–12.9)	9.7 (5.7–13.6)	10.3 (5.5–15.1)	11.1 (6.1–16.2)	12.2 (5.7–18.6)
≥70	10.4 (5.2–15.6)	11.7 (6.0–17.5)	11.8 (5.7–17.9)	12.9 (6.9–18.9)	14.0 (7.4–20.6)
PWV as median (10–90 pc)					
<30	6.0 (5.2–7.0)	6.4 (5.7–7.5)	6.7 (5.8–7.9)	7.2 (5.7–9.3)	7.6 (5.9–9.9)
30–39	6.5 (5.4–7.9)	6.7 (5.3–8.2)	7.0 (5.5–8.8)	7.2 (5.5–9.3)	7.6 (5.8–11.2)
40–49	6.8 (5.8–8.5)	7.4 (6.2–9.0)	7.7 (6.5–9.5)	8.1 (6.8–10.8)	9.2 (7.1–13.2)
50–59	7.5 (6.2–9.2)	8.1 (6.7–10.4)	8.4 (7.0–11.3)	9.2 (7.2–12.5)	9.7 (7.4–14.9)
60–69	8.7 (7.0–11.4)	9.3 (7.6–12.2)	9.8 (7.9–13.2)	10.7 (8.4–14.1)	12.0 (8.5–16.5)
≥70	10.1 (7.6–13.8)	11.1 (8.6–15.5)	11.2 (8.6–15.8)	12.7 (9.3–16.7)	13.5 (10.3–18.2)

SD, standard deviation, 10 pc, the upper limit of the 10th percentile, 90 pc, the lower limit of the 90th percentile; HT, hypertension.

Reference Values for Arterial Stiffness' Collaboration. Eur Heart J 2010;31:2338-50

External and internal factors affecting arterial stiffness



Patel AK, et al. Curr Atheroscler Rep 2016;18:83

Arterial Stiffness and CV risk

Arterial Stiffness

- *Cumulative indicator of arterial health*
- *Associated with CVD and events*
- *Recommended by international guidelines*

Mancia G et al. 2007 Guidelines for the management of arterial hypertension. Eur Heart J 2007;28:1462-536
Laurent S et al. Eur Heart J 2006;27:2588-605

Numerous epidemiological studies have demonstrated that increased arterial stiffness is directly and independently associated with increased risk of CV complications and events

Kroeker EJ and Wood EH. Circ. Res 1955;3:623-32
Remington JW and Wood EH. J Appl Physiol 1956;9:433-42
Rowell LB, et al. Circulation 1968;37:954-64
Kelly RP, et al. Eur Heart J 1990;11:138-44
Blacher J, et al. Hypertension 1999;33:1111-7
Laurent S, et al. Hypertension 2001;37:1236-41
Waddell TK, et al. Hypertension 2001;38:927-31
Cruickshank K, et al. Circulation 2002;106:2085-90
Boutouyrie P, et al. Hypertension 2002;39:10-5
WilluSafar ME, et al. Hypertension 2002;39:735-8
O'Rourke MF. Minerva Med 2003; 94:229-50
Morgan T, et al. Am J Hypertens 2004;17:118-23
m-Hansen T, et al. Circulation 2006;113:664-70
Mattace-Raso,F.U. et al. Circulation 2006;113:657-63
Mancia G. et al. Eur Heart J 2007;28:1462-536
Mitchell GF, et al. Circulation 2010;121:505-11

Framingham Heart Study

- cfPWV was associated with increased risk for a first major CV event with a HR of 1.48 (1.16-1.91; P=0.002) per 1-SD increase in cfPWV, after *adjustment* for all traditional risk factors

Mitchell GF, et al. The Framingham Heart Study. Circulation 2010;121:505-11

Meta-analysis

- Linear graded association of cfPWV with clinical events

- Pooled RRs of
  - total CV events: 2.26 (1.89-2.70)
  - CV mortality: 2.02 (1.68-2.42)
  - all-cause mortality: 1.90 (1.61-2.24)
  - for *high* versus *low* cfPWV

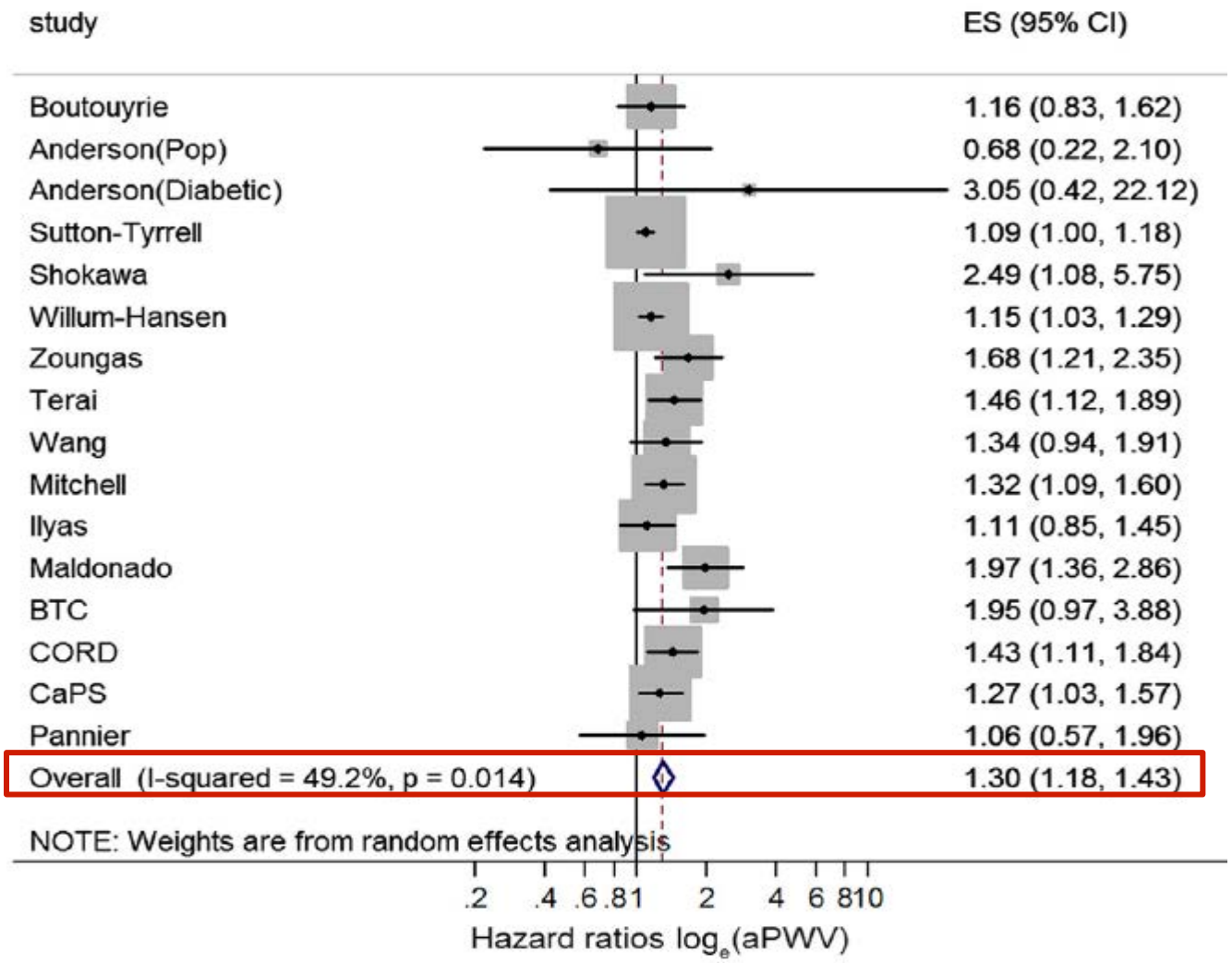
Vlachopoulos C, et al. J Am Coll Cardiol 2010;55:1318-27

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

- An increase in cfPWV by 1 m/s corresponded to an age-, sex-, and risk factor–adjusted risk increase of 15% in total CV events, CV mortality, and all-cause mortality

Vlachopoulos C, et al. J Am Coll Cardiol 2010;55:1318-27

cfPWV is associated with combined CV events



Risk for CVD events per 1 SD log cfPWV

Ben-Shlomo Y, et al. J Am Coll Cardiol 2014;63:636-46

Vlachopoulos C, et al. J Am Coll Cardiol 2014;64:647-9

16 studies, n=17,635

Applanation tonometry

- Measurements of arterial stiffness highly correlate with other non-invasive (high resolution ultrasound) and invasive (catheterization) methods, and can capture small changes in arterial waveforms

- **Validity** has been confirmed with direct arterial measurements (excellent agreement; $r=0.995$, $P<0.001$) in a large number of men and women

- Very high inter- and intra-operator **reproducibility** for PWV and PWA indices in both healthy and diseased populations, and by both experienced and inexperienced technicians (intra-class correlation coefficients: 0.92-0.98)

Arterial stiffness

Independent predictor of

- Stroke

Laurent S, et al. Stroke 2003;34:1203-6
St Mattace-Raso FU, et al. Circulation 2006;113:657-63

- progression of CKD

Taal MW, et al. Nephron Clin Pract 2007;107:c177-81
Bellasi A, et al. Int J Nephrol;2011:734832. Epub 2011 May 23

Associated with

- DM1, DM2, MetSyn, Obesity

Stehouwer CD, et al. Diabetologia 2008;51:527-39
Shin JY, et al. Cardiovasc Diabetol 2011;10:30

- OSA

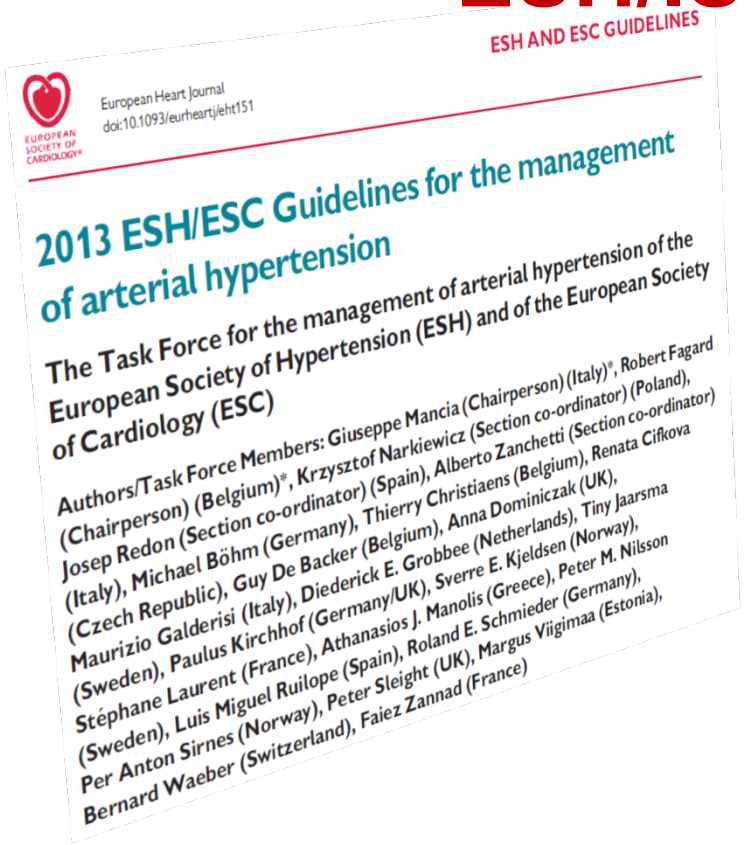
Daskalopoulou S, et al. Hypertens Res 2011;34:23-32

Smoking and Coffee

When smoking and caffeine intake are combined, they interact and exert a synergistic, unfavorable effect on aortic stiffness and wave reflections both acutely and chronically

Daskalopoulou S, et al. Hypertens Res 2010;33:398-410
Vlachopoulos C, et al. J Am Coll Cardiol 2004;44:1911-7

ESH/ISH guidelines



ESH AND ESC GUIDELINES

European Heart Journal
doi:10.1093/eurheartj/eht151

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Authors/Task Force Members: Giuseppe Mancia (Chairperson) (Italy)*, Krzysztof Narkiewicz (Section co-ordinator) (Poland), Josep Redon (Section co-ordinator) (Spain), Alberto Zanchetti (Section co-ordinator) (Italy), Michael Böhm (Germany), Thierry Christiaens (Belgium), Renata Cifkova (Czech Republic), Guy De Backer (Belgium), Anna Dominiczak (UK), Maurizio Galderisi (Italy), Diederick E. Grobbee (Netherlands), Tiny Jaarsma (Sweden), Paulus Kirchhof (Germany/UK), Sverre E. Kjeldsen (Norway), Stéphane Laurent (France), Athanasios J. Manolis (Greece), Peter M. Nilsson (Sweden), Luis Miguel Ruilope (Spain), Roland E. Schmieder (Germany), Per Anton Sirnes (Norway), Peter Sleight (UK), Margus Viigimaa (Estonia), Bernard Waeber (Switzerland), Faiez Zannad (France)

Asymptomatic organ damage
Pulse pressure (in the elderly) ≥60 mmHg
Electrocardiographic LVH (Sokolow–Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV*ms), or
Echocardiographic LVH [LVM index: men >115 g/m²; women >95 g/m² (BSA)][a]
Carotid wall thickening (IMT >0.9 mm) or plaque
Carotid–femoral PWV >10 m/s
Ankle-brachial index <0.9
CKD with eGFR 30–60 ml/min/1.73 m² (BSA)
Microalbuminuria (30–300 mg/24 h), or albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine)

Arteries			
Ultrasound scanning of carotid arteries should be considered to detect vascular hypertrophy or asymptomatic atherosclerosis, particularly in the elderly.	IIa	B	51, 183–185, 188
Carotid–femoral PWV should be considered to detect large artery stiffening.	IIa	B	51, 138, 192–195
Ankle–brachial index should be considered to detect PAD.	IIa	B	198, 199

AHA Scientific Statement

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, FAHA; John R. Cockcroft, FRCP; Kevin S. Heffernan, PhD;
Edward G. Lakatta, MD; Carmel M. McEniery, PhD; Gary F. Mitchell, MD;
Samer S. Najjar, MD; Wilmer W. Nichols, PhD; Elaine M. Urbina, MD, MS, FAHA;
Thomas Weber, MD; on behalf of the American Heart Association Council on Hypertension

Much has been published in the past 20 years on the use of measurements of arterial stiffness in animal and human research studies. This summary statement was commissioned by the American Heart Association to address issues concerning the nomenclature, methodologies, utility, limitations, and gaps in knowledge in this rapidly evolving field. The following represents an executive version of the larger online-only Data Supplement and is intended to give the reader a sense of why arterial stiffness is important, how it is measured, the situations in which it has been useful, its limitations, and questions that remain to be addressed in this field. Throughout the document, pulse-wave velocity (PWV; measured in meters per second) and variations such as carotid-femoral PWV (cfPWV; measured in meters per second) are used. PWV without modification is used in the general sense of arterial stiffness. The addition of lowercase modifiers such as "cf" is used when speaking of specific segments of the arterial circulation.

The ability to measure arterial stiffness has been present for many years, but the measurement was invasive in the early times. The improvement in technologies to enable repeated, minimal-risk, reproducible measures of this aspect of circulatory physiology led to its incorporation into longitudinal cohort studies spanning a variety of clinical populations, including

In the ≈3 decades of clinical use of PWV measures in humans, we have learned much about the importance of this parameter. PWV has proven to have independent predictive utility when evaluated in conjunction with standard risk factors for death and cardiovascular disease (CVD). However, the field of arterial stiffness investigation, which has exploded over the past 20 years, has proliferated without logistical guidance for clinical and translational research investigators. This summary statement, commissioned by the American Heart Association Council on Hypertension, represents an effort to provide such guidance, drawing on the expertise of experienced clinical and basic science investigators in Europe, Australia, and the United States. Recommendations made in this statement are assumed to refer to the research aspect of arterial stiffness investigations, unless accompanied by language that emphasizes clinical use as well, and are based on the grid shown in Table 1.

Section 1. What Is Arterial Stiffness?

Recommendation

1.1 It is reasonable to measure arterial stiffness clinically by determining PWV (*Class IIa; Level of Evidence A*).

Townsend RR, et al. Hypertension 2015;66:698-722

Arterial stiffness - Hypertension cause/ effect?

- Hypertension is associated with increased arterial stiffness

- Elevated BP may cause vascular damage and accelerated conduit arterial stiffening by both functional and structural mechanisms

Aatola H, et al. Hypertension 2010;55:806-811
Blacher J, Safar ME. Hypertension 2006:241–56
Nichols WW, O'Rourke MF. MacDonald's Blood Flow in Arteries, 6th ed. London, UK: Arnold, Hodder Headline Group; 2011

Arterial stiffness – Hypertension effect?

- Presence of hypertension was associated with steeper progression of cfPWV
- Childhood or lifetime burden of SBP was associated with ↑ adult baPWV
- Midlife increased BP was associated with cfPWV 20 years later

Benetos A, et al. Circulation 2002;105:1202-7
Li S, et al Hypertension 2004;43:541-6
McEniery CM, et al. Hypertension 2010;56:36-43
Aatola H, et al. Hypertension 2010;55:806-11

Arterial stiffness – Hypertension cause?

Few studies have investigated whether measures of arterial stiffness are related to future BP or incident hypertension

- Higher proximal aortic stiffness assessed by echocardiography was associated with incident hypertension

Dernellis J, et al. Hypertension 2005;45:426-31

- Higher cfPWV was associated with an increase in SBP and incident hypertension

Najjar SS, et al. J Am Coll Cardiol 2008;51:1377-83

- ba PWV was associated with BP progression and incident hypertension

Takase H, et al. Am J Hypertens 2011;24:667-73

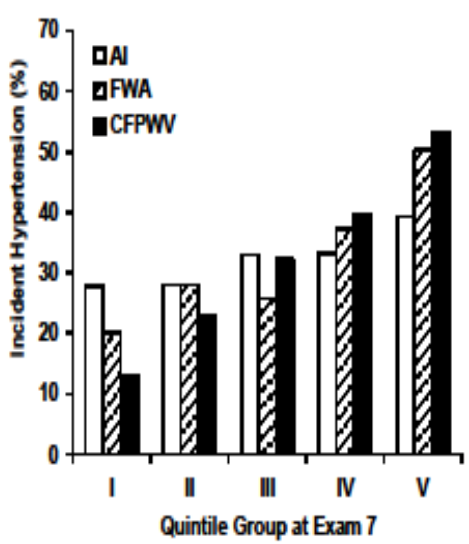
- The Atherosclerosis Risk in Communities cohort reported that higher carotid artery stiffness was associated with incident hypertension

Liao D, et al. Hypertension 1999;34:201-6

Arterial stiffness – Hypertension cause?

Higher arterial stiffness was predictive of incident hypertension

whereas higher initial BP was not predictive of an increase in arterial stiffness



The quintile cutpoints for the various groupings were as follows:

	I-II	II-III	III-IV	IV-V
SBP	105	113	120	127
DBP	64	69	73	79
CFPWV	6.9	7.7	8.6	9.9
FWA	28.4	33.2	37.8	44.6
AI	5.1	10.8	16.9	23.8

SBP, systolic blood pressure; DBP, diastolic blood pressure; CFPWV, carotid-femoral pulse wave velocity; FWA, forward wave amplitude; AI, augmentation index.

Kaess BM, et al. JAMA 2012;308:875-81

Arterial stiffness – Hypertension cause?

- *Results support the notion that arterial stiffness is a precursor rather than the result of hypertension*

Editorial

- "Open up additional therapeutic possibilities"
- "attractive tool to optimize individualized therapeutic strategies and reduce CV morbidity and mortality"
- "interventional target to prevent rather than treat hypertension after it already has developed"

Mukherjee D. Atherogenic vascular stiffness and hypertension: cause or effect? JAMA 2012;308:919-20

Central BP

- Central BP, when compared to peripheral BP, offers a more accurate estimation of the load imposed on the aorta and the left ventricle, and in turn, of overall vascular damage and prognosis

- Even in the elderly central BP is superior to brachial BP for the prognosis of CV events

Sharman JE, et al. BP GUIDE study. Hypertension 2013;62:1138-45
Vlachopoulos C, et al. Eur Heart J 2010; 31:1865-71
McEniery CM, et al. Hypertension 2008; 51:1476-82
Pini R, et al. the ICARe Dicomano Study. J Am Coll Cardiol 2008;51:2432-9
Protogerou AD, et al. J Hypertens 2007; 25:265-72

Central Pressure and Arterial Stiffness are Associated with & Predictive of Increased Risk of CV Disease

First author, year	Cohort	Population (Sample Size)	Device
Safar, 2002		ESRD (n=180)	Tonometer
Williams, 2007	CAFE	Hypertension (n=2068)	SphygmoCor
Roman, 2007	SHS	General Population (n=2289)	SphygmoCor
Pini, 2008	Dicomano	General Population (n=330)	Tonometer
Jankowski, 2008	---	Coronary Patients (n=971)	Catheter
Wang, 2009	---	General Population (n=1257)	Tonometer
Ilyas, 2009	---	CV & Renal Disease (n=279)	SphygmoCor
Weber, 2010	---	Coronary Patients (n=419)	SphygmoCor
Verbeke, 2011	CORD	Dialysis Patients (n=947)	SphygmoCor
Wohlfahrt, 2012	post-MONICA	General Population (n=657)	SphygmoCor
Huang, 2011		General Population (n=1014)	Tonometer
Protogerou, 2011	PROTOGER	Very Elderly (n=259)	Tonometer
Chirinos, 2011	MESA	General Population (n=5934)	Tonometer

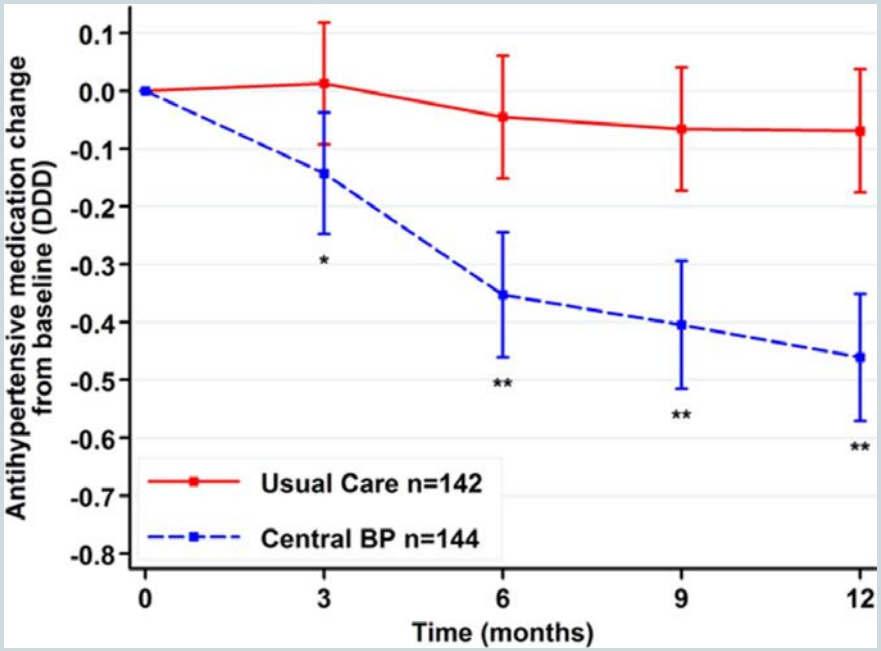
Longitudinal studies on central pressure that have shown increased risk prediction of central over brachial BP

Boutouyrie, 2002	Broussais	Hypertensives (n=820)	Complior
Cruickshank, 2002		Diabetes (n=163)	Doppler
Sutton-Tyrrell, 2005	Health ABC	General Population (n=2453)	Doppler
Shokawa, 2005	Hawaii-Los Angeles-Hiroshima	General population (n=491)	MCG400
Willum Hansen, 2006		General population (n=2592)	Piezoelectric pressure transducers
Zoungas, 2007		CKD patients (n=204)	Tonometer
Terai, 2008	NOAH	Hypertensives (n=604)	PWV-200 Fukuda
Wang, 2009		General population (n=1273)	Doppler
Mitchell, 2010	Framingham	General population (n=2232)	Tonometer
Ilyas , 2009		CV & Renal Disease (n=240)	SphygomoCor
Maldonado, 2011	EDIVA	General population (n=2200)	Complior
Verbeke, 2011	Belgian Transplant Cohort	Renal transplants (n=499)	SphygomoCor
Verbeke, 2011	CORD	Dialysis patients (n=941)	SphygomoCor
CaPS37, unpublished	Caerphilly	General population (n=714)	SphygomoCor
BLSA38, unpublished		General population (n=334)	Doppler
Pannier, unpublished		ESRD (n=1875)	Complior

Longitudinal studies on cfPWV

Using Central Aortic Blood Pressure to Guide Hypertension Management

Between-group **change in daily defined dose (DDD)** of **antihypertensive medications.**



BP GUIDE Study

- Hypertension management guided by CBP resulted in **significantly less medication** needed to maintain brachial BP control
- 16% of CBP guided patients had complete cessation of medication vs. only 2% of usual care
- There were no adverse effects on LVM, aortic stiffness, or quality of life in CBP guided treatment

Sharman J E et al. Hypertension 2013;62:1138-45

Cardiovascular Risk: Assessment and Prediction

Table 2. Studies Comparing Relations of Central and Brachial Blood Pressures to Left Ventricular Mass and Hypertrophy

Study	Population	Phenotype	Methods	Central Correlation	Brachial Correlation	Comparison*
Covic[18]	51 ESRD	LV mass	Radial†, echo	SBP: 0.56; $P<0.001$	SBP: 0.35; $P=0.04$	n/a
Wang[13]	1272 HTN plus NL	LV mass/BSA	Carotid†, echo	PP: 0.286; $P<0.001$	PP: 0.219; $P<0.001$	$P<0.05$
				SBP: 0.410; $P<0.001$	SBP: 0.370; $P<0.001$	$P<0.05$
Roman[21]	3520 AI	LV mass/$Ht^{2.7}$	Radial†, echo	PP: 0.335; $P<0.001$	PP: 0.219; $P<0.001$	$P<0.005$
				SBP: 0.396; $P<0.001$	SBP: 0.370; $P<-0.001$	NS
		RWT		PP: 0.167; $P<0.001$	PP: 0.130; $P<0.001$	$P<0.02$
				SBP: 0.286; $P<0.001$	SBP: 0.250; $P<0.001$	$P<0.005$
Norton[14]	678 black SA	LV mass/$Ht^{1.7}$	Radial†, echo	PP: 0.41; $P<0.0001$‡		See footnote
				P2: 0.41; $P<0.0001$‡		
Neisius[15]	535 HTN plus NL	LV mass/$Ht^{2.7}$	Radial†, echo	PP: 0.385; $P<0.001$	PP: 0.189; $P<0.001$	$P<0.01$
				SBP: 0.391; $P<0.001$	SBP: 0.297; $P<0.001$	$P<0.01$
Wohlfahrt[25]	657 Czechs	LVH	ECG	SBP: AUC, 0.90±0.02	SBP: AUC, 0.83±0.03	$P<0.05$

Studies linking LVM and LVH with central SBP over and above brachial SBP

Roman et al., Hypertension 2014;63:1148-53

Evidence for the Added Value of Central Blood Pressure

In the Strong Heart Study (2,405 individuals):

- When central pulse pressure equals or exceeds 50mmHg, the risk of cardiovascular disease increases by nearly 70%; in individuals <60 years, the increase was 150%.
- 50mmHg represented a threshold above which the risk of a cardiovascular event increases dramatically.
- Brachial pressure did not demonstrate the same threshold for risk.

