Central hemodynamics and prediction of cardiovascular events in patients with erectile dysfunction

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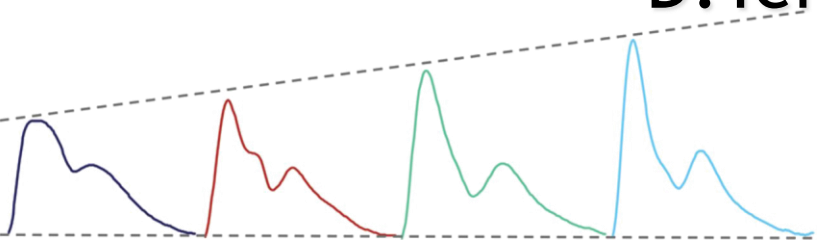
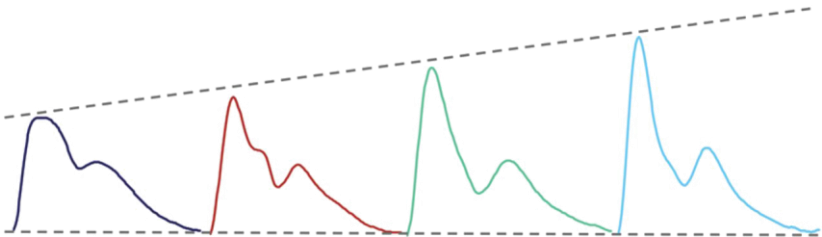


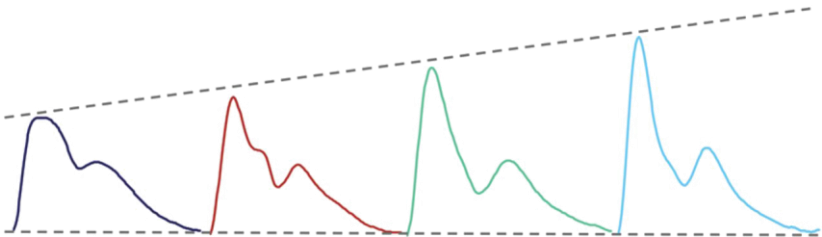
Conflict of interests:

The authors declare no conflict of interest



Central hemodynamics and prediction of CV events in ED patients

- Erectile dysfunction
- Central hemodynamics
- Study protocol
- Statistical analysis & results
- Discussion
- Conclusions

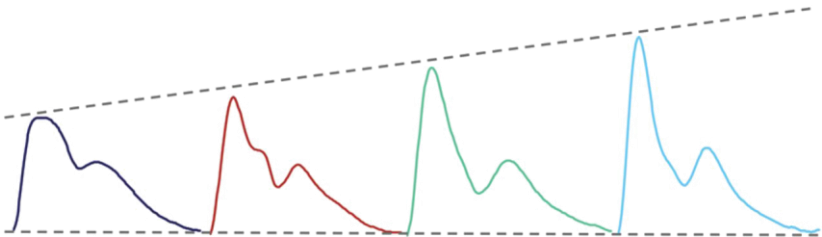


Erectile Dysfunction (ED)

How prevalent is it?

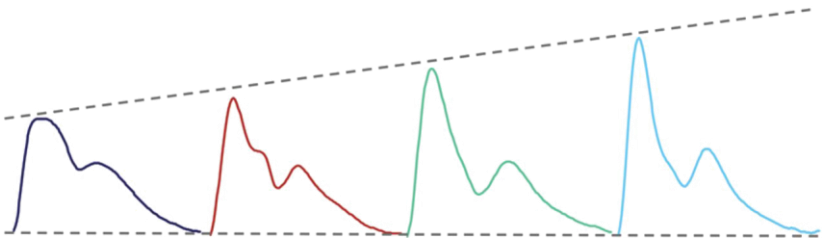
- 1 in 5 American men
- Over 30 million American men
- Over 150 million men worldwide
- Causes: 90% physical, 10% psychogenic

Selvin E, Am Jour of Med 2007(120) 151-157
Sun P, J Urol. 2005 Nov;174(5):1948-52
Mulligan T, Va Med Q. 1991 Spring;118(2):97-9



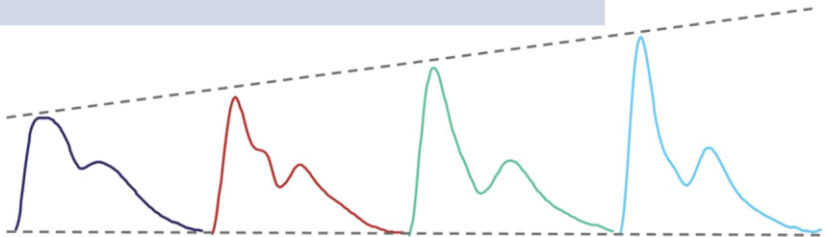
Erectile Dysfunction (previously known as Impotence)

- ED affects about 10% of men aged 40-70 and prevalence increases with age
- ED is common in patients with subclinical or symptomatic coronary artery disease (CAD)
- ED is considered an early manifestation of a generalized vascular disease and predicts all-cause mortality and cardiovascular (CV) events including CAD, stroke and peripheral artery disease (PAD)