Booysen et al. (1,169 individuals) reported that:

- Normal vs. high normal brachial blood pressure did not distinguish those with or without end-organ damage.
- When the same group was divided according to normal vs. high normal central systolic pressure, the groups with and without such damage could be identified.

Saladini et al., (354 young and middle age individuals with untreated Stage 1 hypertension) reported that:

- Those with low central systolic pressure (<125mmHg) were at significantly less risk of requiring antihypertensive medication than those with high central systolic pressure.

ESH/ISH guidelines

In hypertensive patients with a PWV above 10 m/s all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved.	IIa	B

Conduit Artery Function Evaluation (CAFE) trial

- Substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

  (n=2199, f/u 4 yrs)

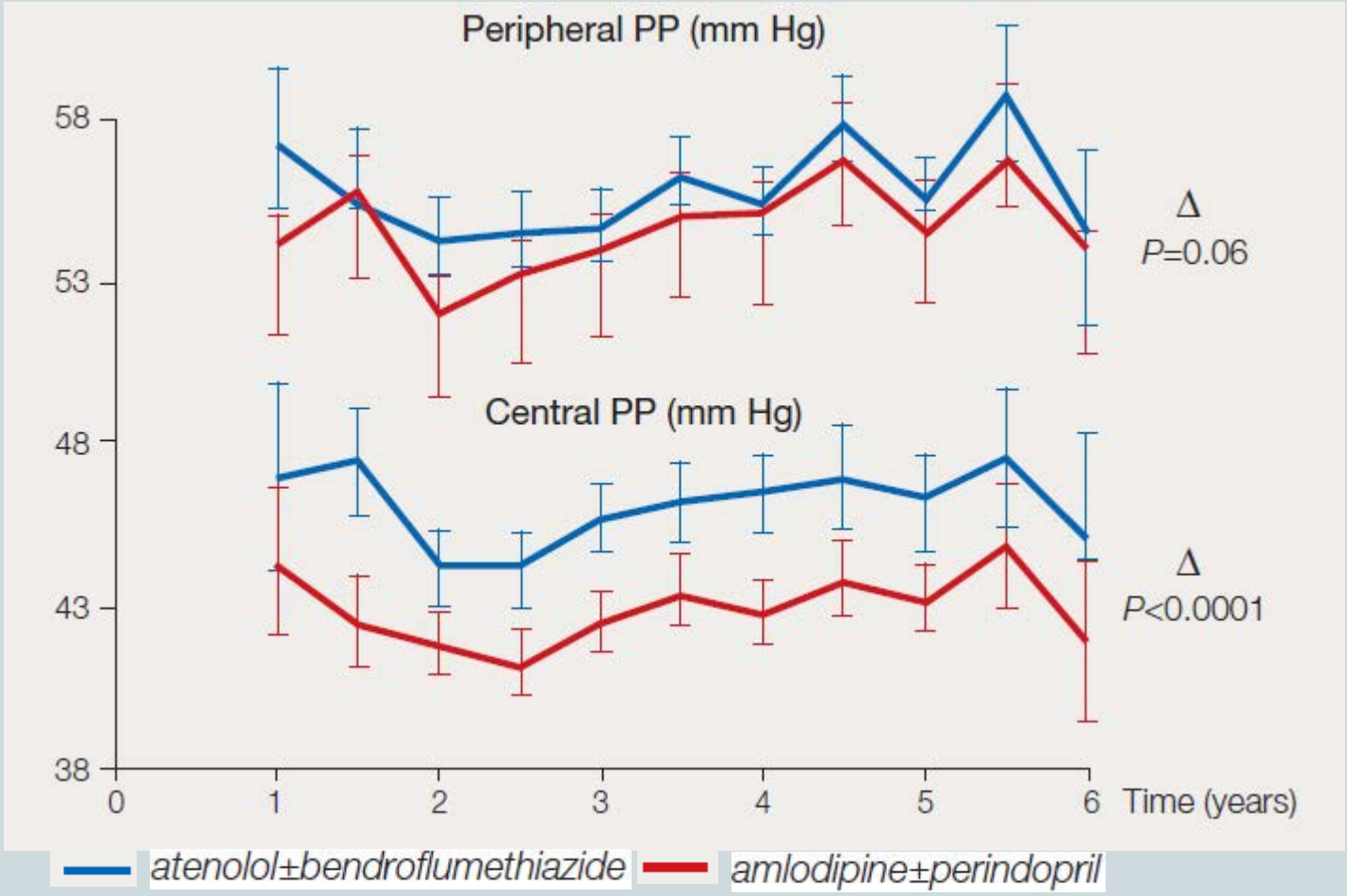
- Atenolol & thiazide vs. amlodipine & perindopril

- Similar effects on brachial SBP and PP

- Greater reductions in central SBP and PP with amlodipine & perindopril

Williams B, et al. Circulation. 2006; 113:1213-25

Conduit Artery Function Evaluation (CAFE) trial



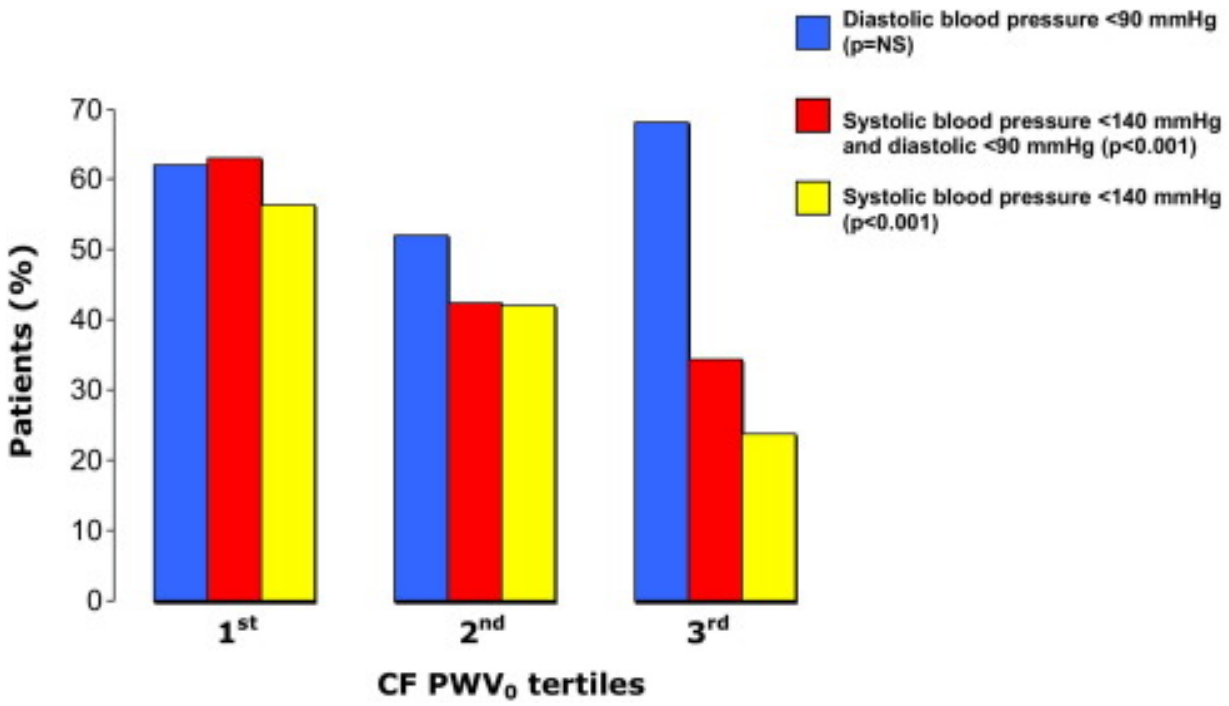
Williams B, et al. Circulation 2006;113:1213-25

Effect of different medications

	Central PWV
ACE inhibitors	↓
Angiotensin receptor blockers	↓
Calcium channel blockers	↓
Thiazide diuretics	↓ (±)
VD β-blockers	↓ (# or ↑)
NON VD β-blockers	(↓) # or ↑

Boutouyrie et al. Drugs 2011
Protogerou AD, rt al. Curr Pharm Des 2009;15:272-89

Role of arterial stiffness on BP response to chronic antihypertensive treatment

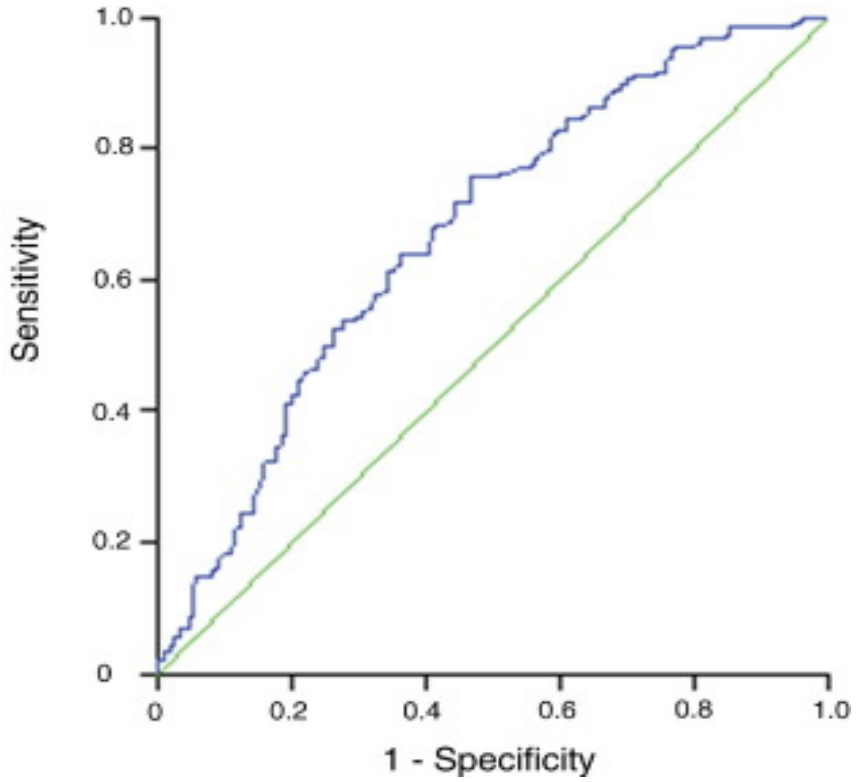


Baseline PWV is a significant predictor of BP response to antihypertensive treatment, independent from age, the need for increasing drug dosage, and the presence of CV risk factors

Achievement of SBP control appears to be influenced by aortic stiffness and by ACE inhibition

Protogerou A, et al. J Am Coll Cardiol 2009;53:445-51

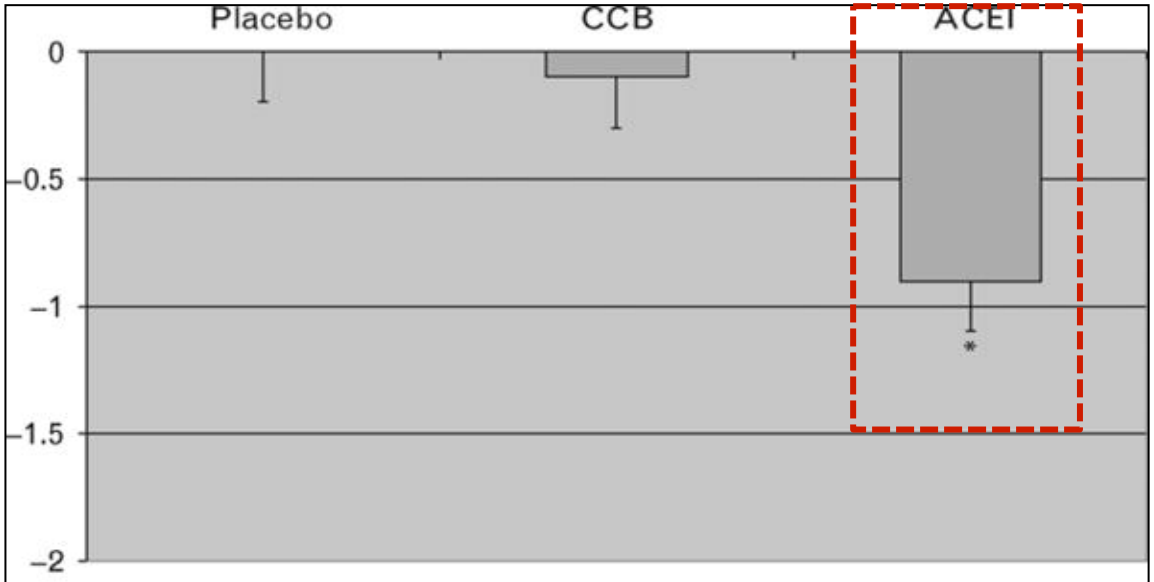
Aortic stiffness predicts SBP response after 12 months of treatment



ROC analysis evaluating the ability of PWV at baseline to predict the adequate control of SBP (<140 mm Hg) after 12 months of treatment (AUC 0.67, p<0.001, 95% CI: 0.62-0.73)

Protogerou A, et al. J Am Coll Cardiol 2009;53:445-51

Effects of antihypertensive-drug class on changes in PWV – short term

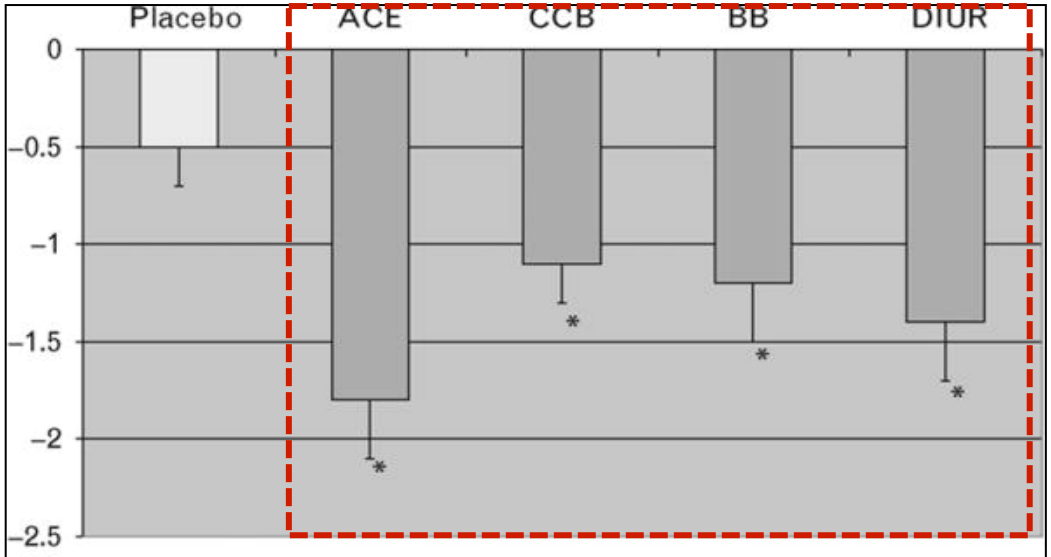


Changes in pulse wave velocity according to hypertensive-drug class in short-term. $*P < 0.05$ compared to placebo. ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

In short-term trials, after adjustment to changes in MBP, changes in HR, sex, risk factors, and adjusted PWV, PWV decreased significantly by **-0.92 m/s with ACEI** compared to 0.003 m/s in the placebo group (P=0.003)

Ong KT, et al. J Hypertens 2011;29:1034-42 – Meta-analyses

Effects of antihypertensive-drug class on changes in PWV – long term



Changes in pulse wave velocity according to hypertensive-drug class in long-term trials. $*P < 0.05$ compared to placebo. ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; CCB, calcium channel blocker; DIUR, diuretic.

In long-term trials, after adjustment to changes in MBP, changes in HR, adjusted PWV, sex, and risk factors, PWV decreased significantly with the four classes of antihypertensive drugs (ACEI, CCB, β-blockers, and diuretics) by **-1.8, -1.1, -1.2, and -1.4 m/s,** respectively, compared to a reduction of -0.5 m/s in the placebo group (P=0.002, P=0.04, P=0.04, and P=0.01 vs. placebo)

Ong KT, et al. J Hypertens 2011;29:1034-42 – Meta-analyses

Pharmacological treatment

- ACEi (peri-, capto-, quina-, rami-, fosinopril)
- ARBs (valsa-, losa-, telmisartan)
- CCBs
- Aldosterone antagonists
- certain β-blockers

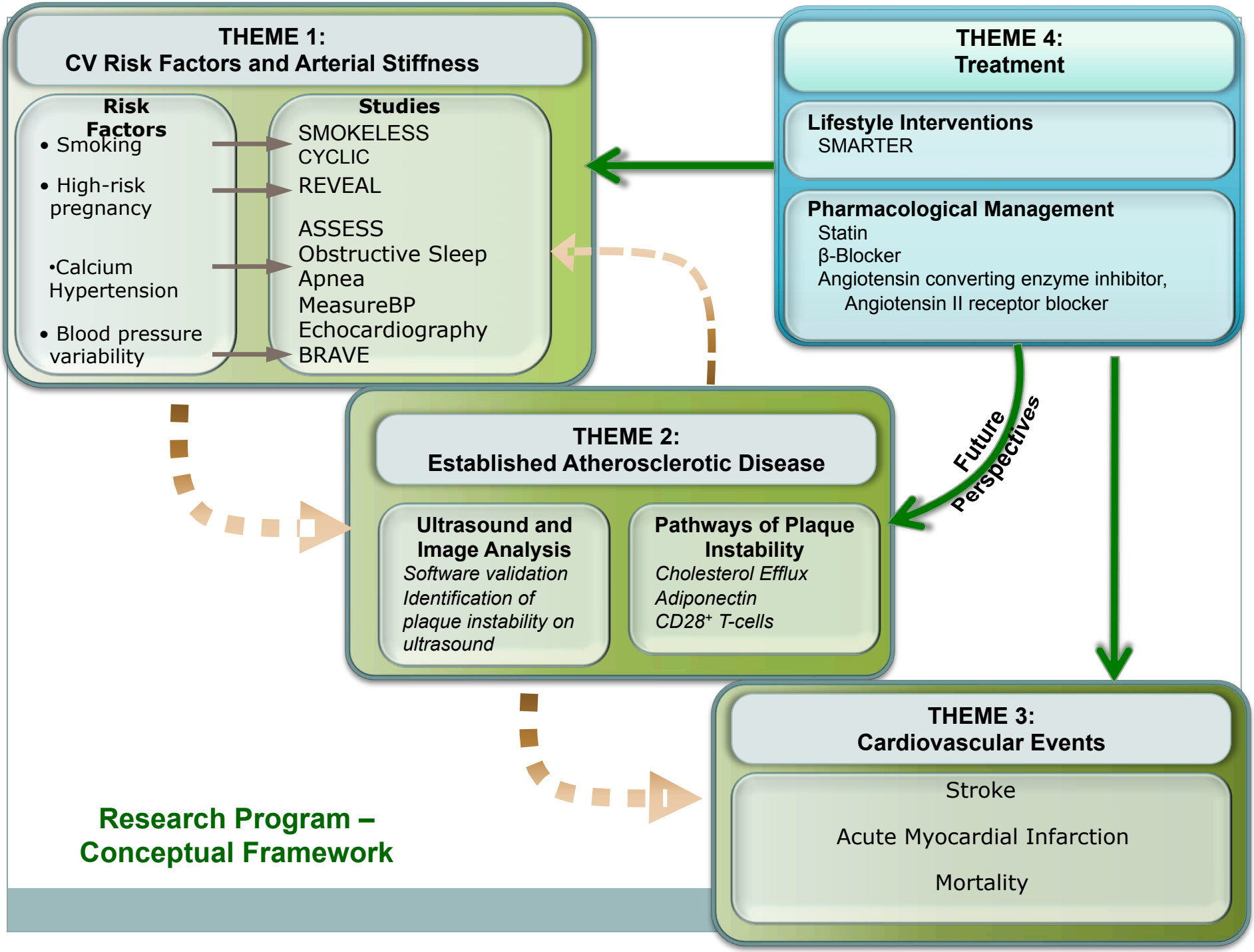
can modify the arterial structure independently of the effect on BP

Winer N, et al. Curr Hypertens Rep 2001;3:297-304
Mahmud A, et al. Expert Rev Cardiovasc Ther 2003;1:65-78
Duprez DA. Cardiovasc Drugs Ther 2010;24:305-10

Summary

- Not all antihypertensive agents reduce stiffness
- The strongest evidence is for ACEi, ARBs, and CCBs, which have been shown to reduce PWV and arterial wave reflection
- Evidence for β-blockers is less clear-cut, although some studies show a reduction in PWV
- Diuretics have limited effect on arterial stiffness
- Combinations maybe better than monotherapy
- Statins may improve stiffness

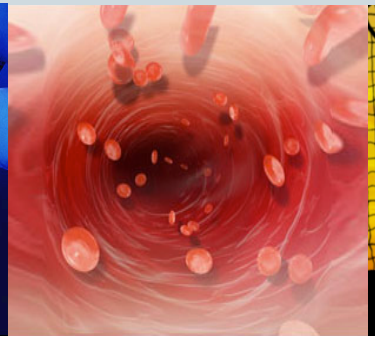

VASCULAR
Health Unit

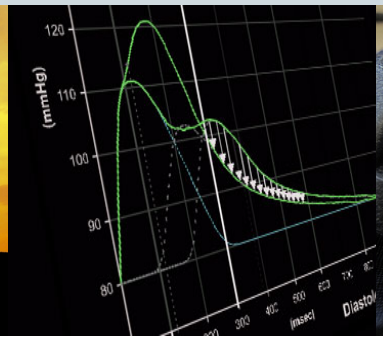

THEME 1:
CV Risk Factors and Arterial Stiffness
Risk Factors
• Smoking
• High-risk pregnancy
•Calcium Hypertension
• Blood pressure variability
Studies
SMOKELESS
CYCLIC
REVEAL
ASSESS
Obstructive Sleep Apnea
MeasureBP
Echocardiography
BRAVE
THEME 4:
Treatment
Lifestyle Interventions
SMARTER
Pharmacological Management
Statin
β-Blocker
Angiotensin converting enzyme inhibitor,
Angiotensin II receptor blocker
Future Perspectives
THEME 2:
Established Atherosclerotic Disease
Ultrasound and Image Analysis
Software validation
Identification of plaque instability on ultrasound
Pathways of Plaque Instability
Cholesterol Efflux
Adiponectin
CD28+ T-cells
THEME 3:
Cardiovascular Events
Stroke
Acute Myocardial Infarction
Mortality
Research Program –
Conceptual Framework

SMOKELESS

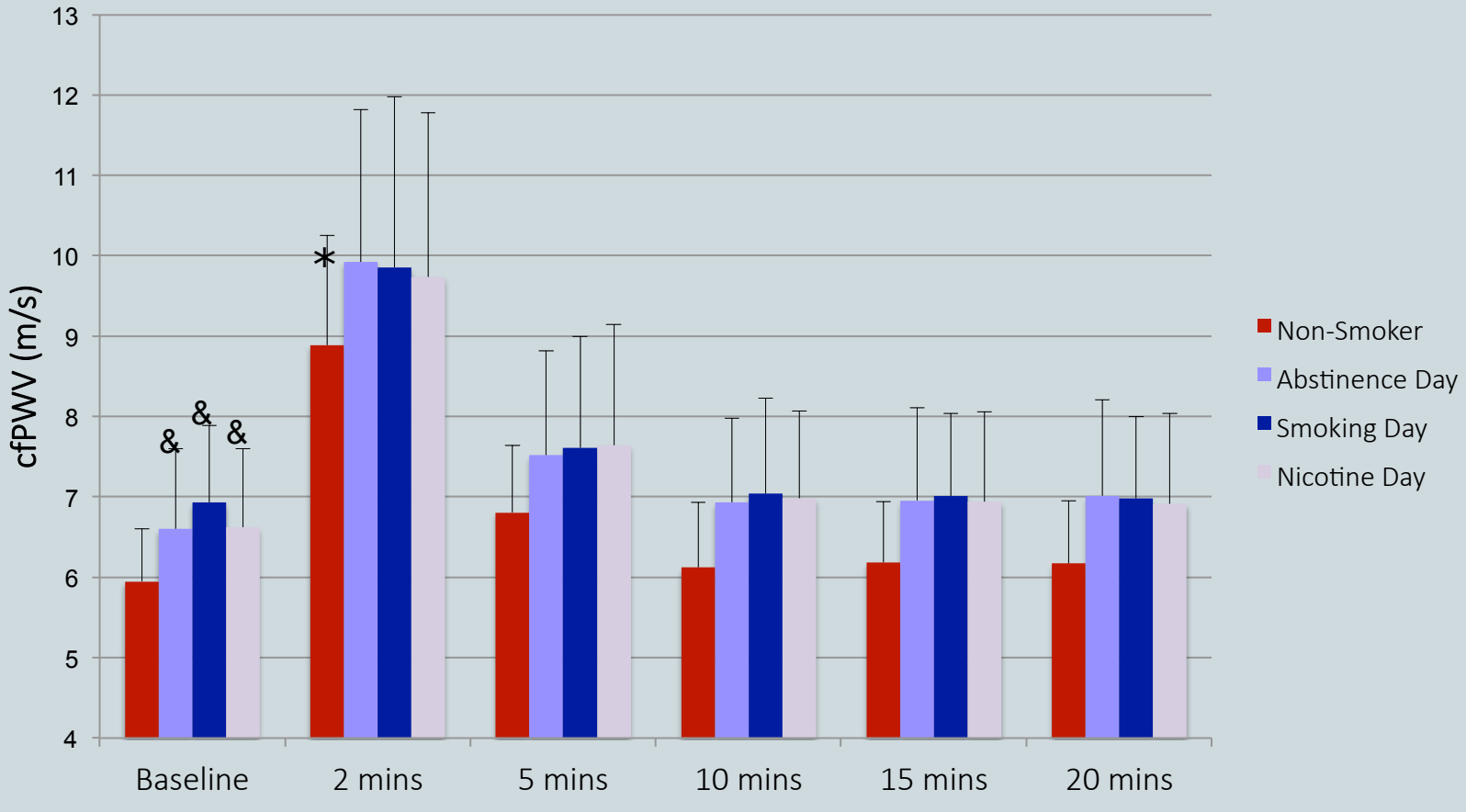
CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

The Effects of Smoking on Vessel Hemodynamics at Rest and Following Acute Physical Stress





cfPWV at rest and after exercise



cfPWV is significantly higher in smokers under all 3 conditions

Greater recovery of cfPWV in non-smokers post-exercise

REVEAL (pRedictivE Value of artEriAl stiffness in the development of pre-ecLampsia)

Overarching objective is to fill important knowledge gaps with respect to the ability of arterial stiffness to predict the development of pre-eclampsia and recovery post-partum in high-risk nulliparous pregnant women with a singleton pregnancy

Fonds de recherche Santé Québec

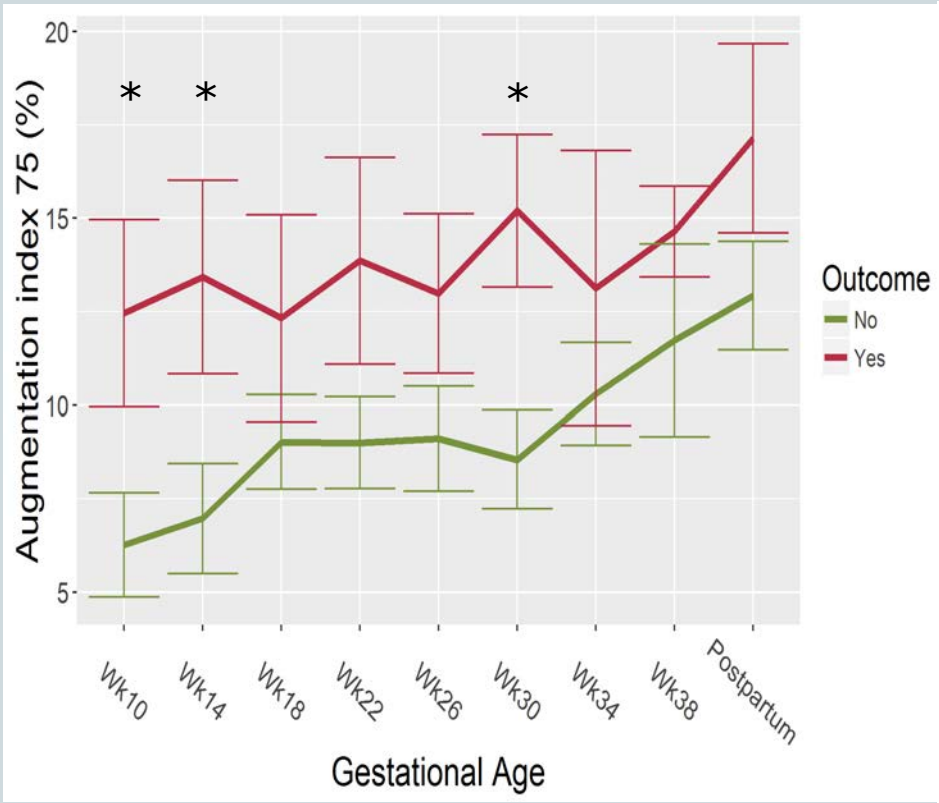
Canadian Foundation for Women's Health / Fondation canadienne de la santé des femmes

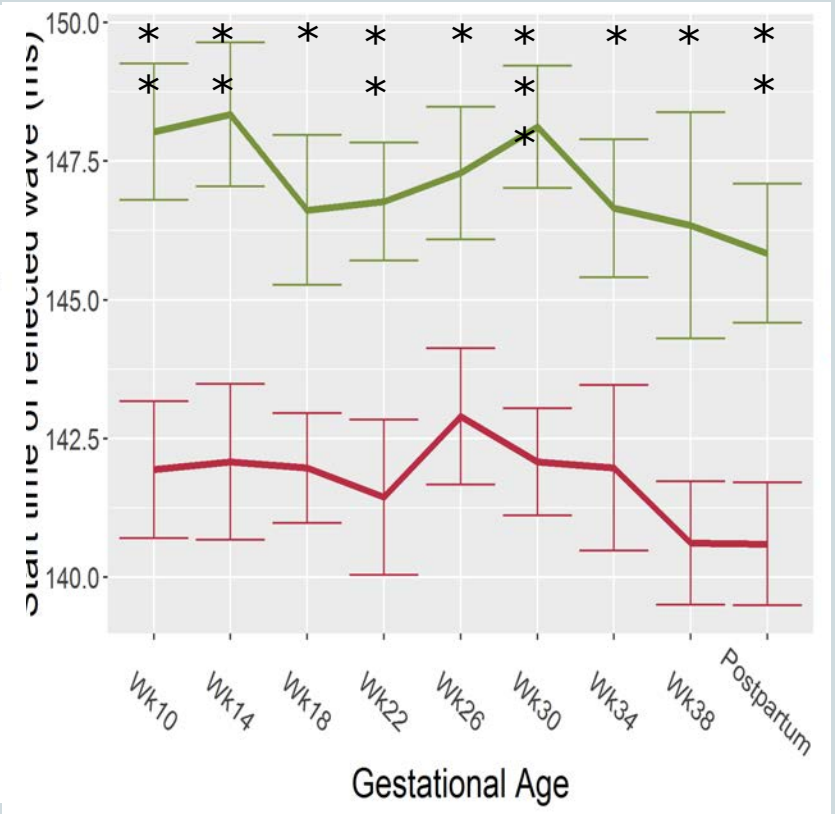
HEART & STROKE FOUNDATION OF CANADA | FONDATION DES MALADIES DU CŒUR DU CANADA

Objective #1

Characterise the trends in arterial stiffness throughout pregnancy and up to 6 weeks post partum in women with high-risk pregnancies who do and do not develop a composite outcome of gestational hypertension and PrE

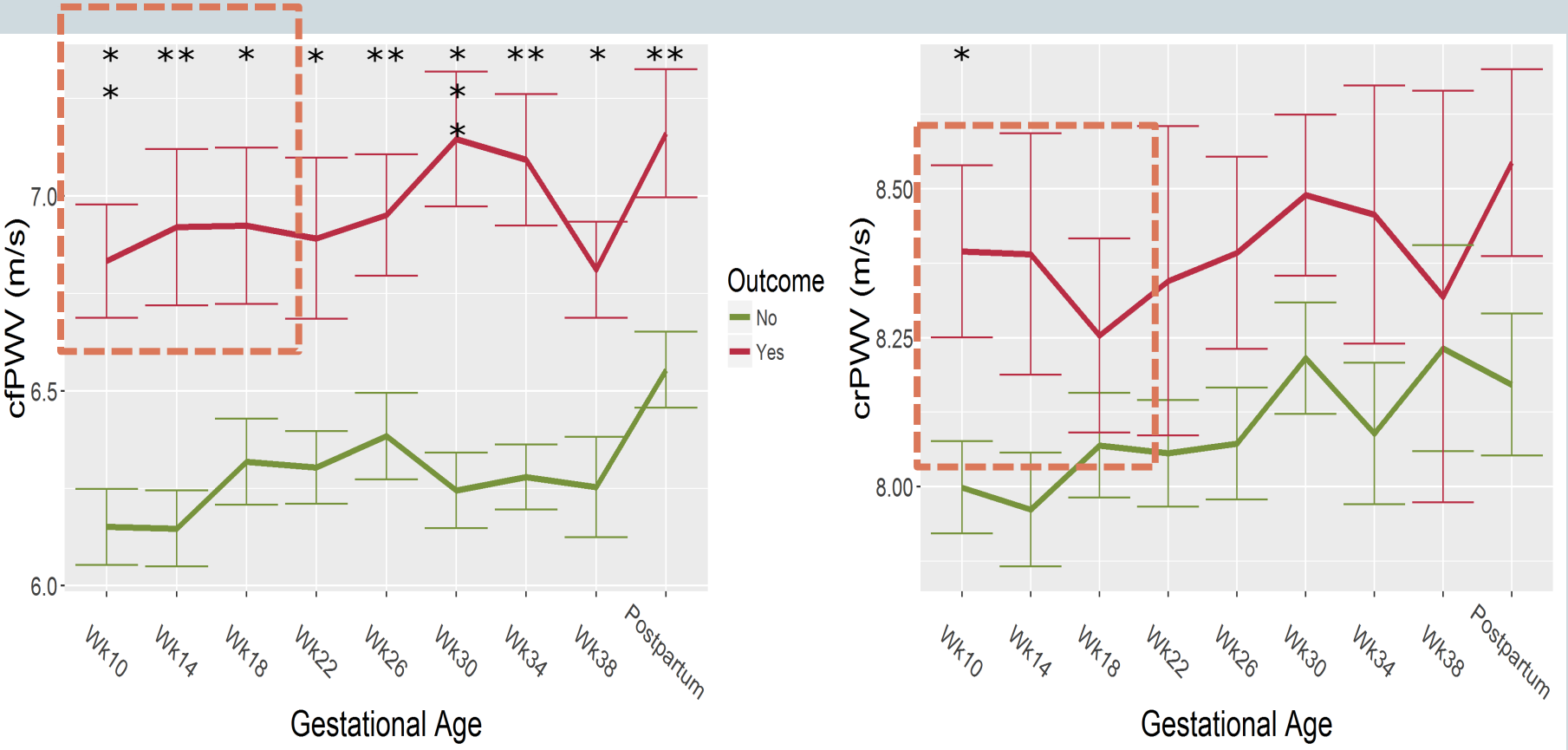
Wave reflection





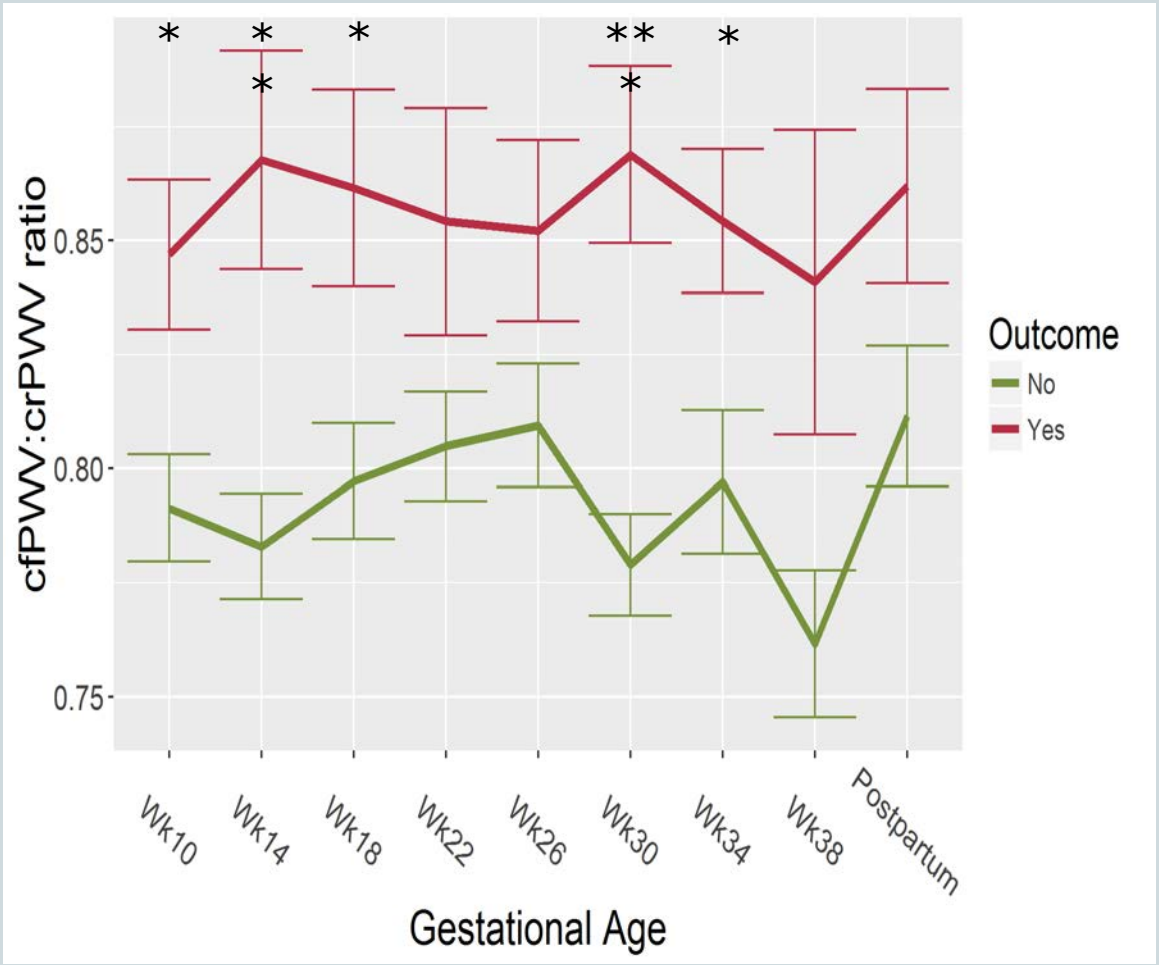
Adjusted for maternal age, BMI, family history of PET; * p-value < 0.05 ** p-value < 0.01 *** p-value < 0.001

Central and peripheral arterial stiffness



Adjusted for maternal age, BMI, family history of PET; * p-value < 0.05 ** p<0.01 *** p<0.001

Central:peripheral stiffness ratio



Adjusted for maternal age, BMI, family history of PET; * p-value < 0.05 ** p-value < 0.01 *** p-value < 0.001

Objective #2

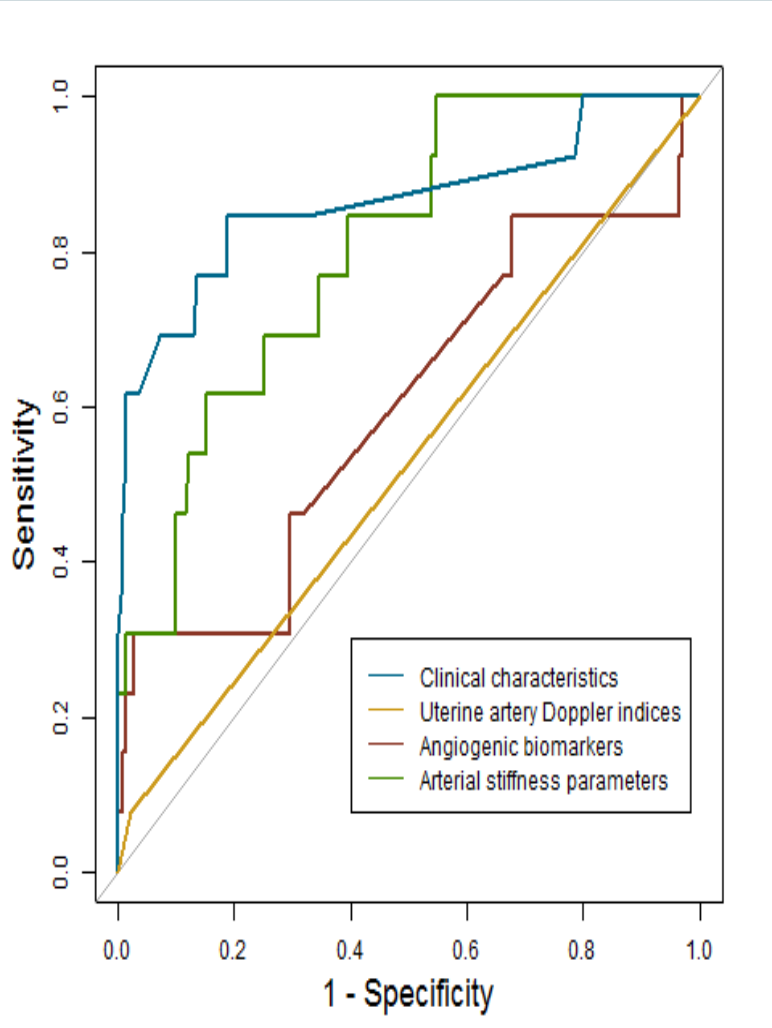
Determine the performance of arterial stiffness for the prediction of a composite outcome of gestational hypertension and PrE

Compare the predictive value of arterial stiffness to angiogenic biomarkers and uterine artery Doppler and their combination for PrE

Pre-eclampsia models

Predictors included	Model	Sensitivity (FPR = 10%)	LR (+)	LR (-)	AUC
Clinical characteristics	Race: African-Canadian + family history of PET + SBP (1st trimester)	69.2	6.9	0.3	0.86 (0.72 – 1)
Uterine artery Doppler	Bilateral notching	15.1	1.5	0.9	0.53 (0.45 – 0.60)
Angiogenic markers	sFlt1:PlGF (2nd trimester)	30.8	3.1	0.8	0.60 (0.41 – 0.79)
Clinical characteristics + uterine artery Doppler + angiogenic markers	Race: African-Canadian + family history of PET + SBP (1st trimester)	69.2	6.9	0.3	0.86 (0.72 – 1)
Arterial stiffness indices	cfPWV (1st trimester) + T1R (1st trimester) + ED	30.8	3.1	0.8	0.80 (0.69 – 0.92)
All predictors	Race: African-Canadian + family history of PET + cfPWV (1st trimester)	79.8	8.0	0.2	0.94 (0.86 – 1)

Pre-eclampsia models

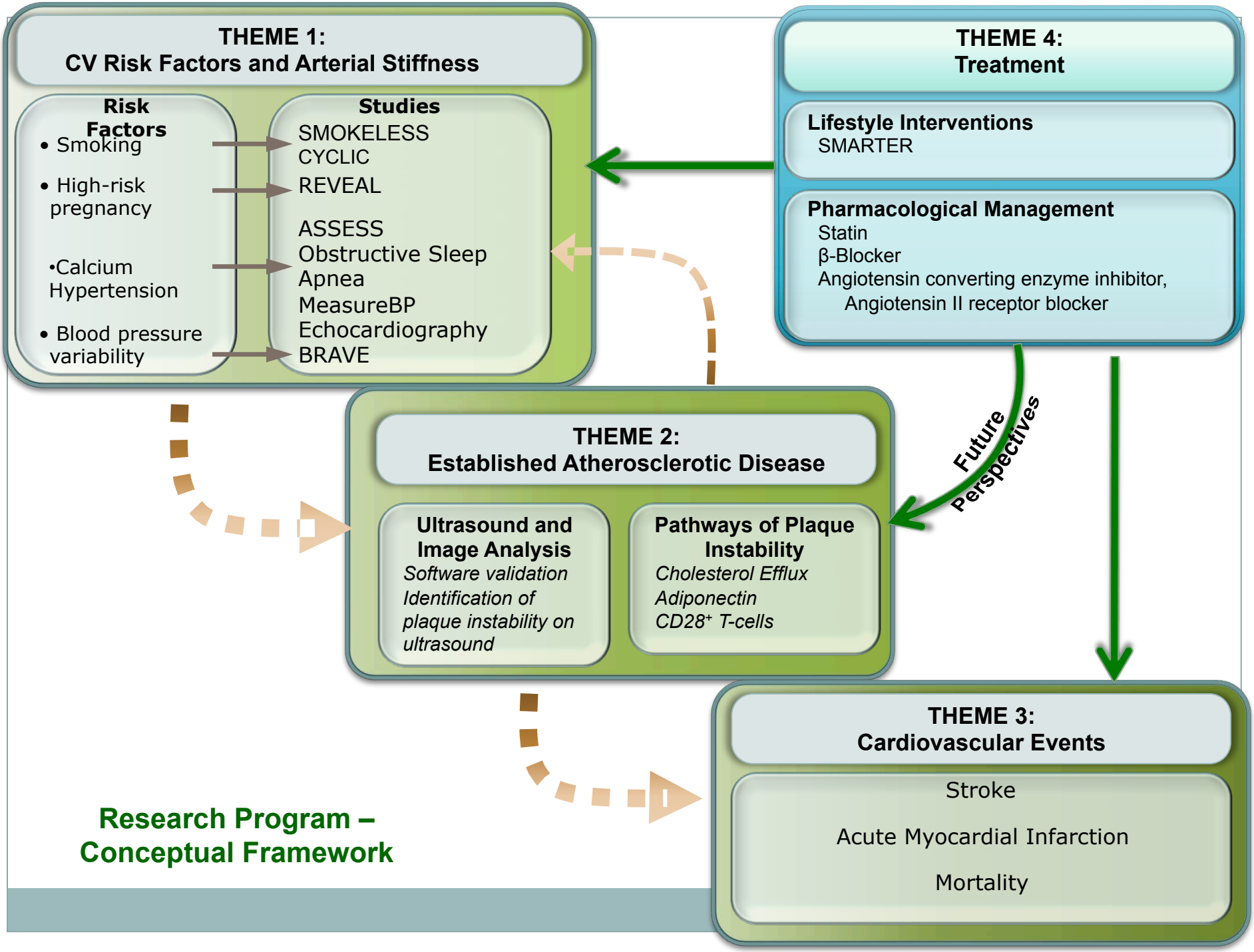


Comparison of AS AUC-ROC with other predictors

$p\text{-value}_{Clinical} = 0.516$

$p\text{-value}_{UAD} < 0.001$

$p\text{-value}_{Angiogenic} = 0.04$


THEME 1:
CV Risk Factors and Arterial Stiffness
Risk Factors
• Smoking
• High-risk pregnancy
•Calcium Hypertension
• Blood pressure variability
Studies
SMOKELESS
CYCLIC
REVEAL
ASSESS
Obstructive Sleep Apnea
MeasureBP
Echocardiography
BRAVE
THEME 4:
Treatment
Lifestyle Interventions
SMARTER
Pharmacological Management
Statin
β-Blocker
Angiotensin converting enzyme inhibitor,
Angiotensin II receptor blocker
Future Perspectives
THEME 2:
Established Atherosclerotic Disease
Ultrasound and Image Analysis
Software validation
Identification of plaque instability on ultrasound
Pathways of Plaque Instability
Cholesterol Efflux
Adiponectin
CD28+ T-cells
THEME 3:
Cardiovascular Events
Stroke
Acute Myocardial Infarction
Mortality
Research Program –
Conceptual Framework

Summary – Arterial stiffness

- Cumulative indicator of arterial health – tissue biomarker
- Inter-relationship between arterial stiffness and atherosclerosis – early marker
- Arterial stiffness is strongly associated with future CVD and events
- Important to study surrogate /early markers of atherosclerosis
- Certain treatment can improve arterial stiffness, independent of BP reduction
- Arterial stiffness measurement could represent a promising screening/monitoring tool in clinical practice for risk stratification

My team…

Special Thanks

- Colleagues & Collaborators
- Team & Students
- Participants

‘When you can measure what you are speaking about and can express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind’

Lord Kelvin, 1891

Thank you!

stella.daskalopoulou@mcgill.ca


Aaron ECKHART
Maria BELLO
Adam BRODY
Sam ELLIOTT
Katie HOLMES
Rob LOWE
William H. MACY
and
Robert DUVALL
Nick Naylor doesn't hide the truth... he filters it.
THANK YOU FOR SMOKING
Based on the best-selling novel
SPRING 2006

REVIEW

The effect of smoking on arterial stiffness

Robert J Doonan[1], Anais Hausvater[1], Ciaran Scallan[1], Dimitri P Mikhailidis[2], Louise Pilote[1] and Stella S Daskalopoulou[1]

- Systematic review of the literature
  - Pubmed, Embase, Cochrane: 39 relevant studies
- Acute smoking causes an acute ↑ arterial stiffness
- Passive smoking ↑ arterial stiffness acutely and chronically
- Majority of studies identified chronic smoking as a risk factor for ↑ arterial stiffness
- Effect of smoking cessation could not be determined and remains to be established

Doonan, Daskalopoulou, et al. Hypertens Res 2010;33:398-410

Vascular Reserve

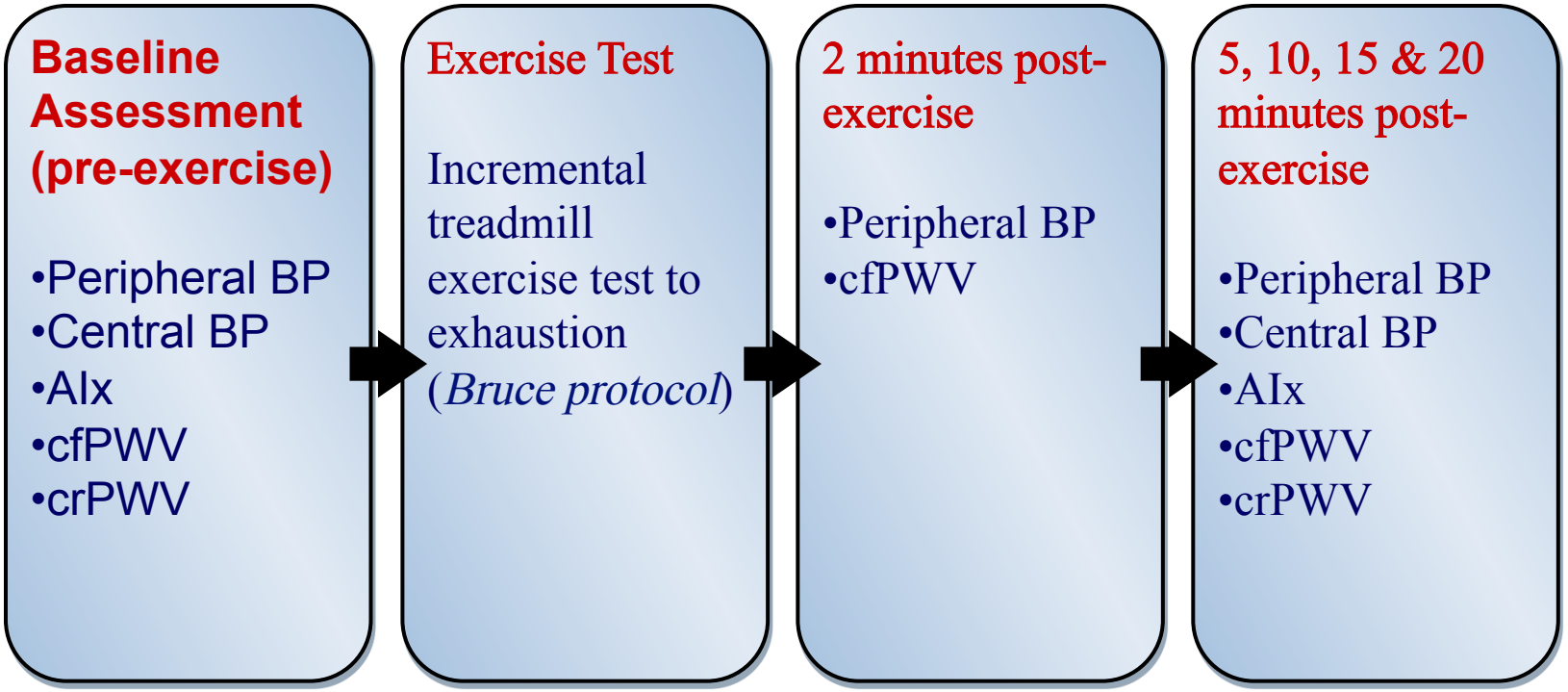
The ability of the blood vessels to respond to increased demands (maximal physical stress)

Arterial Stress Test

- Novel concept, designed in the lab to quantify the vascular reserve
- Arterial stiffness is measured before and after physical stress
- Somewhat analogous to cardiac stress test

Arterial Stress Test

Analogous to cardiac stress test



SMOKELESS (quantification of the effect of SMOKing on artEriaL stiffnESS)

Objectives:

1. the effect of smoking, both acute and chronic, on arterial stiffness at rest and the ability of the vascular system to respond to physical stress, such as acute exercise (vascular reserve)

2. the extent to which smoking cessation improves arterial stiffness at rest and vascular reserve

3. the extent to which smoking-related changes in arterial stiffness at rest and the vascular reserve correlate with changes in plasma endothelin-1 levels

CIHR IRSC
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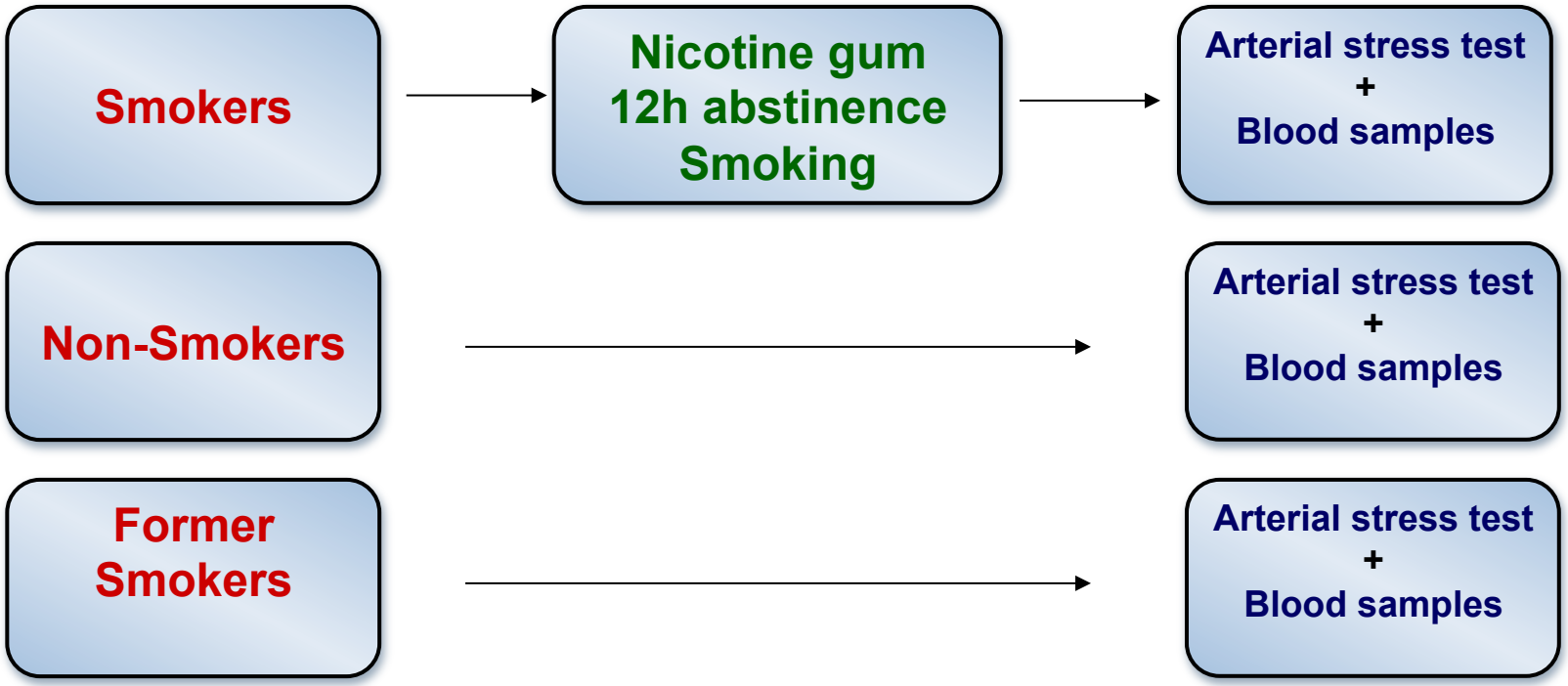
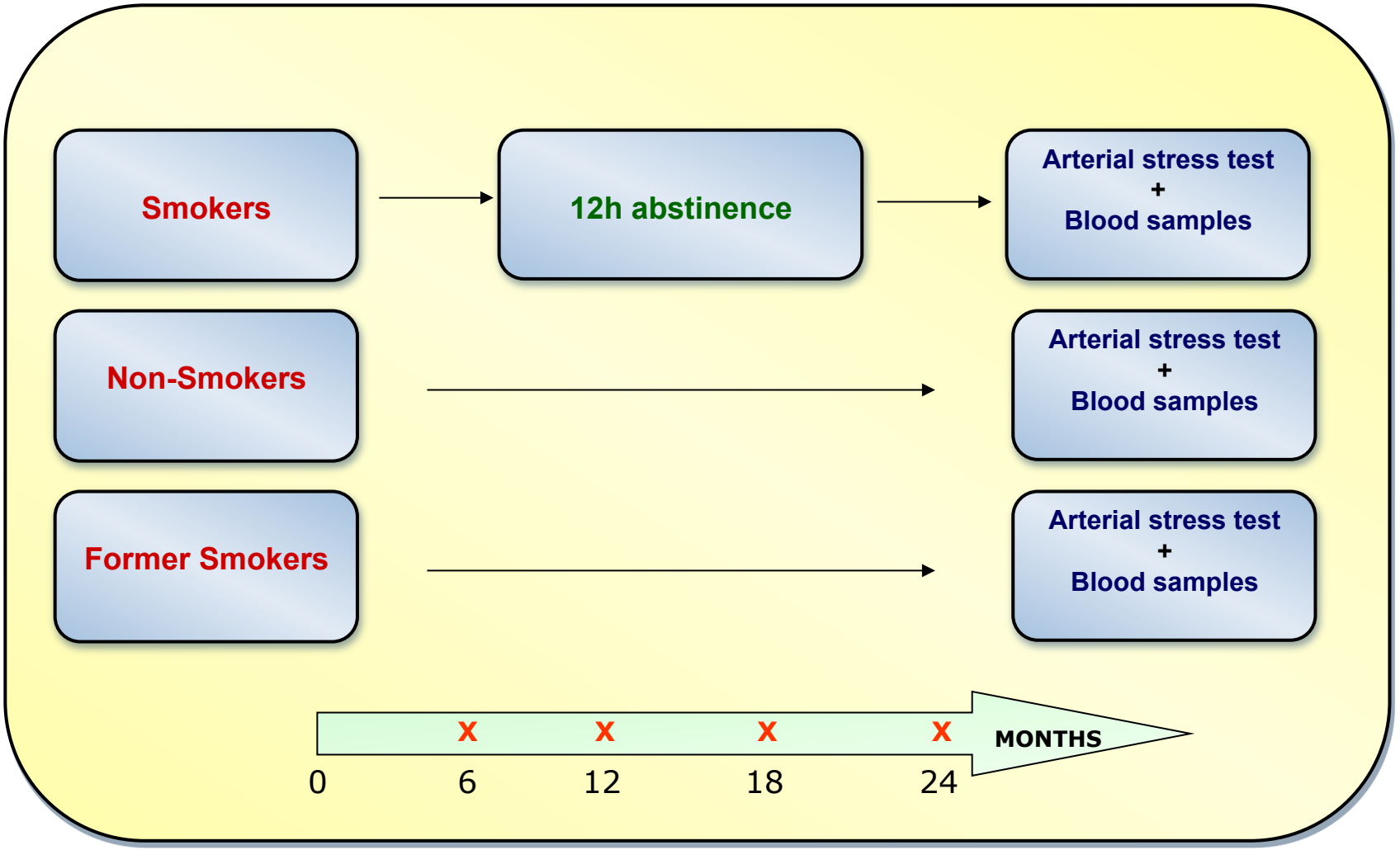
Cross-sectional Component



Longitudinal Component



Resting Test

Table 2 - Resting Hemodynamic Parameters
Non- Smokers vs. Chronic Smoking, vs. Acute Smoking, vs. Nicotine Intake

	Non-Smokers	Smokers (Abstinence)	Smokers (Nicotine)	Smokers (Smoking)
HR (bpm)	59.4 +/- 8.4	61.0 +/- 6.2	65.9 +/- 7.6 *	74.2 +/- 10.1 *
AIx75 (%)	-7.15 +/- 11.84	1.16 +/- 9.03 *	1.59 +/- 10.16 *	1.98 +/- 8.78 *
SEVR (%)	179.6 +/- 36.1	174.3 +/- 21.3	156.9 +/- 24.5 *	135.5 +/- 25.9 *
cfPWV (m/s)	5.95 +/- 0.65	6.60 +/- 1.00 *	6.62 +/- 0.98 *	6.93 +/- 0.96 *

PWV: 'establishing normal and reference values'

Distribution of pulse wave velocity (PWV) values (m/s) in the reference value population (11 092 subjects) according to age and blood pressure category

Age category (years)	Blood pressure category				
	Optimal	Normal	High normal	Grade I HT	Grade II/III HT
PWV as mean (±2 SD)					
<30	6.1 (4.6–7.5)	6.6 (4.9–8.2)	6.8 (5.1–8.5)	7.4 (4.6–10.1)	7.7 (4.4–11.0)
30–39	6.6 (4.4–8.9)	6.8 (4.2–9.4)	7.1 (4.5–9.7)	7.3 (4.0–10.7)	8.2 (3.3–13.0)
40–49	7.0 (4.5–9.6)	7.5 (5.1–10.0)	7.9 (5.2–10.7)	8.6 (5.1–12.0)	9.8 (3.8–15.7)
50–59	7.6 (4.8–10.5)	8.4 (5.1–11.7)	8.8 (4.8–12.8)	9.6 (4.9–14.3)	10.5 (4.1–16.8)
60–69	9.1 (5.2–12.9)	9.7 (5.7–13.6)	10.3 (5.5–15.1)	11.1 (6.1–16.2)	12.2 (5.7–18.6)
≥70	10.4 (5.2–15.6)	11.7 (6.0–17.5)	11.8 (5.7–17.9)	12.9 (6.9–18.9)	14.0 (7.4–20.6)
PWV as median (10–90 pc)					
<30	6.0 (5.2–7.0)	6.4 (5.7–7.5)	6.7 (5.8–7.9)	7.2 (5.7–9.3)	7.6 (5.9–9.9)
30–39	6.5 (5.4–7.9)	6.7 (5.3–8.2)	7.0 (5.5–8.8)	7.2 (5.5–9.3)	7.6 (5.8–11.2)
40–49	6.8 (5.8–8.5)	7.4 (6.2–9.0)	7.7 (6.5–9.5)	8.1 (6.8–10.8)	9.2 (7.1–13.2)
50–59	7.5 (6.2–9.2)	8.1 (6.7–10.4)	8.4 (7.0–11.3)	9.2 (7.2–12.5)	9.7 (7.4–14.9)
60–69	8.7 (7.0–11.4)	9.3 (7.6–12.2)	9.8 (7.9–13.2)	10.7 (8.4–14.1)	12.0 (8.5–16.5)
≥70	10.1 (7.6–13.8)	11.1 (8.6–15.5)	11.2 (8.6–15.8)	12.7 (9.3–16.7)	13.5 (10.3–18.2)

SD, standard deviation, 10 pc, the upper limit of the 10th percentile, 90 pc, the lower limit of the 90th percentile; HT, hypertension.

Reference Values for Arterial Stiffness' Collaboration. Eur Heart J 2010;31:2338-50

Resting Test

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SEVR (%)	179.6 +/- 36.1	174.3 +/- 21.3	156.9 +/- 24.5 *	135.5 +/- 25.9 *

- Chronic smoking (abstinence day vs. non-smokers) causes:
  - ↑ AIx75
  - ↑ cfPWV

Resting Test

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Non- Smokers vs. Chronic Smoking, vs. Acute Smoking, vs. Nicotine Intake

	Non-Smokers	Smokers (Abstinence)	Smokers (Nicotine)	Smokers (Smoking)
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SEVR (%)	179.6 +/- 36.1	174.3 +/- 21.3	156.9 +/- 24.5 *	135.5 +/- 25.9 *
cfPWV (m/s)	5.85 +/- 0.65	6.60 +/- 1.00 *	6.62 +/- 0.98 *	6.93 +/- 0.96 *

∅ Immediately after a) smoking a cigarette, and b) chewing nicotine gum smokers (vs. abstinence day) additionally demonstrate:
↑ Resting HR
Further ↑ in AIx75 and cfPWV
↓ SEVR

Resting Test

Table 2 - Resting Hemodynamic Parameters
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cfPWV (m/s)	5.95 +/- 0.65	6.60 +/- 1.00 *	6.62 +/- 0.98 *	6.93 +/- 0.96 *

Ø The ↑ in arterial stiffness and ↓ in SEVR after chewing **nicotine gum** was intermediate between the acute response to cigarette smoking and the 12hr-abstinence period

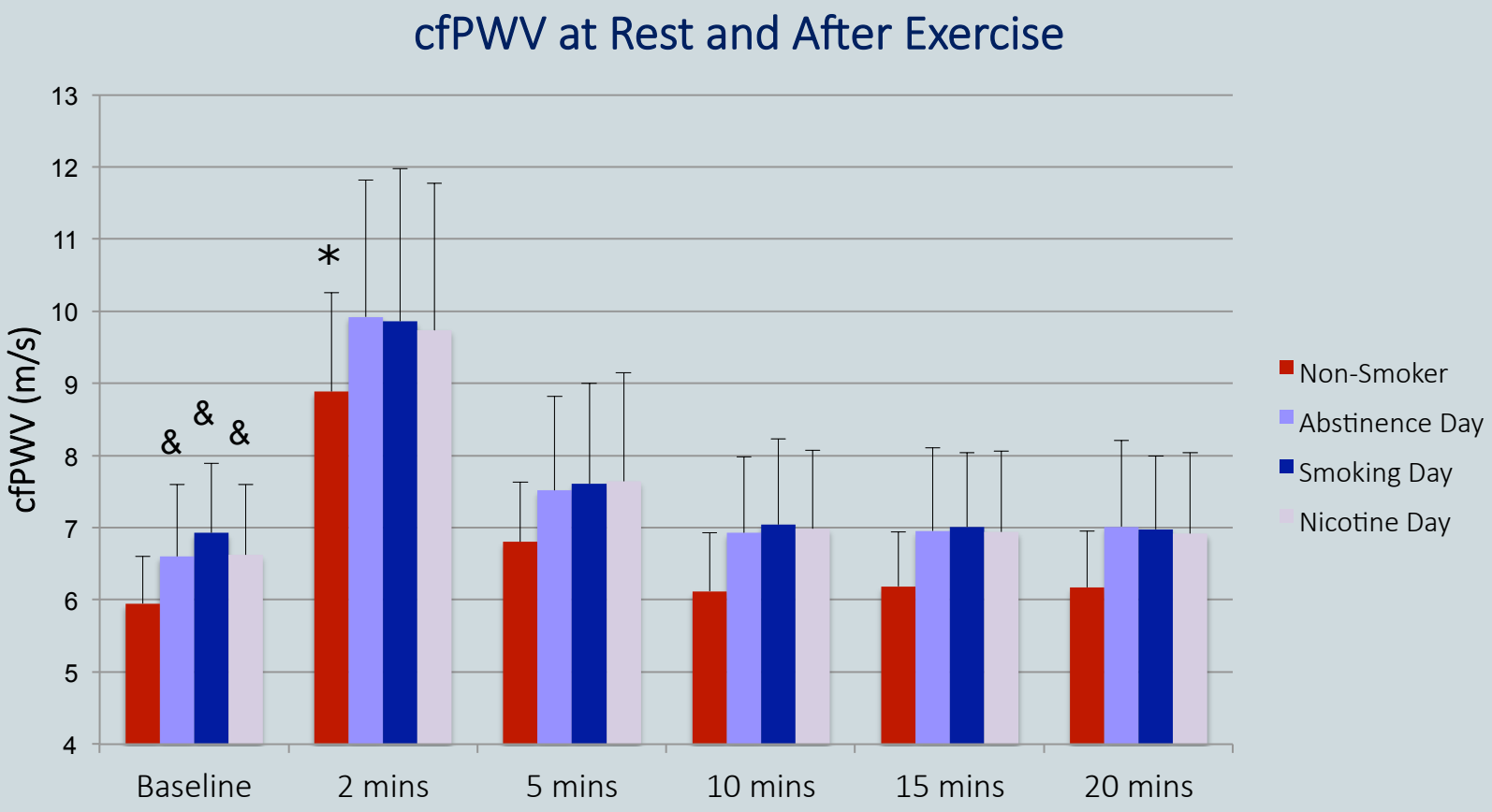
Exercise Test

Table 3 - Exercise Parameters				
	Non-Smokers	Smokers (Abstinence)	Smokers (Nicotine)	Smokers (Smoking)
Max HR (bpm)	191.2 +/- 10.15	182.1 +/- 14.11*	183.8 +/- 13.44*	182.2 +/- 13.41*
Max Exercise time (mins)	15.9 +/- 2.6	15.4 +/- 2.4	15.5 +/- 2.4	15.1 +/- 2.6

* P<0.05 vs. non-smokers after adjustment for age, sex, BMI, resting MAP

Ø Maximum HR and exercise time were higher in non-smokers compared to smokers under all conditions

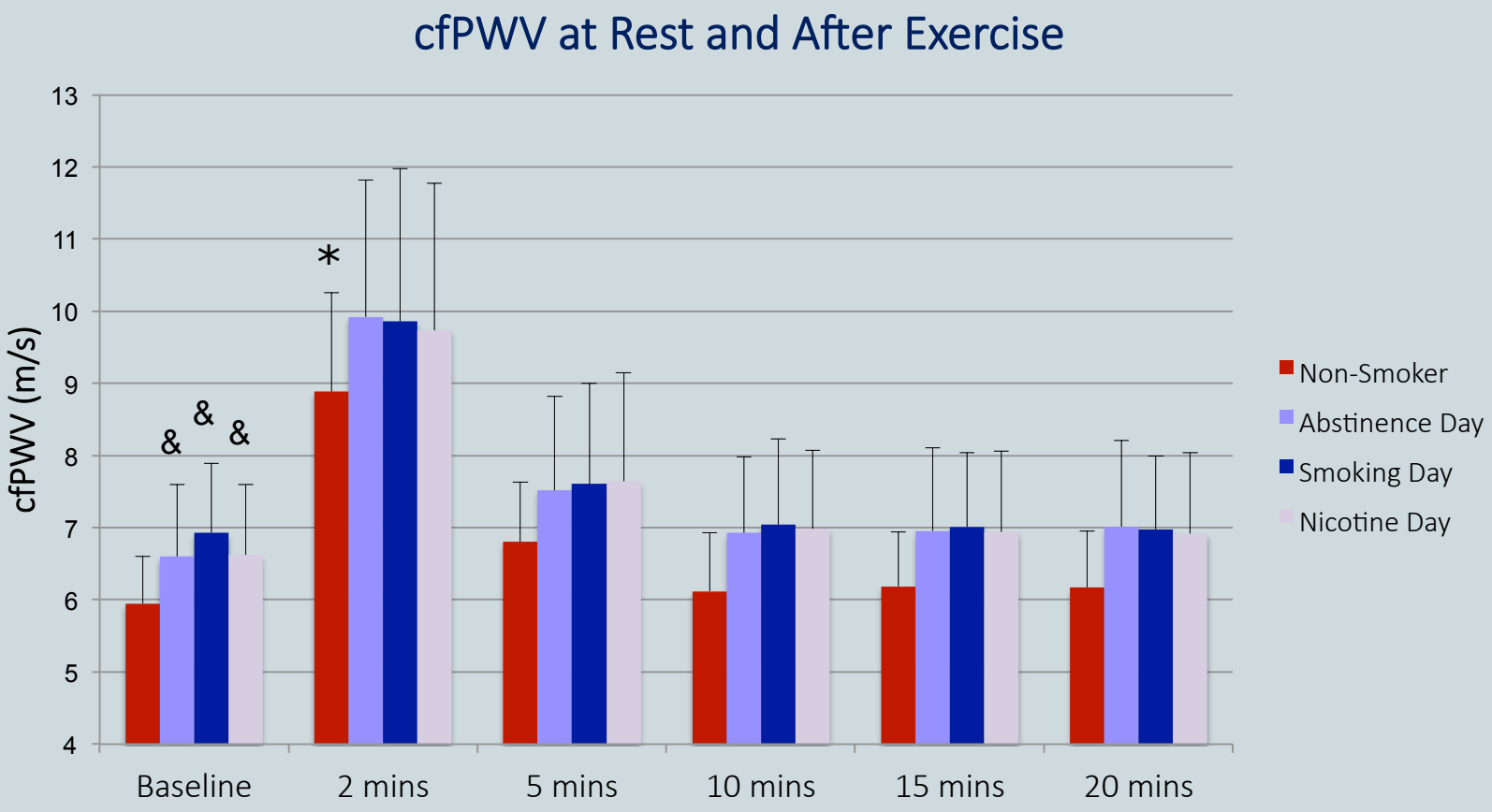
cfPWV



&P<0.05 vs. resting value in non-smokers, adjusted for age, sex, BMI, and MAP

*P<0.05 vs. resting value of the parameter, adjusted for resting MAP and exercise time

cfPWV



cfPWV is significantly higher in smokers under all 3 conditions

Greater recovery of cfPWV in non-smokers post-exercise

OPEN ACCESS Freely available online

PLoS one

Altered Arterial Stiffness and Subendocardial Viability Ratio in Young Healthy Light Smokers after Acute Exercise

Robert J. Doonan[1], Patrick Scheffler[1], Alice Yu[1], Giordano Egiziano[1], Andrew Mutter[1], Simon Bacon[2,3,4], Franco Carli[5], Marios E. Daskalopoulos[6], Stella S. Daskalopoulou[1]*

1 Department of Medicine, McGill University, Montreal, Quebec, Canada, **2** Department of Exercise Science, Concordia University, Montreal, Quebec, Canada, **3** Montreal Behavioural Medicine Centre, Hopital du Sacre-Coeur de Montreal, Montreal, Quebec, Canada, **4** Research Centre, Montreal Heart Institute, Montreal, Quebec, Canada, **5** Department of Anesthesia, Faculty of Medicine, McGill University, Montreal, Quebec, Canada, **6** Department of Vascular Surgery, Athens University, Athens, Greece

- Healthy light smokers and non-smokers
- Smokers under 3 conditions:
  - Abstinence day (chronic)
  - Smoking day (acute)
  - Nicotine
- Arterial stiffness measurements before and after exercise test to exhaustion

Doonan, Daskalopoulou, et al. PLoS One 2011;6:e26151

- Using the arterial stress test able to elicit evidence of vascular impairment in young healthy light smokers at an early stage

- Even light smoking in young healthy individuals appears to affect the ability of the vasculature to respond to increased demands

Clinical Implications

- The *arterial stress test* could facilitate better stratification of individual risk
- Smoking not a binary risk factor (presence/absence) and vascular damage not estimated indirectly (e.g. pack/years), but measured directly, by quantifying the vascular reserve through the arterial stress test
- This project act as models to study the effect of other risk factors, e.g. hypertension, diabetes, dyslipidemia, on arterial stiffness and the vascular reserve

Understanding the Mechanisms

Circulating miRNAs

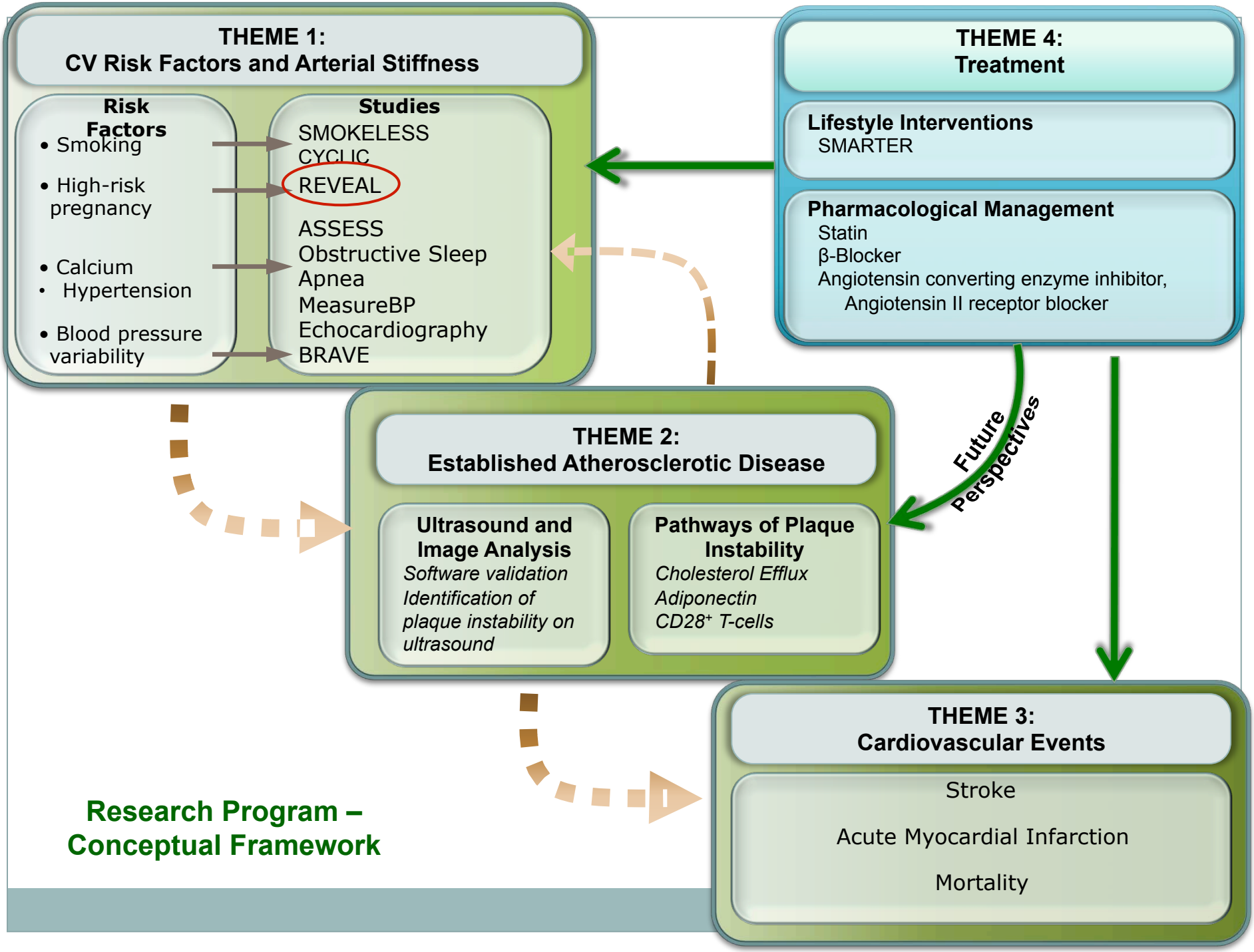
miRNA 221/222	miRNA 126	miRNA 210	miRNA 146a	miRNA 21	miRNA 133

Angiogenesis

Hypoxia Adaptation

Skeletal/Cardiac Muscle Contractility

Inflammation


THEME 1:
CV Risk Factors and Arterial Stiffness
Risk Factors
• Smoking
• High-risk pregnancy
• Calcium
• Hypertension
• Blood pressure variability
Studies
SMOKELESS
CYCLIC
REVEAL
ASSESS
Obstructive Sleep Apnea
MeasureBP
Echocardiography
BRAVE
THEME 4:
Treatment
Lifestyle Interventions
SMARTER
Pharmacological Management
Statin
β-Blocker
Angiotensin converting enzyme inhibitor,
Angiotensin II receptor blocker
Future Perspectives
THEME 2:
Established Atherosclerotic Disease
Ultrasound and Image Analysis
Software validation
Identification of plaque instability on ultrasound
Pathways of Plaque Instability
Cholesterol Efflux
Adiponectin
CD28+ T-cells
THEME 3:
Cardiovascular Events
Stroke
Acute Myocardial Infarction
Mortality
Research Program –
Conceptual Framework

PRE-ECLAMPSIA

Ten-Year, Thirty-Year, and Lifetime Cardiovascular Disease Risk Estimates Following a Pregnancy Complicated by Preeclampsia

Graeme N. Smith, MD, PhD,[1,2] Jessica Pudwell, MPH,[1,2] Mark Walker, MD, MSc,[3] Shi-Wu Wen, MB, PhD[3]; for the Pre-Eclampsia New Emerging Team

[1]Department of Obstetrics & Gynaecology, Kingston General Hospital, Queen's University, Kingston ON

[2]Department of Biomedical and Molecular Sciences, Kingston General Hospital, Queen's University, Kingston ON

[3]Department of Obstetrics and Gynecology, Ottawa Health Research Institute, University of Ottawa, Ottawa ON

Parts of this data were presented at the Society for Maternal–Fetal Medicine (2012) and Society for Gynecologic Investigation (2012).

10-year risk: OR 13.08 (95% CI 3.38-85.5)

30-year risk: OR 8.43 (95% CI 3.48-23.23)

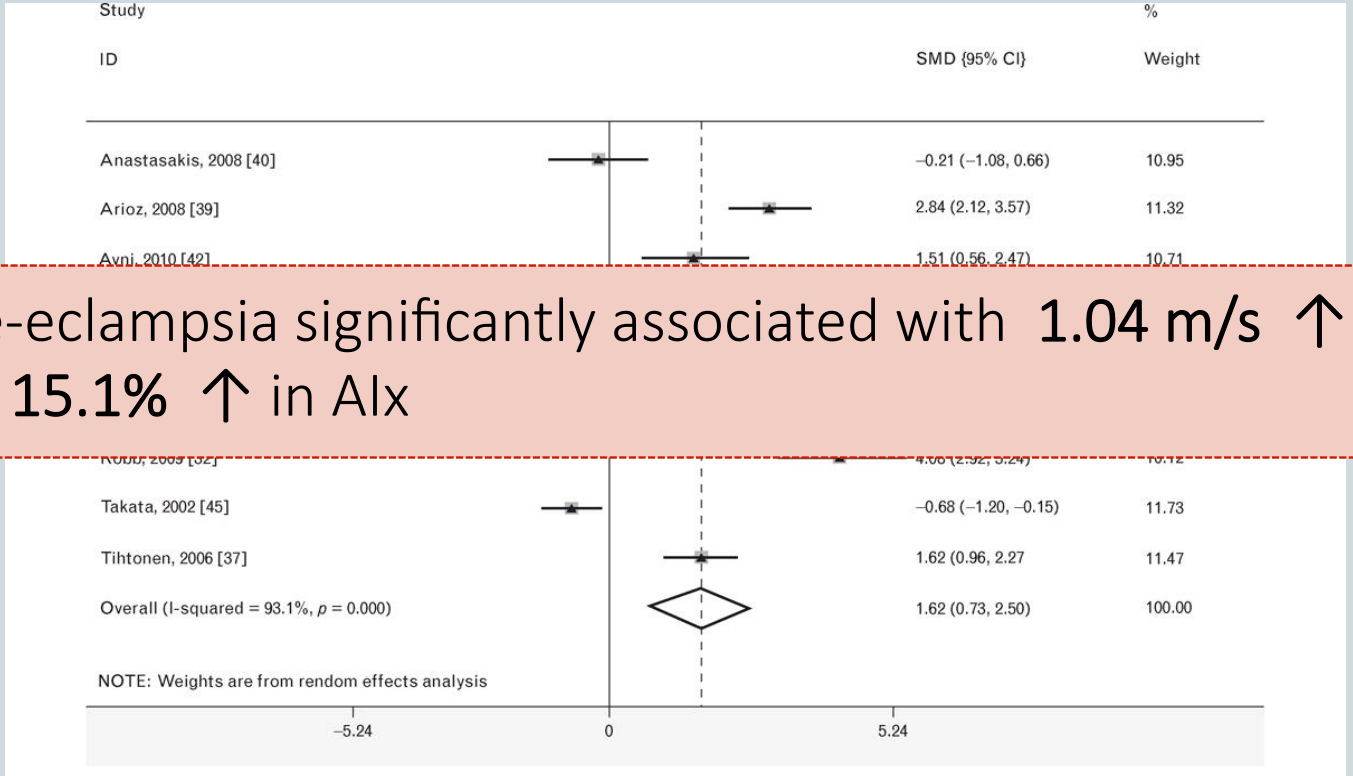
Lifetime risk: OR 3.25 (95% CI 1.76-6.11)

The association of preeclampsia with the future development of CVD makes pregnancy an early window of opportunity for the preservation of health and prevention of CVD

Smith, et al. J Obstet Gynaecol Can 2012;34:830-5

The association between preeclampsia and arterial stiffness

Anaïs Hausvater[a], Tania Giannone[a], Yessica-Haydee Gomez Sandoval[a], Robert J. Doonan[a,b], Constantine N. Antonopoulos[c], Ioannis L. Matsoukis[c], Eleni T. Petridou[c] and Stella S. Daskalopoulou[a,b]



M/a: Pre-eclampsia significantly associated with **1.04 m/s** ↑ in cfPWV & **15.1%** ↑ in AIx

Arterial stiffness is ↑ in pre-eclamptic women at the time of diagnosis

Hausvater, Daskalopoulou, et al. J Hypertens 2011;30:17-33

REVEAL (pRedictivE Value of artEriAl stiffness in the development of pre-ecLampsia)

Overarching objective is to fill important knowledge gaps with respect to the ability of arterial stiffness to predict the development of pre-eclampsia and recovery post-partum in high-risk nulliparous pregnant women with a singleton pregnancy

Fonds de recherche Santé Québec

Canadian Foundation for Women's Health / Fondation canadienne de la santé des femmes

HEART & STROKE FOUNDATION OF CANADA | FONDATION DES MALADIES DU CŒUR DU CANADA

REVEAL

Objective 1:

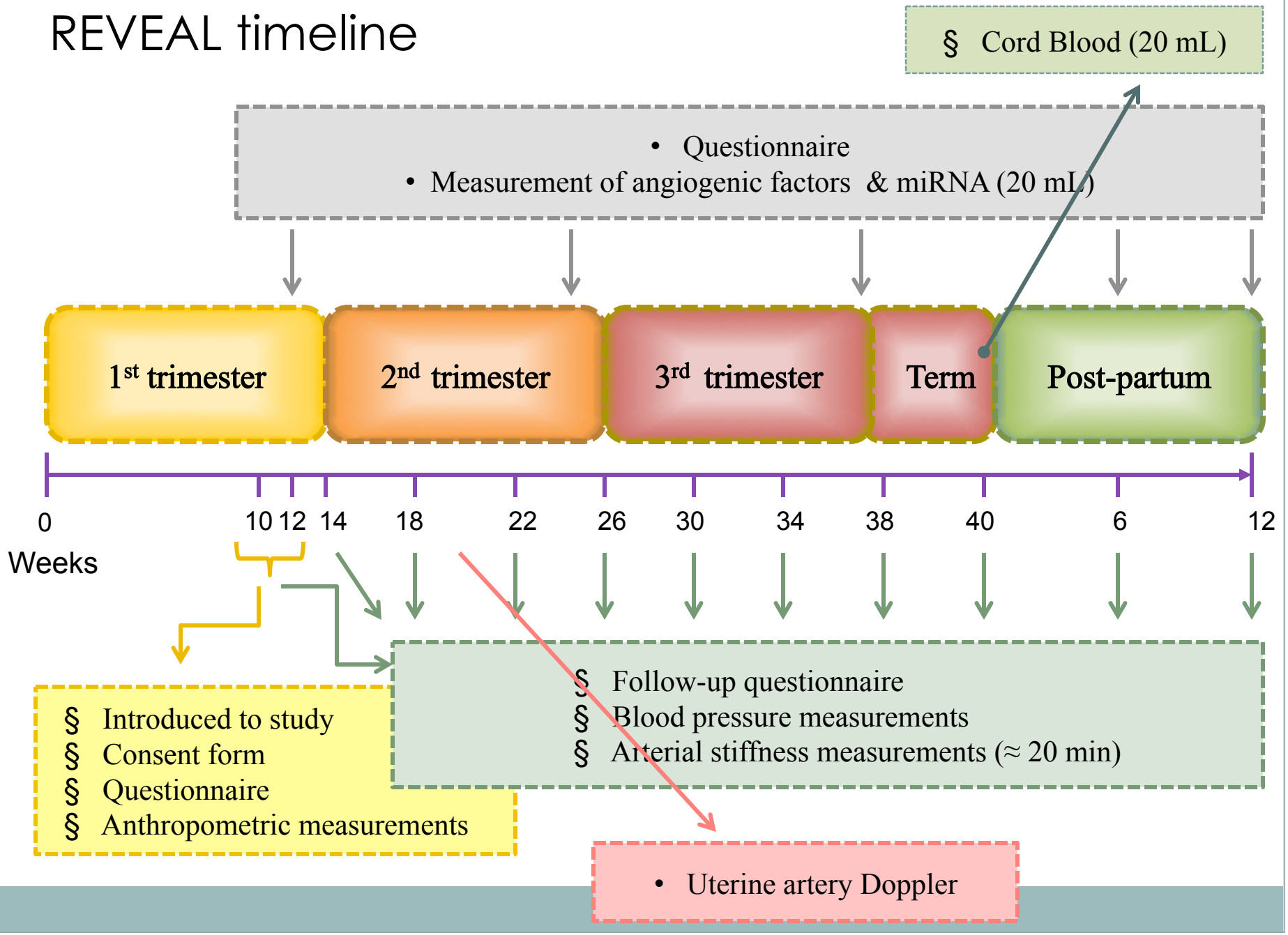
temporal changes in arterial stiffness during pregnancy and up to 12 weeks postpartum of those who develop versus those who do not develop pre-eclampsia

Objective 2:

a) the predictive value of arterial stiffness (according to level and timing) for pre-eclampsia as compared with the predictive value for pre-eclampsia of specific angiogenic factors or/and uterine artery Doppler (UAD), and

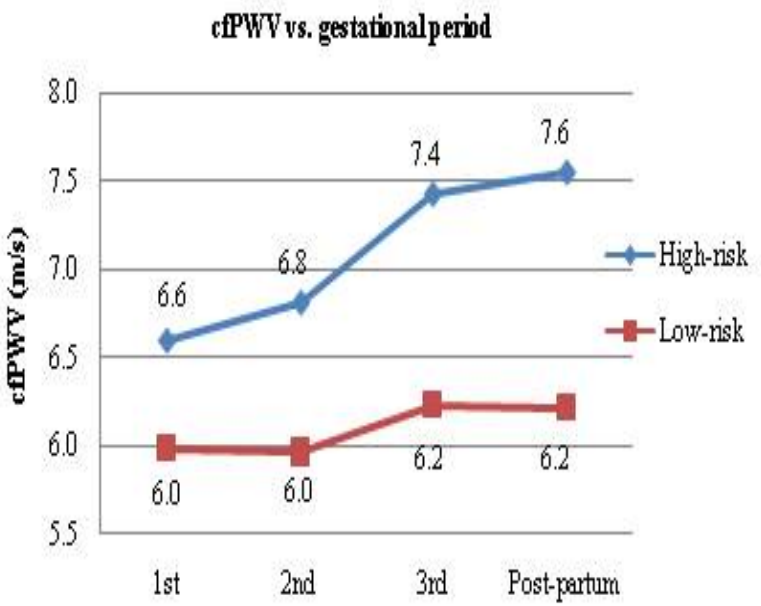
b) the additive value of arterial stiffness to angiogenic factors or/and UAD in predicting pre-eclampsia

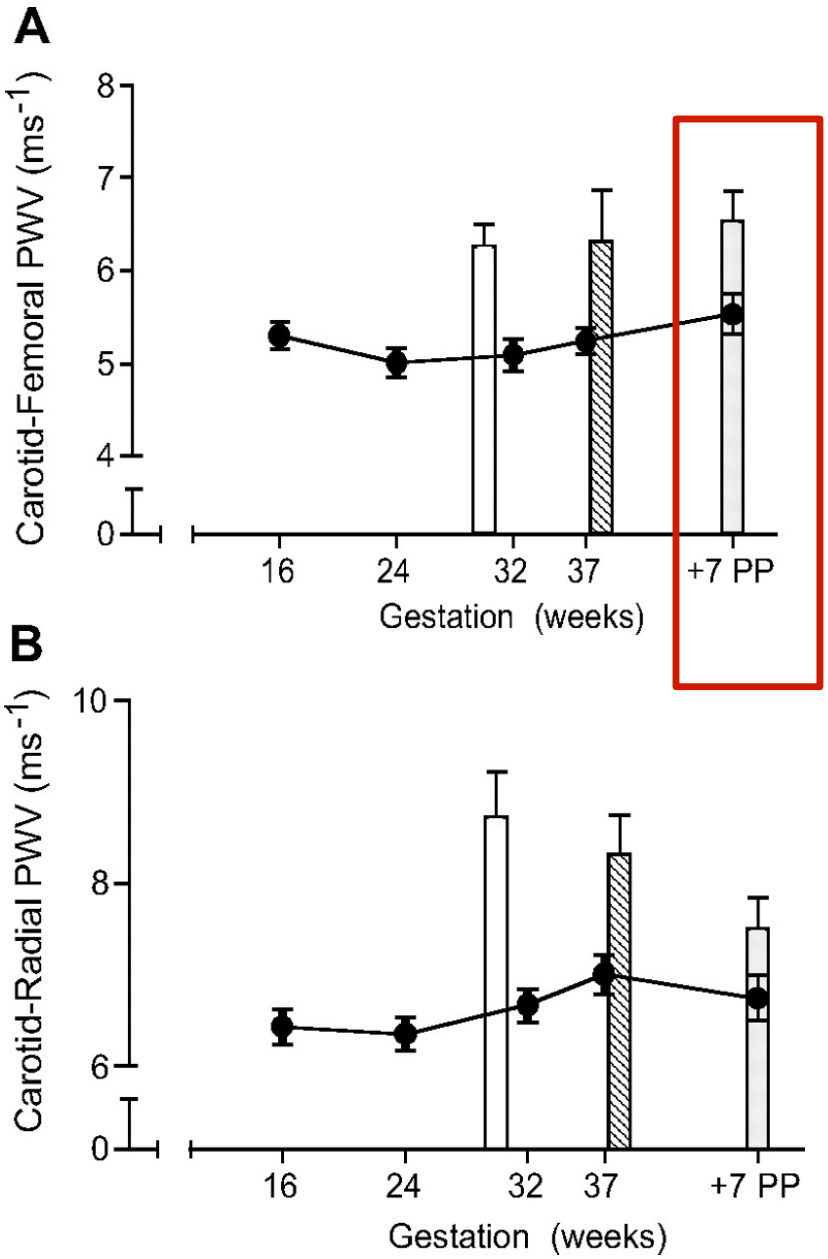
REVEAL timeline



REVEAL

Variable	Low-risk (n=36)	High-risk (n=13)
Age, y	33.6 (5.5)	36.1 (4.4)
Gestational week (weeks)	21.3 (7.8)	19.1 (8.4)
Body mass index (kg/m^2)	26.3 (6.1)	29.6 (4.1)
Peripheral systolic BP (mm Hg)	109.8 (9.0)	117.6 (13.1)
Peripheral diastolic BP (mm Hg)	65.2 (16.0)	74.9 (11.6)
Central systolic BP (mm Hg)	94.8 (9.5)	105.1 (15.1)
Central diastolic BP (mm Hg)	68.3 (10.5)	75.8 (11.6)
cfPWV (m/s)	6.0 (0.6)	6.6 (0.9)
crPWV (m/s)	7.5 (1.0)	8.0 (0.9)
AIx (%)	5.5 (11.5)	15.3 (13.3)



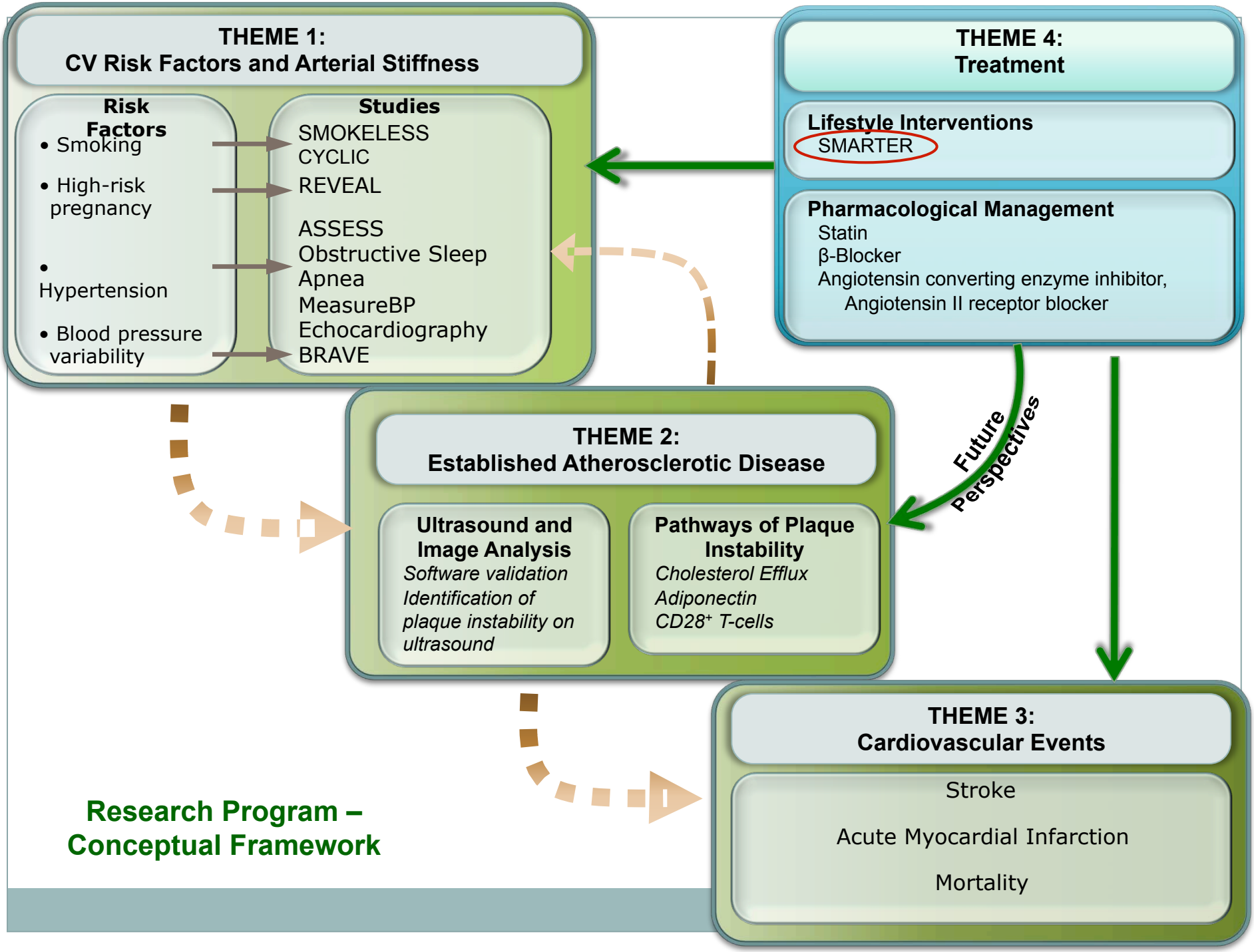


Robb, et al. Hypertension 2009, 53:952-8

CYCLIC (The effect of oral Contraceptive pills and the natural menstrual cYCLe on arterial stiffness and hemodynamICs)

	Early Follicular Phase			Late Follicular Phase			Luteal Phase		
	OCP-	OCP+	P	OCP-	OCP+	P	OCP-	OCP+	P
CfPWV (m/sec)	5.3±0.6	5.6±0.6	NS	5.3±0.6	5.5±0.7	NS	5.4±0.6	5.6±0.7	NS
CrPWV (m/sec)	7.2±1.1	7.7±0.9	NS	7.4±1.2	7.7±1.0	NS	7.1±0.8	7.8±1.0	NS
AIx (%)	-2.8±9.7	-0.9±11.1	NS	-2.5±8.9	-1.7±10.2	NS	-3.9±8.2	-3.0±10.3	NS
AIx75 (%)	-7.0±8.9	-6.0±12.5	NS	-7.6±10.2	-5.5±10.8	NS	-8.4±7.7	-8.4±10.2	NS
Heart rate (bpm)	63.0±7.0	62.7±9.5	NS	61.9±7.9	65.7±10.0	NS	63.8±7.6	64.1±10.1	NS
aorSBP (mmHg)	88.7±4.4	91.2±7.3	NS	89.1±5.4	92.0±8.2	0.03	88.3±5.1	91.3±6.0	0.02
aorDBP (mmHg)	66.9±5.1	68.8±6.7	NS	68.6±5.8	68.4±7.8	NS	67.6±4.6	68.3±5.5	NS
aorPP (mmHg)	21.8±3.7	22.3±4.6	NS	20.5±3.2	23.6±4.6	0.008	20.7±3.0	23.0±4.7	0.043
perMAP (mmHg)	77.1±4.5	79.3±7.0	NS	78.0±5.8	79.5±8.0	NS	77.1±4.6	79.1±5.3	NS
perSBP (mmHg)	103.6±5.8	105.6±8.8	NS	102.9±6.3	106.8±9.6	0.02	102.8±6.5	106.8±7.8	0.01
perDBP (mmHg)	66.3±5.2	68.7±6.0	NS	68.0±5.9	67.5±7.6	NS	66.9±4.5	67.8±5.7	NS
perPP (mmHg)	37.3±7.0	36.9±7.4	NS	34.9±5.5	39.3±7.3	0.011	35.9±5.2	39.0±7.0	NS
PPampl	1.71±0.15	1.66±0.16	NS	1.70±0.9	1.67±0.10	NS	1.73±0.09	1.70±0.10	NS

Yu, Daskalopoulou, et al. J Hypertens 2014 Jan;32:100-7

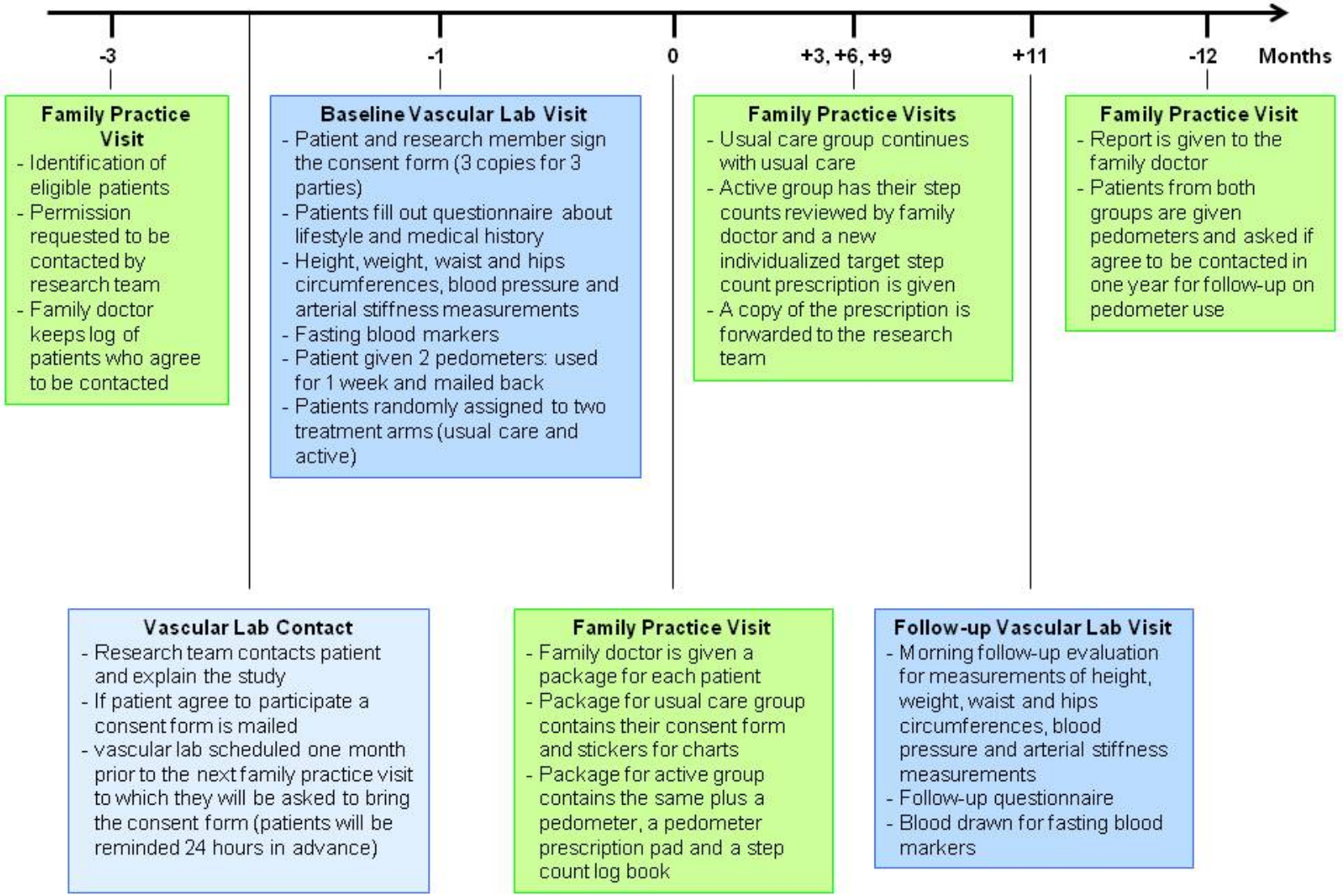

THEME 1:
CV Risk Factors and Arterial Stiffness
Risk Factors
• Smoking
• High-risk pregnancy
• Hypertension
• Blood pressure variability
Studies
SMOKELESS
CYCLIC
REVEAL
ASSESS
Obstructive Sleep Apnea
MeasureBP
Echocardiography
BRAVE
THEME 4:
Treatment
Lifestyle Interventions
SMARTER
Pharmacological Management
Statin
β-Blocker
Angiotensin converting enzyme inhibitor,
Angiotensin II receptor blocker
Future Perspectives
THEME 2:
Established Atherosclerotic Disease
Ultrasound and Image Analysis
Software validation
Identification of plaque instability on ultrasound
Pathways of Plaque Instability
Cholesterol Efflux
Adiponectin
CD28+ T-cells
THEME 3:
Cardiovascular Events
Stroke
Acute Myocardial Infarction
Mortality
Research Program –
Conceptual Framework

SMARTER (Step Monitoring to improve ARTERial health)

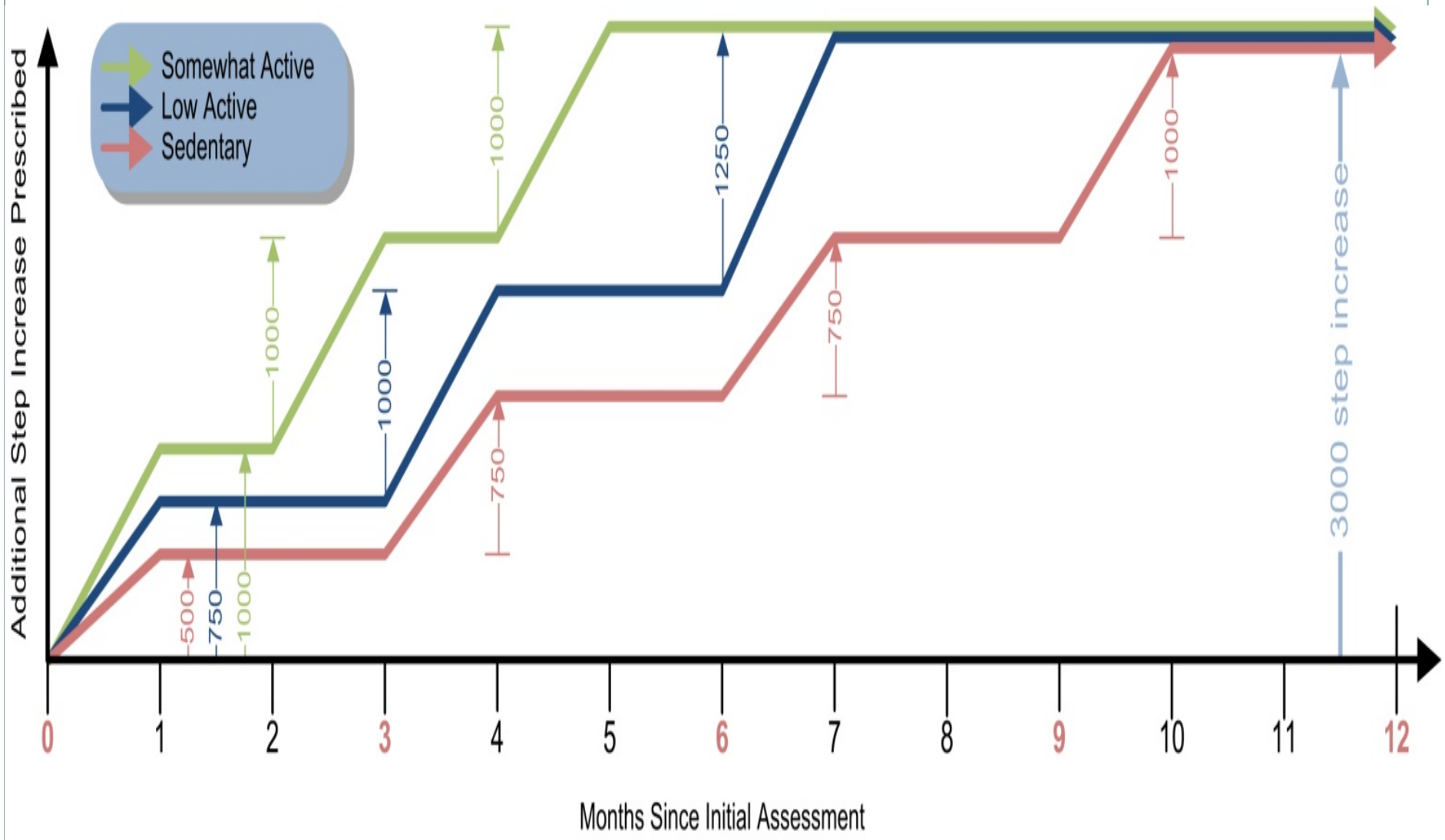
- Among sedentary overweight/obese adults with diabetes and/or hypertension do physician-delivered step count prescriptions integrated into usual care reduce arterial stiffness more than usual care alone, over a one-year period?

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

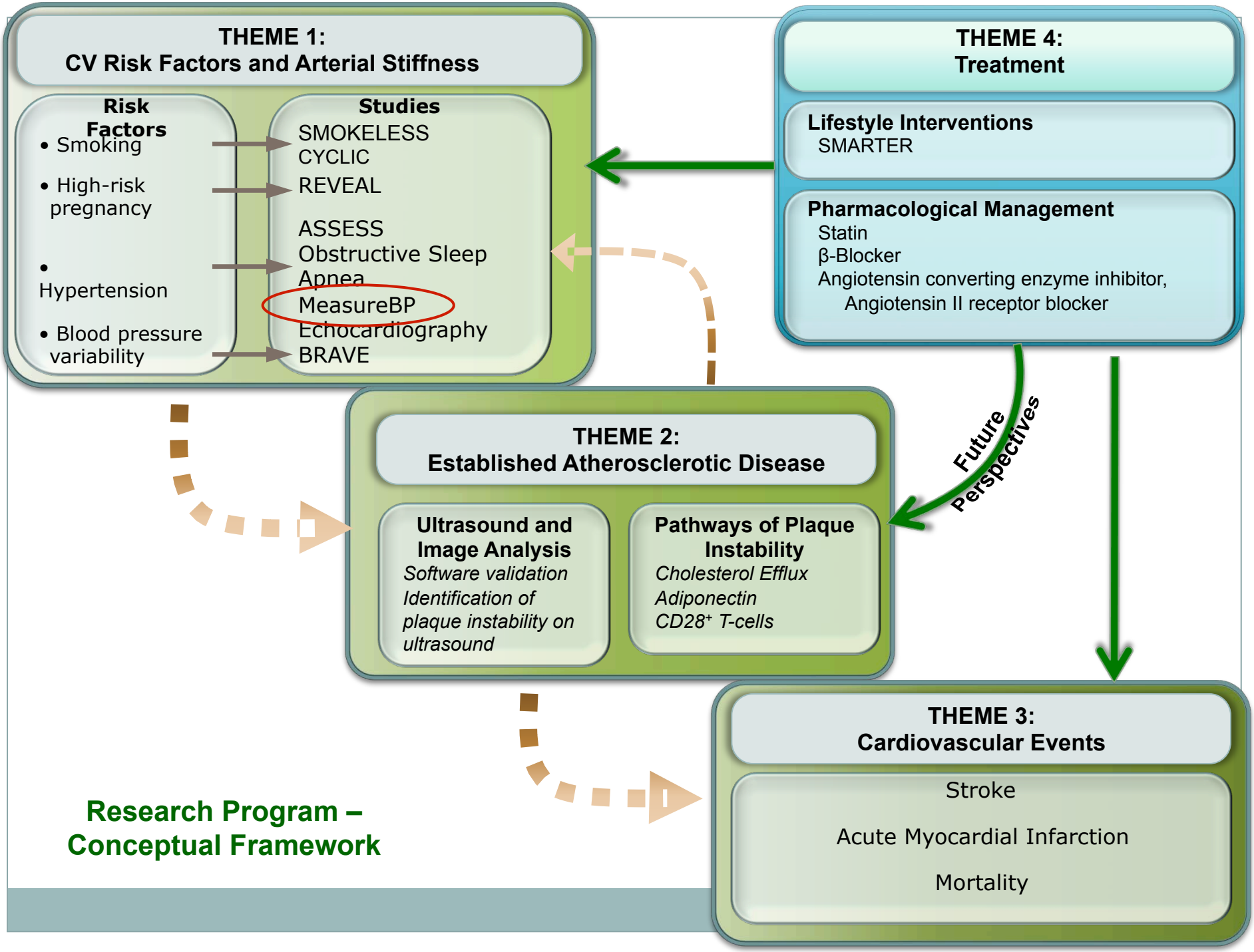
Dasgupta K, Rosenberg E, Daskalopoulou SS; SMARTER collaborators. Cardiovasc Diabetol 2014;13:7



Dasgupta K, Rosenberg E, Daskalopoulou SS; SMARTER collaborators. Cardiovasc Diabetol 2014;13:7



Dasgupta K, Rosenberg E, Daskalopoulou SS; SMARTER collaborators. Cardiovasc Diabetol 2014;13:7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Adiponectin
CD28+ T-cells
THEME 3:
Cardiovascular Events
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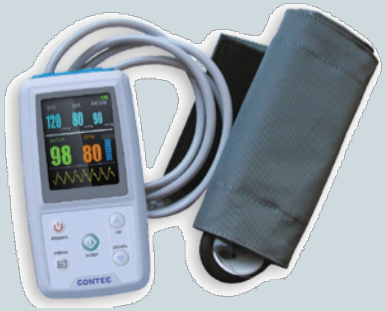
MeasureBP (MEthods of ASsessing blood pressUre: identifying thReshold and target valuEs)



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Aim

- To synthesize the available evidence to define the comparability between the **standardized manual OBPM** and:
  - Automated OBPM
  - ABPM
  - HBPM
- Through two components
  - Knowledge creation
  - Knowledge -to-action

My team…

Special Thanks

- Colleagues & Collaborators
- Team & Students
- Participants

Special Thanks

‘When you can measure what you are speaking about and can express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind’

Lord Kelvin, 1891

Thank you!

stella.daskalopoulou@mcgill.ca

Arterial stiffness

- Stiffening of the aortic wall and improper matching between aortic diameter and flow are associated with unfavorable alterations in pulsatile hemodynamics, including an increase in forward arterial pressure wave amplitude, which increases pulse pressure

- Stiffening of the aortic wall also is associated with elevated PWV and premature wave reflection. The resulting increase in pulsatile hemodynamic load increases cardiac afterload, reduces diastolic coronary flow, and damages microcirculation, particularly in high-flow organs, such as the kidneys and brain

Table 4. Correlates of Incident Hypertension During Examination Cycle 8

Predictor Variables During Examination Cycle 7	Odds Ratio (95% CI)	*P* Value
Tonometry model[a]		
Systolic blood pressure	3.3 (2.3-4.7)	<.001
Diastolic blood pressure	1.5 (1.1-1.9)	.004
Forward wave amplitude	1.6 (1.3-2.0)	<.001
Augmentation index	1.7 (1.4-2.0)	<.001
CFPWV	1.3 (1.0-1.6)	.04
Brachial artery model[b]		
Flow-mediated dilation	0.80 (0.67-0.96)	.01
Baseline brachial artery flow	1.23 (1.04-1.46)	.01

Abbreviation: CFPWV, carotid-femoral pulse wave velocity.

[a] Odds ratios per 1-SD difference derived from a single multivariable model in 1048 participants free of hypertension during examination cycle 7 (338 incident cases of hypertension, 32%); model was further adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), height, and triglycerides.

[b] Odds ratios per 1-SD difference derived from a single multivariable model in 957 participants free of hypertension with complete brachial artery data during examination cycle 7 (316 incident cases of hypertension, 33%); model was further adjusted for age, sex, body mass index, height, triglycerides, systolic and diastolic blood pressure, CFPWV, forward wave amplitude, and augmentation index.

Figure Legend:

JAMA. 2012;308(9):875-881. doi:10.1001/2012.jama.10503

Stroke and arterial stiffness

Rotterdam Study: arterial stiffness is an independent predictor of stroke in a population-based study of apparently healthy subjects

Adjusted HR for stroke in subjects in the 2nd and 3rd tertiles of the aortic PWV compared with the reference group were 1.22 and 2.28

Mattace-Raso FU, et al. Circulation 2006;113:657-63

Aortic stiffness is an independent predictor of fatal stroke in essential hypertension

Laurent S, et al. Stroke 2003;34:1203-6

Renal disease and arterial stiffness

Among patients with CKD stages 4 and 5, PWV and AIx were independent predictors for progression to ESRD

Arterial stiffness was an independent risk predictor of adverse CV outcomes in peritoneal dialysis patients after 2 years f/u

Arterial stiffness in CKD: the usefulness of a marker of vascular damage

Taal MW, et al. Nephron Clin Pract 2007;107:c177-81
Sipahioglu MH, et al. Perit Dial Int 2011 Mar 31. [Epub ahead of print]
Bellasi A, et al. Int J Nephrol;2011:734832. Epub 2011 May 23

Renal disease and arterial stiffness

- 95 recipients of kidney grafts f/u 107 ± 41 m (pairs recipients-donors)

- Donor cfPWV was a strong and independent predictor of the composite recipient outcome (MI, stroke, CV death, doubling of serum creatinine or development of ESRD)

Aoun Bahous S, et al. Nephrol Dial Transplant 2011 Oct 6. [Epub ahead of print]

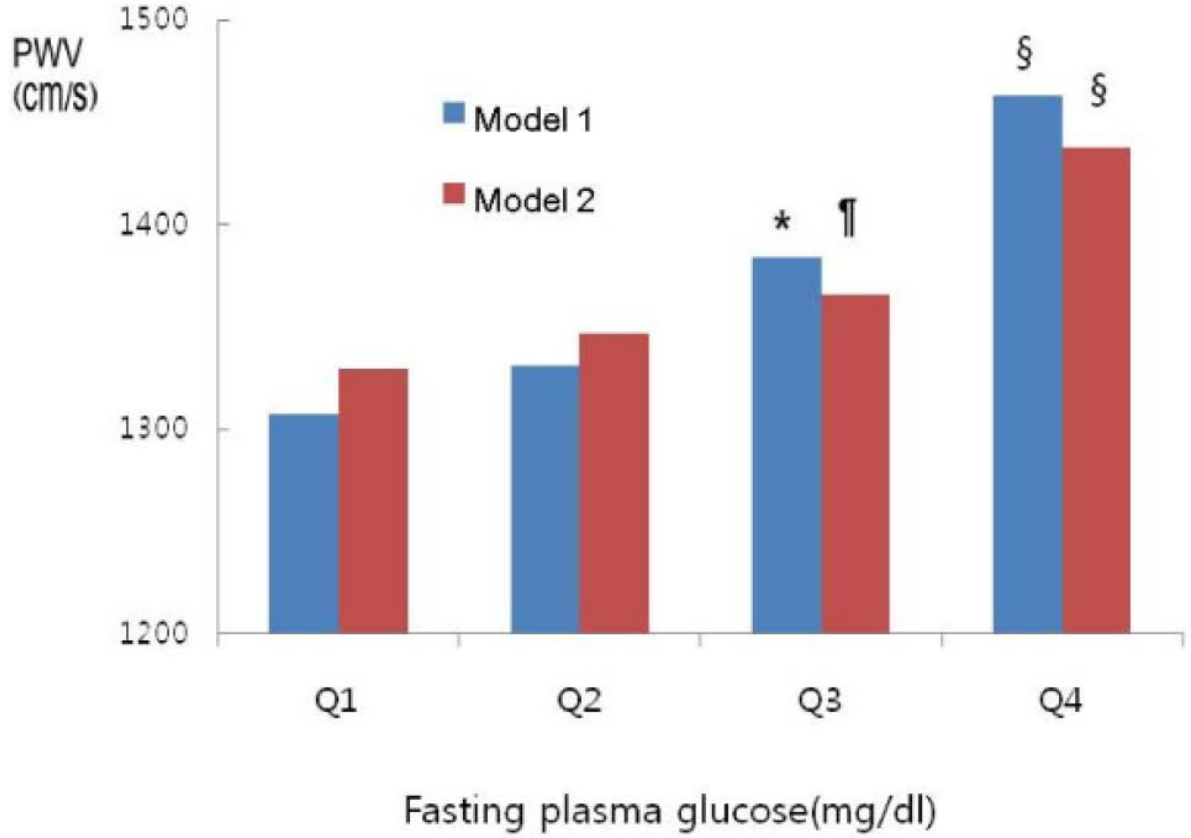
DM 1 & 2 / MetS and arterial stiffness

Arterial stiffness in diabetes and the metabolic syndrome—review of the evidence

- Arterial stiffness is increased in type 1 diabetes
  —this is an early phenomenon that occurs before the onset of clinically overt micro- or macrovascular complications
- Arterial stiffness is increased in type 2 diabetes
  —this is an early phenomenon, as much occurs in the impaired glucose metabolism state
  —the presence of micro- and macrovascular complications is associated with a further increase in arterial stiffness
- Arterial stiffness is also increased in the metabolic syndrome and in insulin-resistant states
  —subtle changes in metabolic variables (not fully developed diabetes) affect arterial stiffness from an early age

Diabetes is a disease of accelerated arterial ageing, as shown by stiffer arteries and consequent steeper increases in pulse pressure with age in these subjects

Stehouwer CD, et al. Diabetologia 2008;51(4):527-39



Mean values of brachial-ankle PWV according to FPG quartile in non-diabetic healthy subjects

*P<0.05 vs. Q1 and Q2, § P<0.05 vs. Q1, Q2, and Q3, ¶ P<0.05 vs. Q1
Model 1; adjusted for age, sex
Model 2; adjusted for age, sex, SBP, DBP, BMI, resting HR, hs-CRP, HDL-c, and non HDL-c

Shin JY, et al. Cardiovasc Diabetol 2011;10:30

MetS and childhood and arterial stiffness

- MetS in childhood was associated with a higher aortic PWV after 21-year f/u when compared with those without MetS in childhood ($P < 0.007$)
- An increasing number of the MetS components in childhood were associated with increased PWV in adulthood (P for trend = 0.005)
- Subjects who recovered from the MetS during the 21-year follow-up period had lower PWV than those with persistent MetS ($P < 0.001$)

Koivistoinen T, et al. Ann Med 2011;43(4):312-9

Obesity and childhood and arterial stiffness

CCC 2010: Dr. Harris from B.C. Children's Hospital

Obese kids (13 y.o.) significantly higher arterial stiffness than normal weight counterparts

OSA and arterial stiffness

Hypertension Research (2011) 34, 23–32
 0916-9636/11 $32.00
www.nature.com/hr

REVIEW

Increased arterial stiffness in obstructive sleep apnea: a systematic review

Robert J Doonan[1], Patrick Scheffler[1], Marek Lalli[1], R John Kimoff[2], Eleni Th Petridou[3], Marios E Daskalopoulos[4] and Stella S Daskalopoulou[1]

Obstructive sleep apnea is a prevalent disease that is associated with significant morbidity and mortality, particularly due to cardiovascular disease. An emerging cardiovascular risk factor, arterial stiffness, may also be involved in the cardiovascular complications of obstructive sleep apnea. The purpose of this review was to summarize the current literature regarding the effect of obstructive sleep apnea on arterial stiffness. We conducted a systematic literature review using PubMed, Embase and the Cochrane Library. We identified 24 studies that met search criteria investigating the effect of obstructive sleep apnea on arterial stiffness. Arterial stiffness was found to be increased in obstructive sleep apnea patients compared with controls or increased in severe compared with mild sleep apnea. In some studies, a positive correlation was identified between the degree of arterial stiffness and sleep apnea severity. In the two randomized, controlled trials and the two nonrandomized trials identified, treatment of obstructive sleep apnea with continuous positive airway pressure led to significant decreases in arterial stiffness. Obstructive sleep apnea appears to have an independent effect on arterial stiffness, which may be one of the mechanisms accounting for sleep apnea-associated cardiovascular risk.
Hypertension Research (2011) **34**, 23–32; doi:10.1038/hr.2010.200; published online 21 October 2010

Keywords: arterial stiffness; obstructive sleep apnea; pulse wave velocity; sleep disordered breathing

Doonan RJ, et al. Hypertens Res 2011;34(1):23-32

Arterial stiffness and bone demineralization: the Baltimore longitudinal study of aging

Arterial stiffness is inversely related to cortical bone area in women, independent of age and other shared risk factors

Giallauria F, et al. Am J Hypertens 2011;24(9):970-5

Treatment & Arterial Stiffness

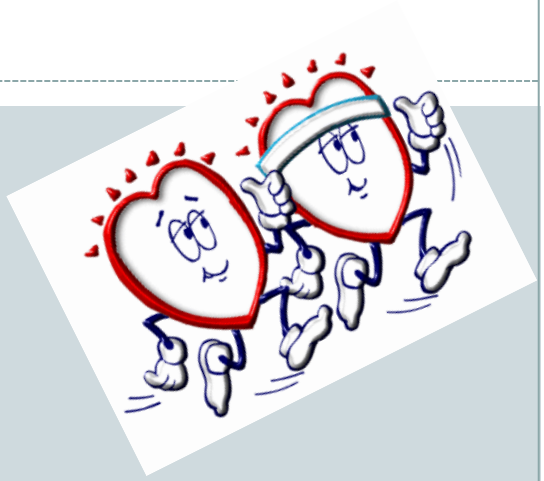
Wine - Chocolate

- Review – controversial
- Red wine, arterial stiffness and central hemodynamics
- Acutely, decreases AIx and central BP due to central vasodilatatory effect

- Higher chocolate intake was an independent determinant of low arterial stiffness and wave reflection and lower central PP

Karatzi K, et al. Curr Pharm Des 2009;15:321-8
Vlachopoulos CV, et al. Am J Cardiol 2007;99:1473-5

Exercise and arterial stiffness



- Aerobic Exercise
- Interval better than continuous
- Low-intensity resistant exercise

- High- & medium–intensity resistant exercise
- Eccentric

Conduit Artery Function Evaluation (CAFE) trial

- Substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

  (n=2199, f/u 4 yrs)

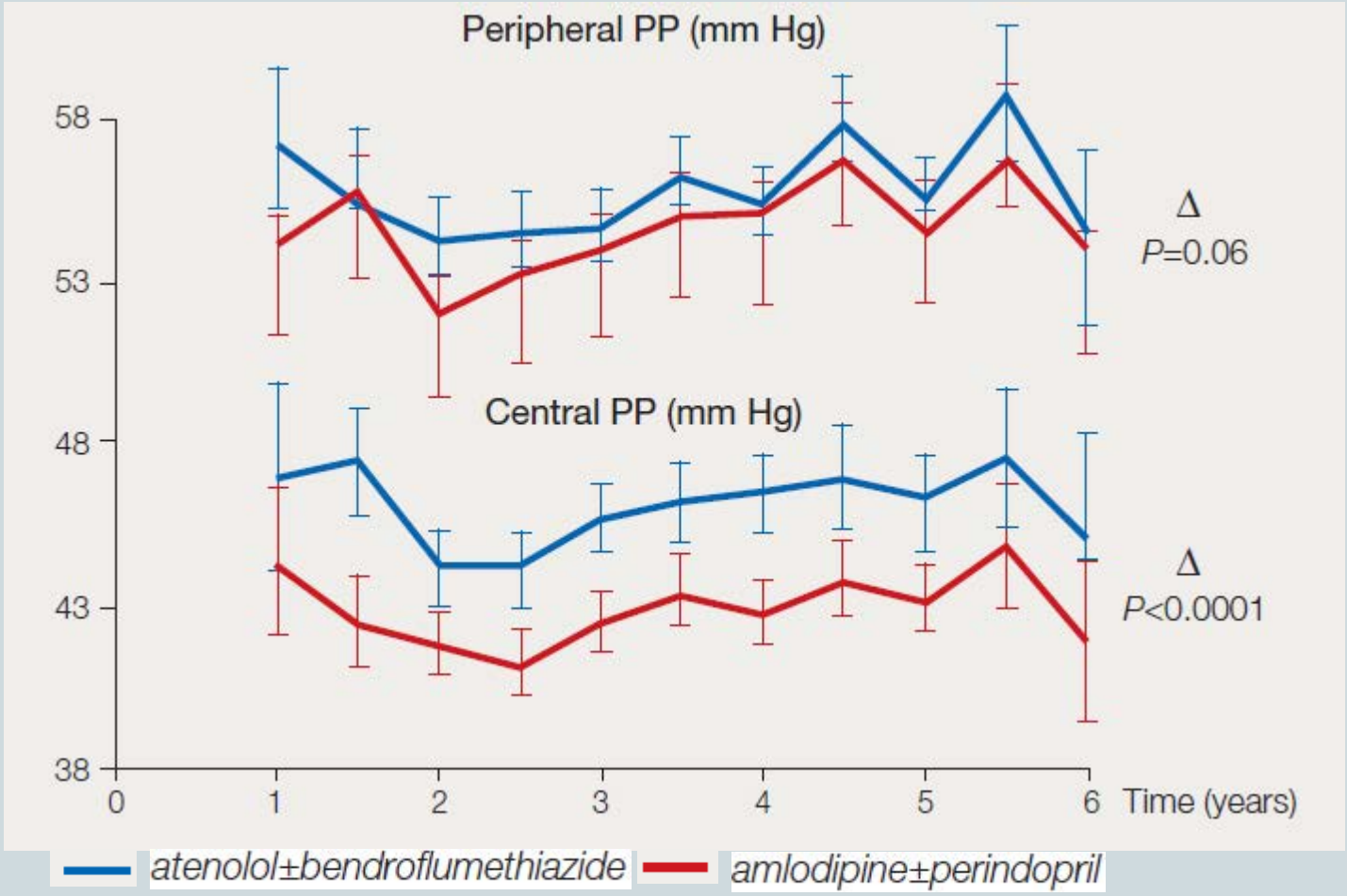
- Atenolol & thiazide vs. amlodipine & perindopril

- Similar effects on brachial SBP and PP

- Greater reductions in central SBP and PP with amlodipine & perindopril

Williams B, et al. Circulation 2006; 113:1213-25

Conduit Artery Function Evaluation (CAFE) trial



Williams B, et al. Circulation 2006; 113:1213-25

Pharmacological treatment

- ACEi (peri-, capto-, quina-, rami-, fosinopril)
- ARBs (valsa-, losa-, telmisartan)
- CCBs
- Aldosterone antagonists
- certain β-blockers

can modify the arterial structure independently of the effect on BP

Winer N, et al. Curr Hypertens Rep 2001;3:297-304
Mahmud A, et al. Expert Rev Cardiovasc Ther 2003;1:65-78
Duprez DA. Cardiovasc Drugs Ther 2010;24:305-10

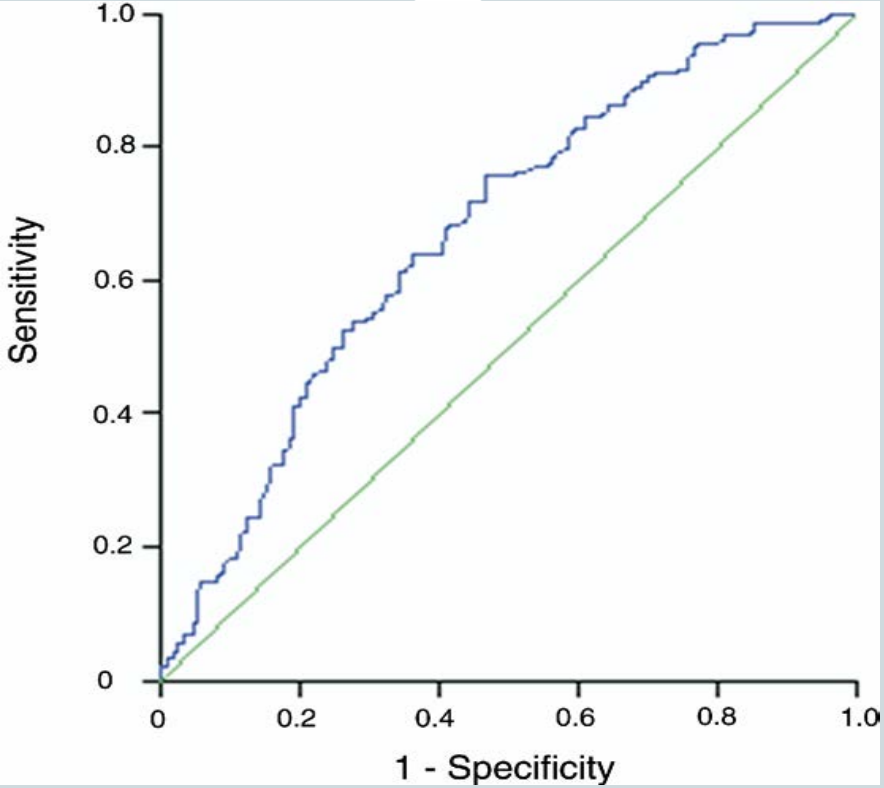
REASON (perindopril & indapamide vs. atenolol)

cfPWV measured in hypertensive subjects before initiation of antihypertensive drug treatment was

- associated with the degree of treatment-induced BP reduction
- an independent predictor of effective BP control after 12 months of treatment

Protogerou A, et al. J Am Coll Cardiol 2009;53:445–51

REASON



ROC analysis evaluating the ability of cfPWV at baseline to predict the adequate control of SBP (140 mm Hg) after 12 months of drug treatment (area under curve 0.67, p 0.001, 95% CI 0.62-0.73)

Protogerou A, et al. J Am Coll Cardiol 2009;53:445-51

Summary

- Not all antihypertensive agents reduce stiffness
- The strongest evidence is for ACEi, ARBs, and CCBs, which have been shown to reduce PWV and arterial wave reflection
- Evidence for β-blockers is less clear-cut, although some studies show a reduction in PWV
- Diuretics have limited effect on arterial stiffness
- Combinations maybe better than monotherapy
- Statins may improve stiffness

Arterial Stiffness: Cause or Effect of Hypertension

Arterial Stiffness: Cause and Effect of Hypertension

‘When you can measure what you are speaking about and can express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind’

Lord Kelvin, 1891

Thank you!

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Complior study

- First interventional trial using PWV as the end point
- 1703 hypertensive patients (50±12 y.o.)

At baseline: SBP, 158±15 mm Hg; DBP, 98±7 mm Hg; cfPWV, 11.6±2.4 m/s

- 6 m treatment perindopril, adding indapamide if BP >140/90 mm Hg

At 2 and 6 months: significant decreases (*P<0.001*) in

- BP (SBP, -23.7±16.8 mm Hg; DBP, -14.6±10 mm Hg)
- cfPWV (-1.1±1.4 m/s)

Asmar R, et al.; on behalf of the Scientific, Quality Control, Coordination and Investigation Committees of the Complior Study. J Hypertens 2001;19:813-8

ACEi

- Perindopril accutely and chronically improved aortic compliance, mainly by increasing distensibilty

- Also evidence with captopril, quinapril, ramipril, fosinopril

Benetos A, et al. J Hypertens 1990;8: 819-26
Kool MJ, et al. J Hypertens 1995:13:839–48

ACEi vs. diuretics

- ACEi perindopril vs. HCTZ + amiloride for 6 m in pts with mild-to-moderate hypertension

- For the same brachial BP reduction

  HCTZ + amiloride decreased brachial artery stiffness only but had no effect on carotid and femoral distensiblity

  perindopril decreased stiffness in all 3 arteries

Kool MJ, et al. J Hypertens 1995:13:839-48

Impact of aortic stiffness attenuation on survival of patients in ESRD

- 150 ESRD patients (52±16 y.o.) – f/u 51±38 m
- BP was controlled by adjustment of "dry weight" and, when necessary, with ACEi, CCBs, and/or ß-blockers, or in combination
- 59 deaths

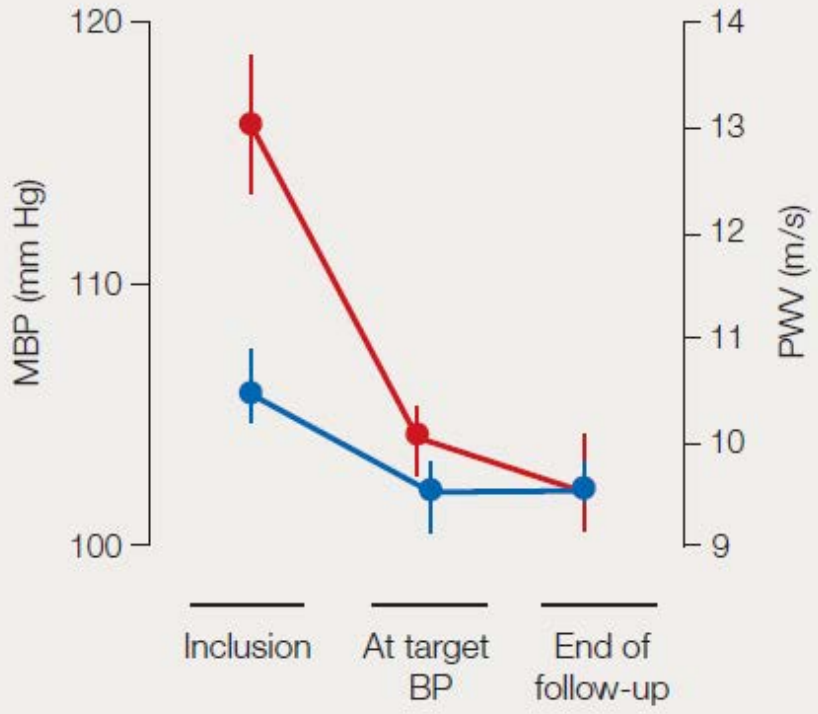
Results

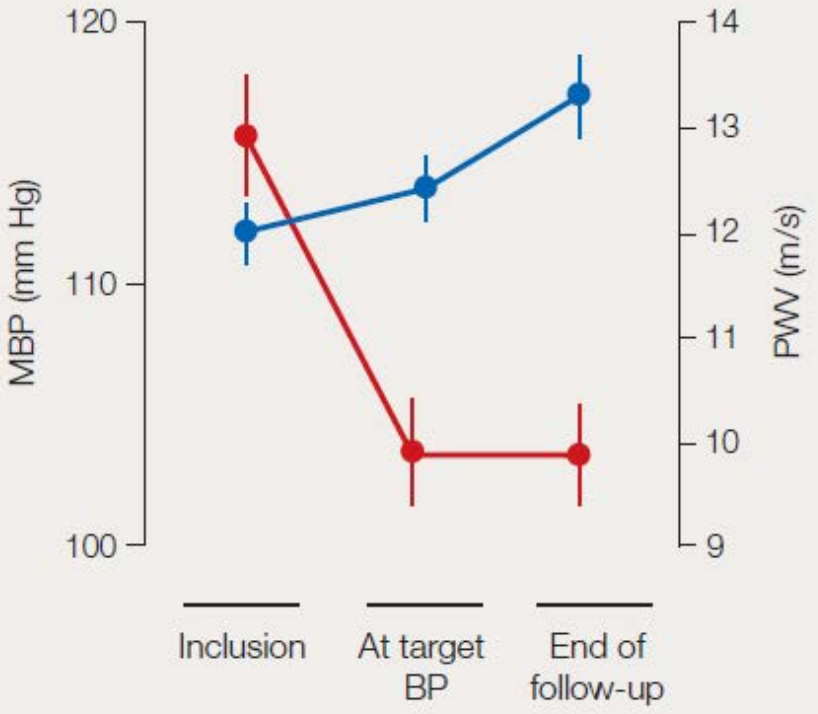
Absence of PWV decrease in response to BP decrease was an independent predictor
adjusted risk ratio 2.59, 95% CI 1.51-4.43 for all-cause mortality
2.35, 95% CI 1.23-4.41 for CV mortality

Survival was positively associated with ACEi use
adjusted risk ratio 0.19, 95% CI 0.14-0.43 for all-cause mortality
0.18, 95% CI 0.06-0.55 for CV mortality

Guerin AP, et al. Circulation. 2001;103:987-92

Impact of aortic stiffness attenuation on survival of patients in ESRD





Guerin AP, et al. Circulation. 2001;103:987-92

REASON study

- The ACE inhibitor perindopril, combined with low-dose indapamide, was compared for 1 year of treatment with the ß-blocker atenolol
- For a similar DBP reduction, perindopril/indapamide decreased SBP significantly more than atenolol, especially central than brachial SBP
- After 1 year, the difference between brachial and central SBP was maintained by perindopril/indapamide (8.28 ± 1.53 mm Hg) and significantly attenuated by atenolol (0.29 ± 1.61 mm Hg)
- The two drugs lowered PWV equally, but only perindopril/indapamide reduced central PP and AIx
- Perindopril/indapamide decreased cardiac hypertrophy more than atenolol
- Similar findings were observed when atenolol was compared to the ARB irbesartan

London GM, et al.; on behalf of the REASON Project. J Am Coll Cardiol 2004;43:92-9
de Luca N, et al. J Hypertens 2004;22:1623-30
Schneider MP, et al. J Renin Angiotensin Aldosterone Syst 2008;9:49-56

Substudy of ASCOT

- Brachial BP did not differ significantly between groups
- Carotid SBP was significantly lower (P<0.001) in amlodipine / perindopril (127±12 mm Hg vs. 133 ±15 mm Hg
- This difference is probably due to a lesser magnitude of wave reflection

Manisty CH, et al. Hypertension 2009;54:724-30

Changes in central hemodynamic parameters and PWV from baseline to week 12

Type 2 DM and HTN – Treatment with valsartan for 12 weeks

Sphygmocor parameter	Baseline value	Week 12 value	*P* value
Heart rate, bpm	71.3±11.4	69.7±10.8	0.054
Aortic augmentation index, %	29.5±7.4	27.8±7.9	<0.05
Aortic pulse pressure, mm Hg	44.4±8.5	38.9±10.2	<0.001
Subendocardial viability ratio	144.5±26.3	147.9±28.1	0.060
Ejection duration, msec	372.0±74.0	368.0±41.0	0.092
PWV, m/sec (n=47)	10.9±1.1	10.0±1.2	<0.05

Continuous parameters are presented as mean±standard deviation.
PWV, pulse wave velocity.

Also evidence for losartan and telmisartan

Kim JH, et al. Diabetes Metab J 2011;35(3):236-42

CCB vs. Diuretic

- 207 pts with HTN treated with olmesartan for 12 w followed by additional use of either CCB (azelnidipine) or diuretic (HCTZ) for 24 w
- Similar reduction in brachial SBP (2.6 mm Hg, 95% CI, –2.2 to 7.5]; P=0.29)
- The reduction in central SBP in the olmesartan/azelnidipine group was significantly greater than that in the olmesartan/diuretic group (difference between groups 5.2 mm Hg, 95% CI, 0.3 to 10.2; P=0.039)
- Aortic PWV showed significantly greater reduction with the olmesartan/azelnidipine than with olmesartan/HCTZ (0.8 m/s, 95% CI, 0.5 to 1.1; P<0.001)

Matsui Y, et al. Hypertension 2009;54:716-23

CCB vs. Diuretic

The combination of olmesartan / azelnidipine had a more beneficial effect on central SBP and aortic stiffness than the combination of olmesartan / hydrochlorothiazide, despite the lack of a significant difference in brachial SBP reduction between the two treatments

Matsui Y, et al. Hypertension 2009;54:716-23

Statins

Some preliminary data suggest that statins may also lower arterial stiffness

RCT, CKD stage 2–4

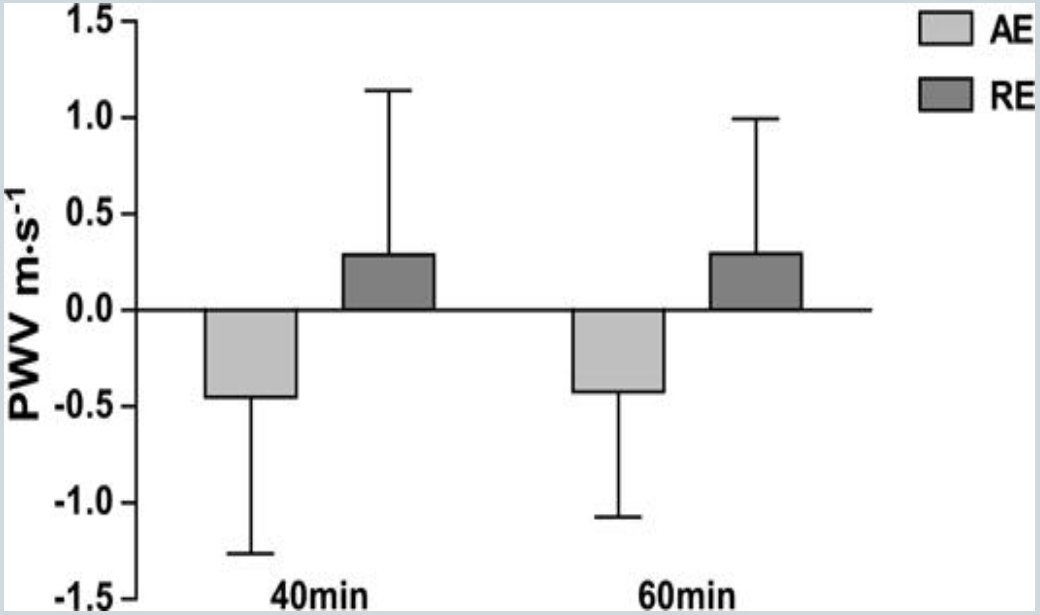
atorvastatin 10 mg (n=19) vs. placebo (n=18) for 3 yrs

Aortic PWV significantly increased in the placebo group, but not in the atorvastatin group

Fassett RG, et al. J Atheroscler Thromb 2010;17(3):235-41

Changes in arterial distensibility after acute resistance vs. aerobic exercise

- After ***aerobic exercise*** central PWV ↓ 8% and remained at this level through 60 min
- After ***resistance exercise*** central PWV ↑ 9.8% at 40 and 60 min post-exercise



Scott C, et al. J Strength Cond Res 2010;24:2846-52

Effects of Continuous Positive Airway Pressure (CPAP) treatment for OSA in arterial stiffness: A meta-analysis

- 13 studies (n=531 patients)
- 5 different meta-analyses were performed assessing:
- a) all indices of arterial stiffness, b) AIx, c) all PWV, d) brachial-ankle PWV, and e) cf PWV

Results

- a) A significant improvement of all indices of arterial stiffness was observed (SMD= -0.71; 95% CI: -1.12 to -0.30)
- b) AIx (WMD= -3.88; 95% CI: -6.57 to -1.19)
- c) all PWV (WMD=-0.87; 95% CI: -0.98 to -0.77)
- d) brachial-ankle PWV (WMD= -0.86; 95% CI: -0.97 to -0.75)
- e) cfPWV (WMD= -1.21; 95% CI:-1.92 to -0.50)

Significant improvements in all different indices of arterial stiffness after CPAP treatment in patients with OSA

Vlahantoni I, et al. Sleep Medicine Reviews 2011

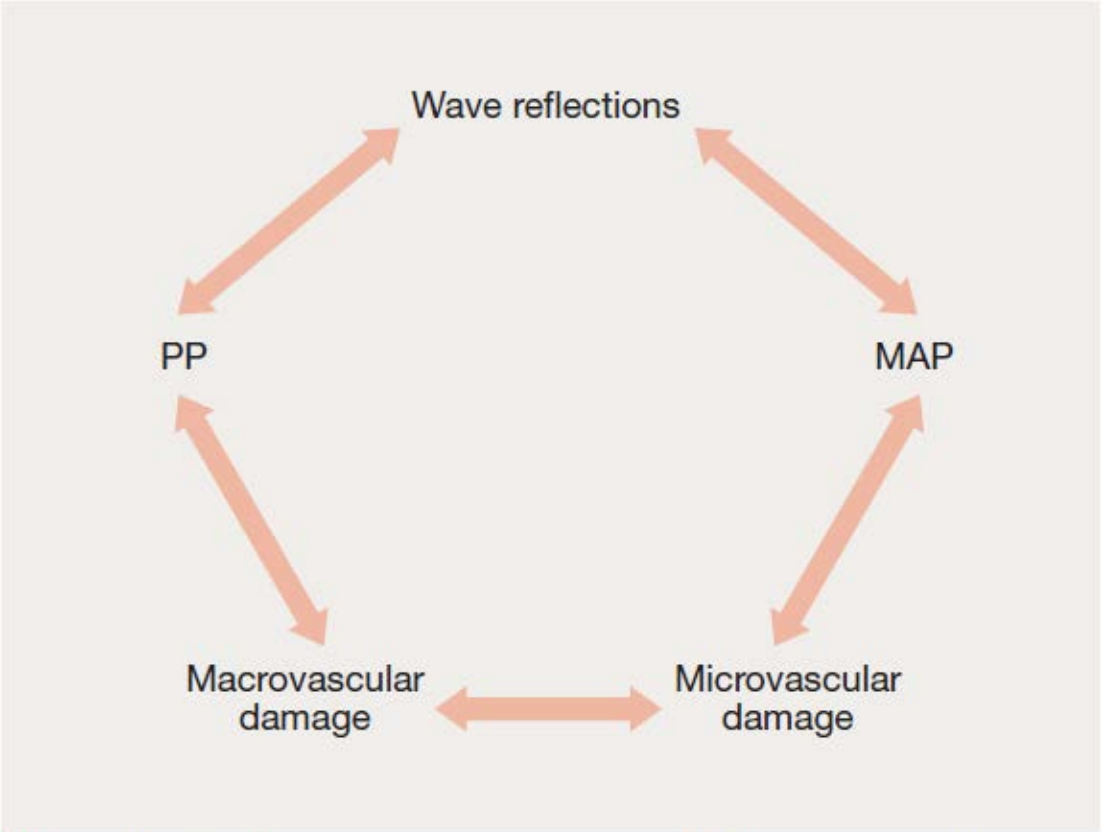


Figure 6. Cardiovascular prevention and its treatment: a vicious circle involving macro- and microcirculation.

Abbreviations: MAP, mean arterial pressure; PP, pulse pressure.

Conclusion

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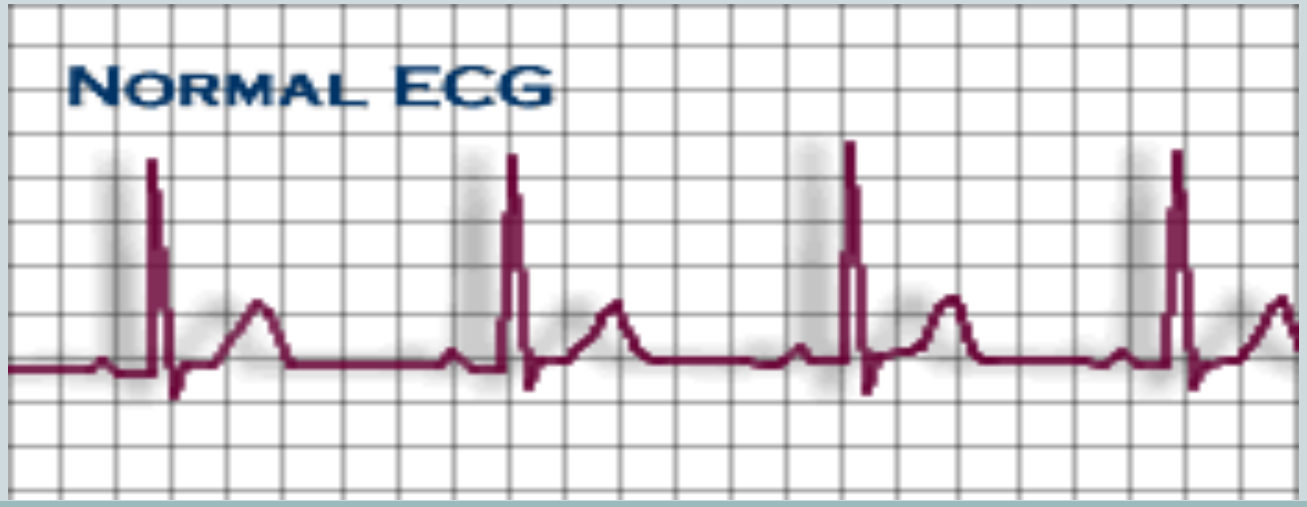
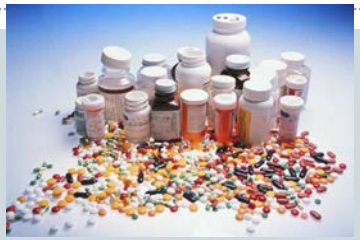
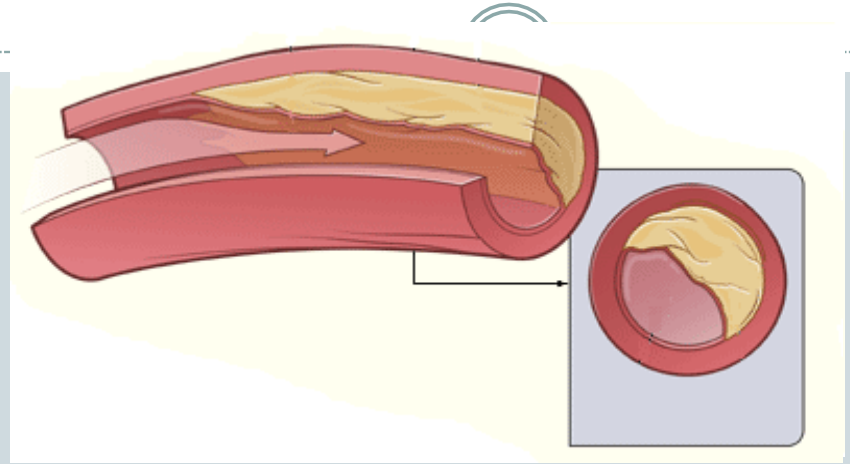
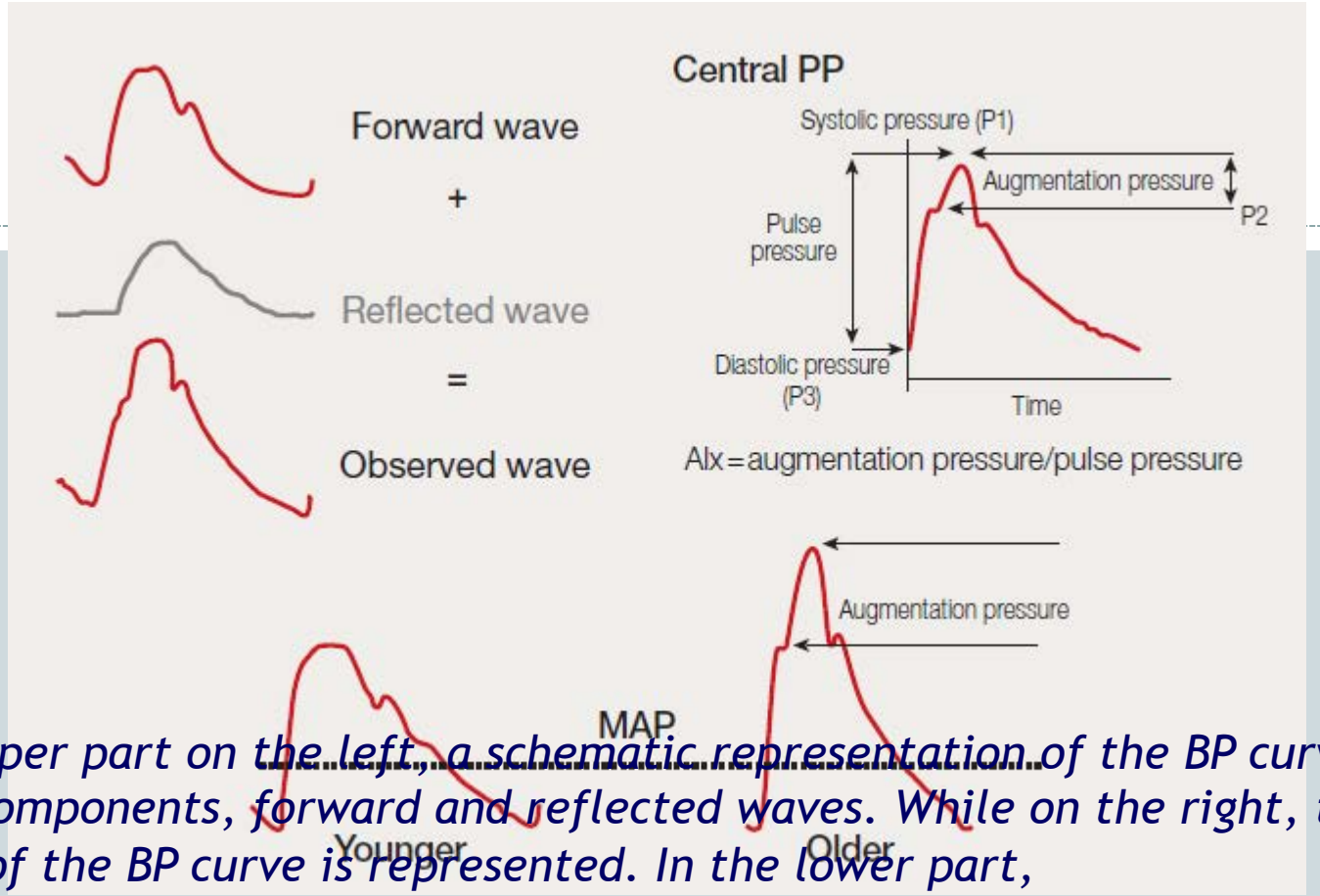


Treatment







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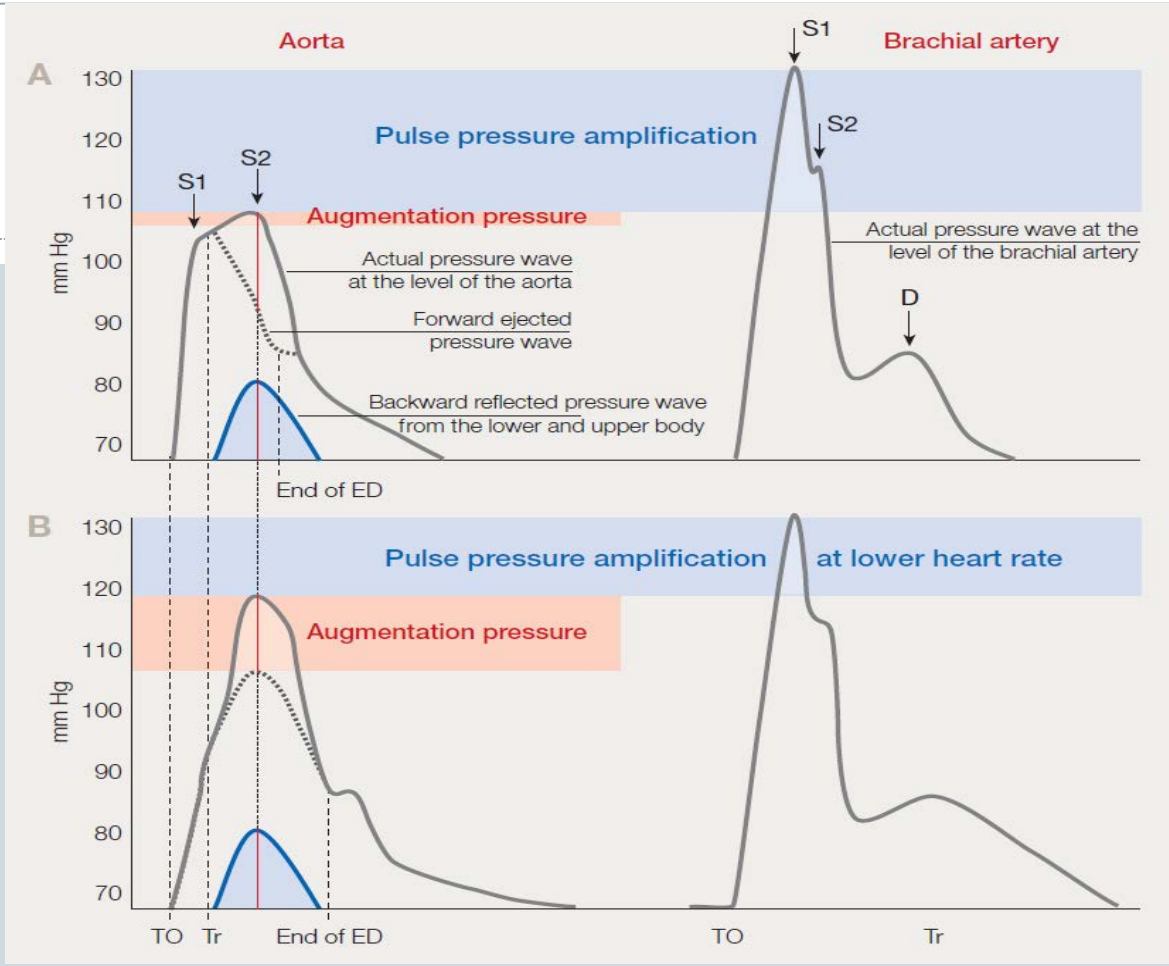

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PLoS one

Altered Arterial Stiffness and Subendocardial Viability Ratio in Young Healthy Light Smokers after Acute Exercise

Robert J. Doonan[1], Patrick Scheffler[1], Alice Yu[1], Giordano Egiziano[1], Andrew Mutter[1], Simon Bacon[2,3,4], Franco Carli[5], Marios E. Daskalopoulos[6], Stella S. Daskalopoulou[1]*

1 Department of Medicine, McGill University, Montreal, Quebec, Canada, **2** Department of Exercise Science, Concordia University, Montreal, Quebec, Canada, **3** Montreal Behavioural Medicine Centre, Hopital du Sacre-Coeur de Montreal, Montreal, Quebec, Canada, **4** Research Centre, Montreal Heart Institute, Montreal, Quebec, Canada, **5** Department of Anesthesia, Faculty of Medicine, McGill University, Montreal, Quebec, Canada, **6** Department of Vascular Surgery, Athens University, Athens, Greece

Abstract

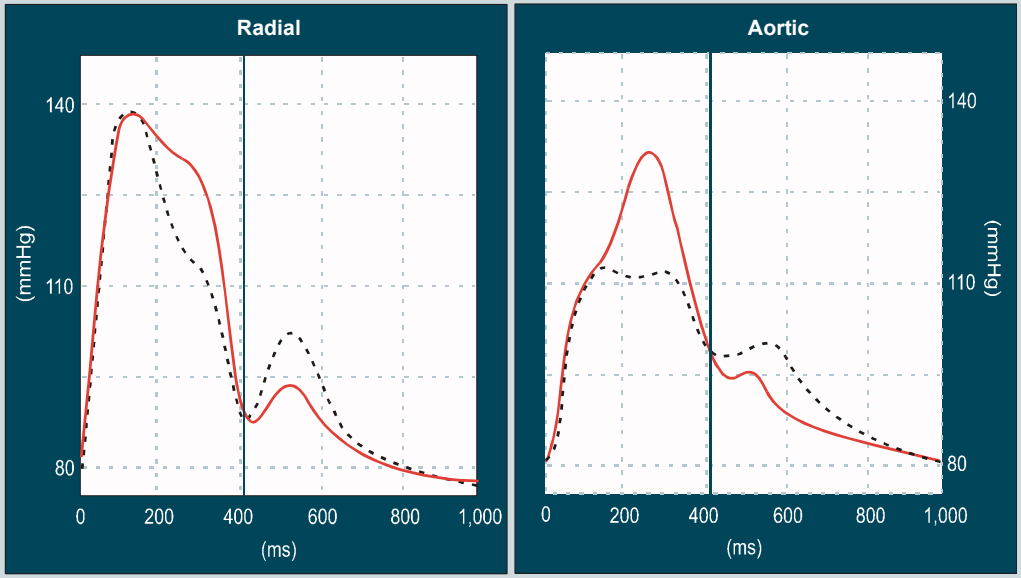
Background: Studies showed that long-standing smokers have stiffer arteries at rest. However, the effect of smoking on the ability of the vascular system to respond to increased demands (physical stress) has not been studied. The purpose of this study was to estimate the effect of smoking on arterial stiffness and subendocardial viability ratio, at rest and after acute exercise in young healthy individuals.

Methods/Results: Healthy light smokers (n = 24, pack-years = 2.9) and non-smokers (n = 53) underwent pulse wave analysis and carotid-femoral pulse wave velocity measurements at rest, and 2, 5, 10, and 15 minutes following an exercise test to exhaustion. Smokers were tested, 1) after 12h abstinence from smoking (chronic condition) and 2) immediately after smoking one cigarette (acute condition). At rest, chronic smokers had higher augmentation index and lower aortic pulse pressure than non-smokers, while subendocardial viability ratio was not significantly different. Acute smoking increased resting augmentation index and decreased subendocardial viability ratio compared with non-smokers, and decreased subendocardial viability ratio compared with the chronic condition. After exercise, subendocardial viability ratio was lower, and augmentation index and aortic pulse pressure were higher in non-smokers than smokers in the chronic and acute conditions. cfPWV rate of recovery of was greater in non-smokers than chronic smokers after exercise. Non-smokers were also able to achieve higher workloads than smokers in both conditions.

Conclusion: Chronic and acute smoking appears to diminish the vascular response to physical stress. This can be seen as an impaired 'vascular reserve' or a blunted ability of the blood vessels to accommodate the changes required to achieve higher workloads. These changes were noted before changes in arterial stiffness or subendocardial viability ratio occurred at rest. Even light smoking in young healthy individuals appears to have harmful effects on vascular function, affecting the ability of the vascular bed to respond to increased demands.

Clinical Problems

Cuff BP vs. Central BP - Case #1



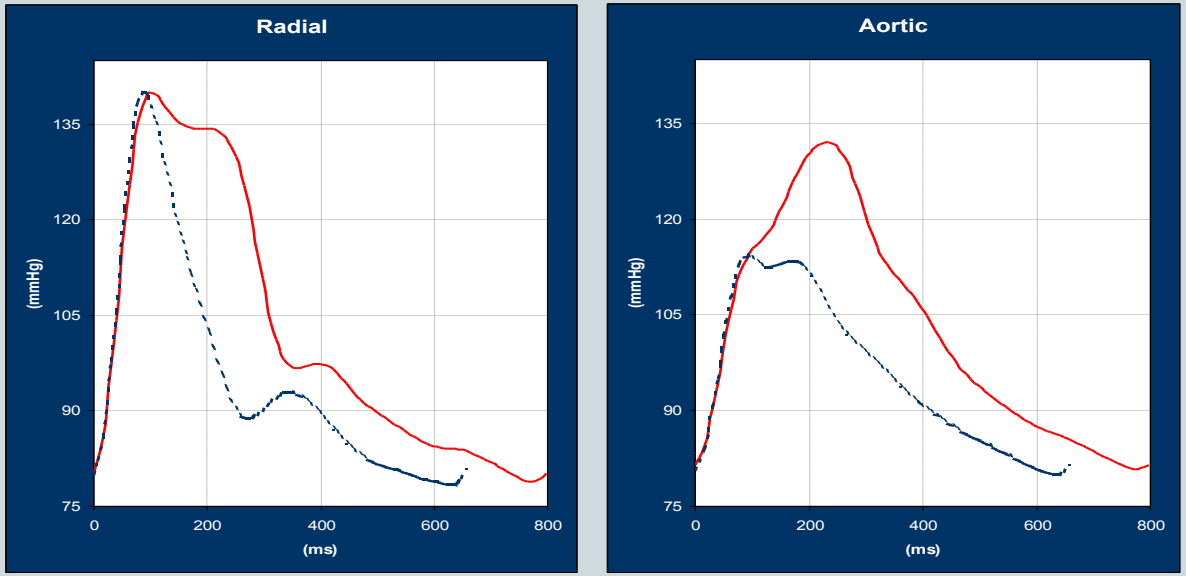
TWO PATIENTS …Radial shows red & black have identical cuff BP (140/80)

- BUT... Aortic shows critical Systolic BP (Sp) difference between patients:
  => Brachial cuff BP is NOT adequate for Systolic BP management.

- WHY Different Aortic Sp?…the patients have different Arterial Stiffness

Clinical Problems

Cuff BP vs. Central BP - Case #2



SAME PATIENT - before / after drug intervention (GTN for angina)

- No change in Cuff Sp …BUT…. Big change Aortic Sp
  => managing CV drug therapies needs the aortic BP profile data
- Hypertension, Diabetes, Renal, Heart Failure
  => ALL require CV drug therapies

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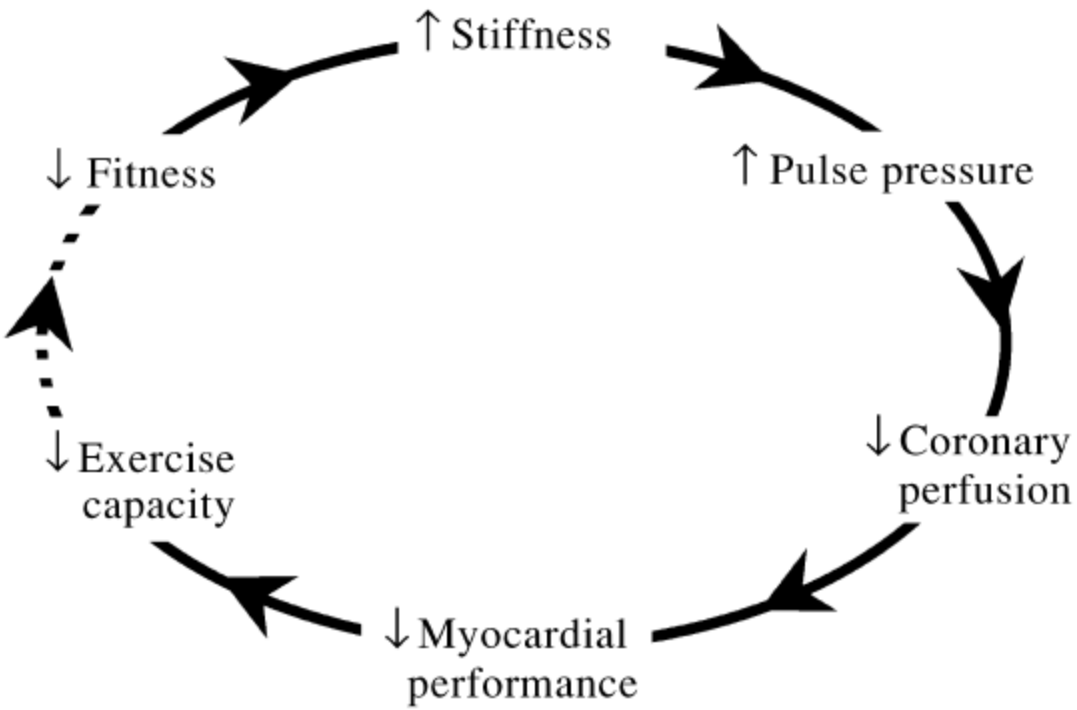
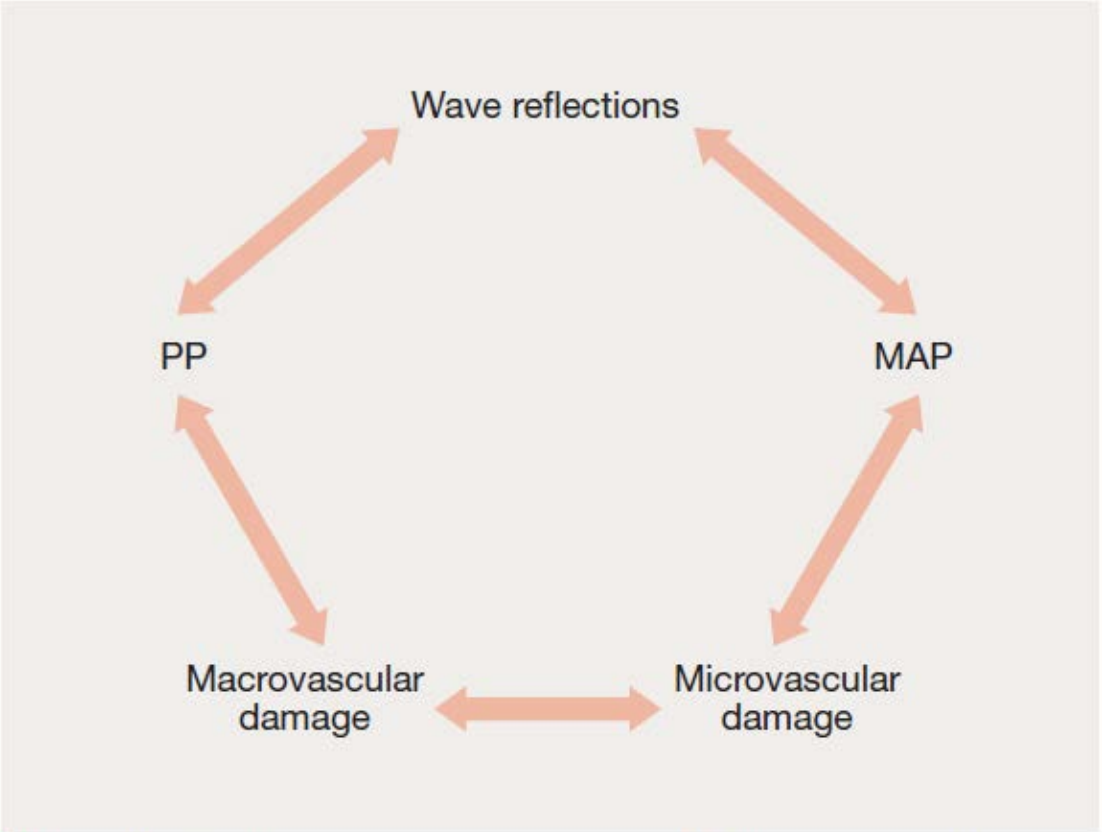


Circular nature of the relationship between large artery stiffness, physical work capacity and cardiac risk



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Doonan RJ, et al. PLoS One 2011

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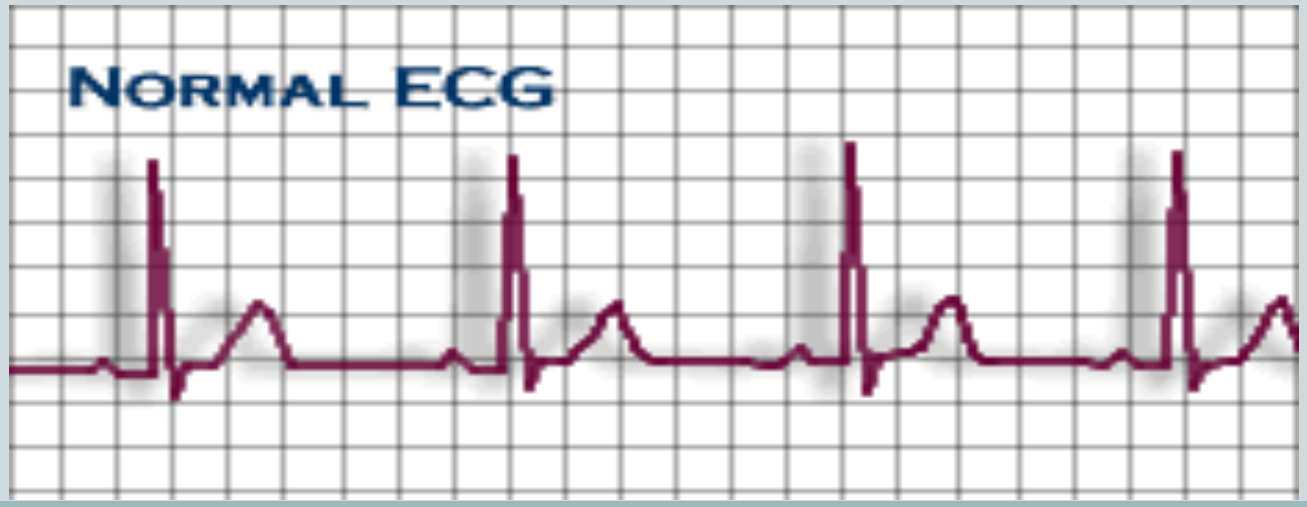
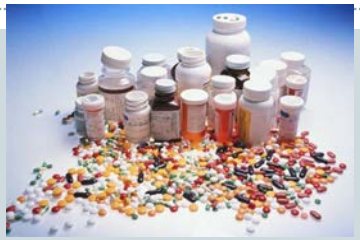
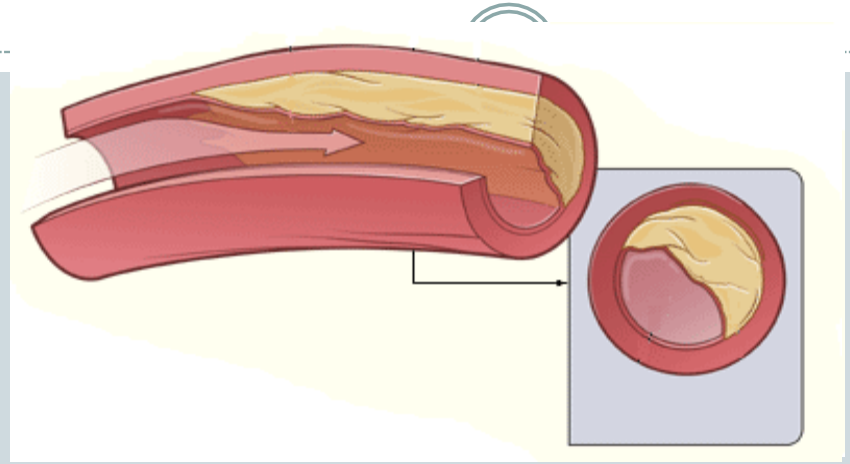
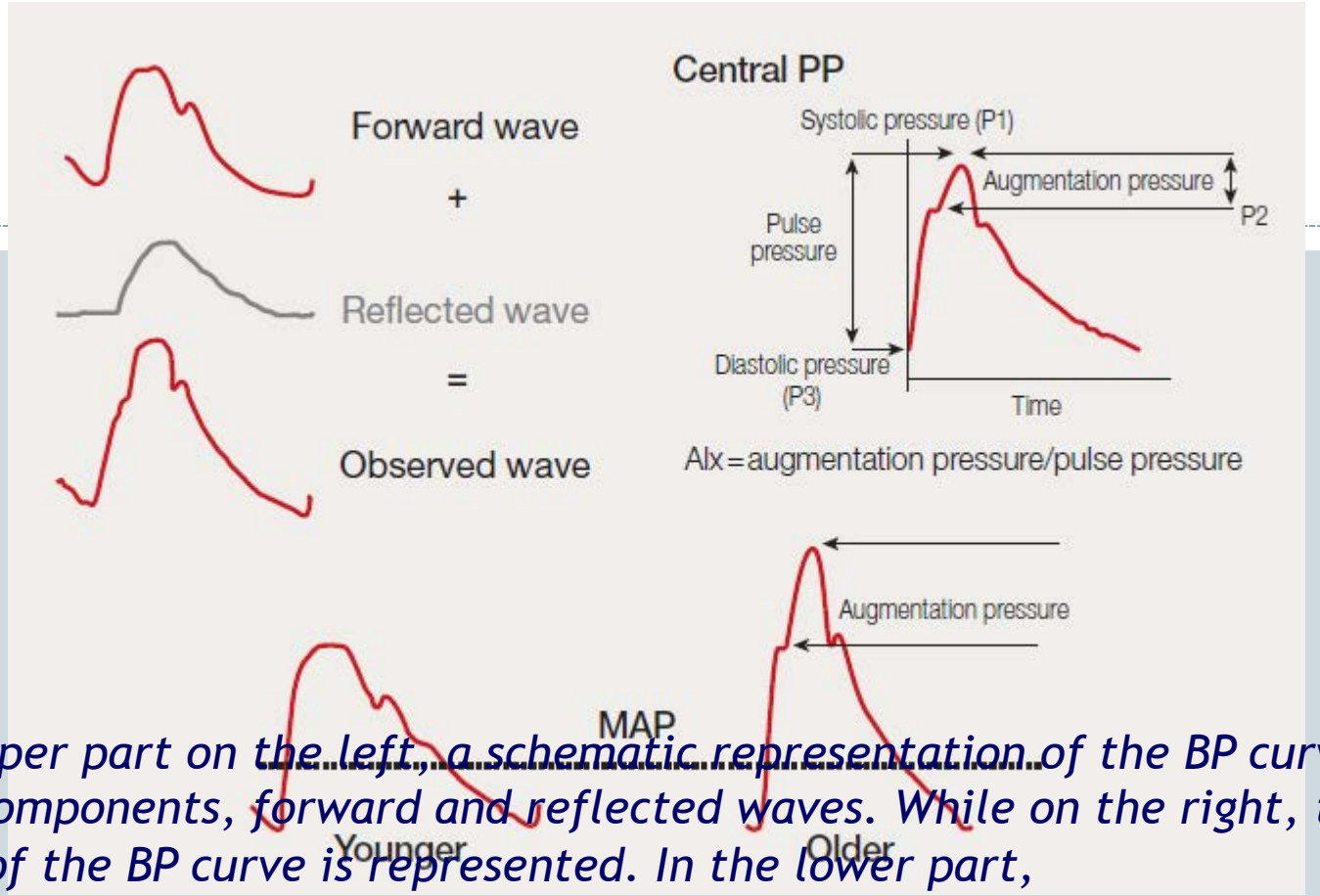


Treatment







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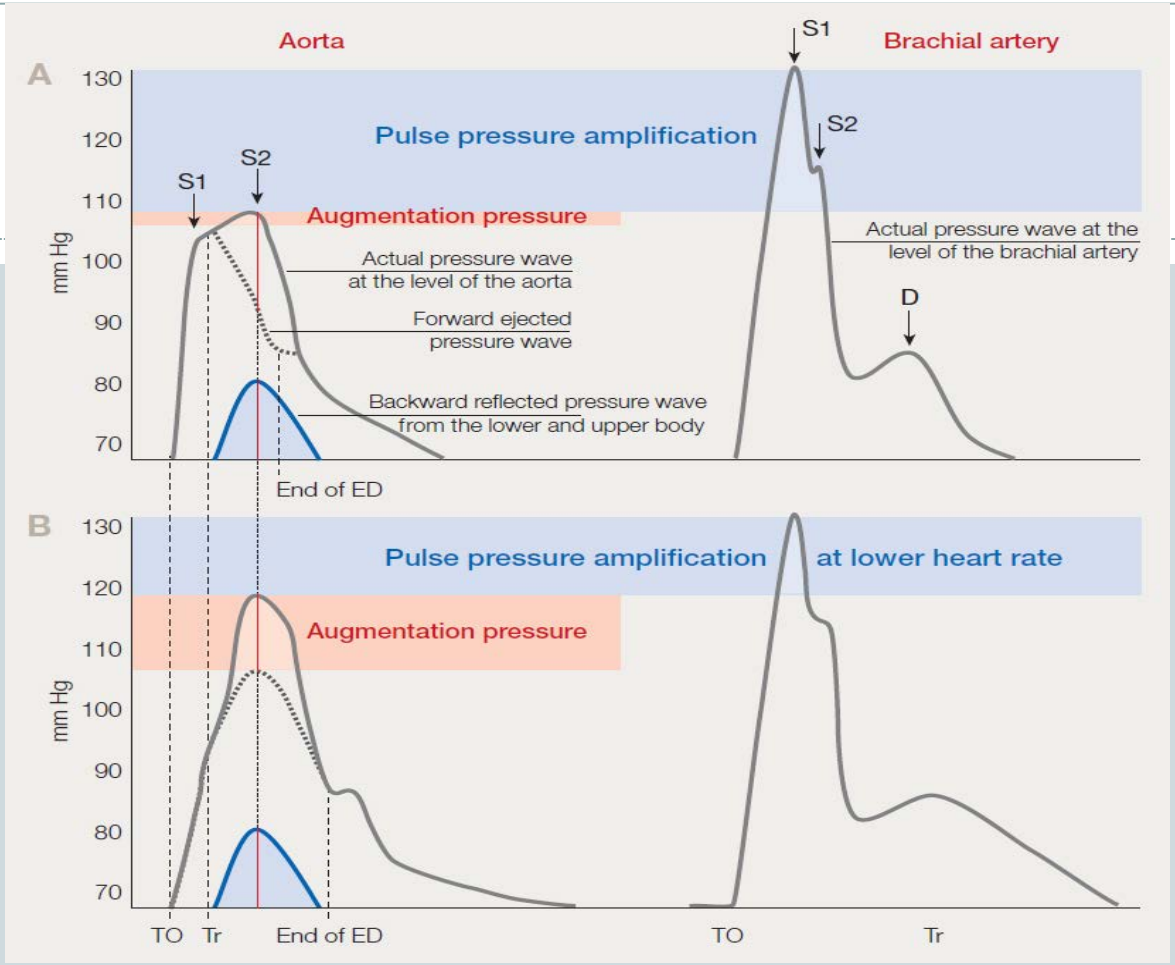

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REASON study

- The ACE inhibitor perindopril, combined with low-dose indapamide, was compared for 1 year of treatment with the ß-blocker atenolol
- For a similar DBP reduction, perindopril/indapamide decreased SBP significantly more than atenolol, especially central than brachial SBP
- After 1 year, the difference between brachial and central SBP was maintained by perindopril/indapamide (8.28 ± 1.53 mm Hg) and significantly attenuated by atenolol (0.29 ± 1.61 mm Hg)
- The two drugs lowered PWV equally, but only perindopril/indapamide reduced central PP and AIx
- Perindopril/indapamide decreased cardiac hypertrophy more than atenolol
- Similar findings were observed when atenolol was compared to the ARB irbesartan

London GM, et al.; on behalf of the REASON Project. J Am Coll Cardiol 2004;43:92-9
de Luca N, et al. J Hypertens 2004;22:1623-30
Schneider MP, et al. J Renin Angiotensin Aldosterone Syst 2008;9:49-56

Central BP but not brachial BP predicts CV events in an unselected geriatric population

- Central BP, compared to brachial BP, was significantly associated with CV events

- Even in the elderly, who are characterized by low PP amplification, central BP is superior to brachial BP for the prognosis of CV events

Pini R, et al. the ICARe Dicomano Study. J Am Coll Cardiol 2008;51:2432-9

Arterial stiffness and hypertension

- higher aortic stiffness, FWA, and augmentation index were associated with higher risk of incident hypertension;
- however, initial blood pressure was not independently associated with risk of progressive aortic stiffening
- higher arterial
- stiffness was predictive of incident
- hypertension, whereas higher initial
- blood pressure was not predictive of an
- increase in arterial stiffness

Kaess BM, et al. JAMA 2012;308:875-81

- Elevated BP may cause vascular damage and accelerated conduit artery stiffening

- Aortic or vascular stiffening increases pressure pulsatility and thereby may increase SBP

Aatola H, et al. Hypertension 2010;55:806-811

- Arterial stiffness and function may therefore be important potential targets for interventions aimed at preventing incident hypertension

Detrimental effect of smoking on arterial stiffness

Hypertension Research (2010), 1–13
 0916-9636/10 $32.00
www.nature.com/hr

REVIEW

The effect of smoking on arterial stiffness

Robert J Doonan[1], Anais Hausvater[1], Ciaran Scallan[1], Dimitri P Mikhailidis[2], Louise Pilote[1] and Stella S Daskalopoulou[1]

A systematic literature review was conducted using PubMed, Embase and the Cochrane Library to determine the effect of acute, chronic and passive smoking on arterial stiffness and to determine whether these effects are reversible after smoking cessation. A total of 39 relevant studies were identified and included. Acute smoking was found to cause an acute increase in arterial stiffness. Similarly, passive smoking increased arterial stiffness acutely and chronically. The majority of studies identified chronic smoking as a risk factor for increasing arterial stiffness. However, some studies found no statistical difference in arterial stiffness between nonsmokers and long-term smokers, although chronic smoking seems to sensitize the arterial response to acute smoking. In addition, whether arterial stiffness is reversed after smoking cessation and the timeline in which this may occur could not be determined from the identified literature. The effect of smoking discontinuation on arterial stiffness remains to be established by prospective smoking cessation trials.
Hypertension Research advance online publication, 9 April 2010; doi:10.1038/hr.2010.25

Keywords: arterial stiffness; elasticity; pulse wave velocity; smoking; smoking cessation

Doonan RJ, et al. Hypertens Res 2010;33(5):398-410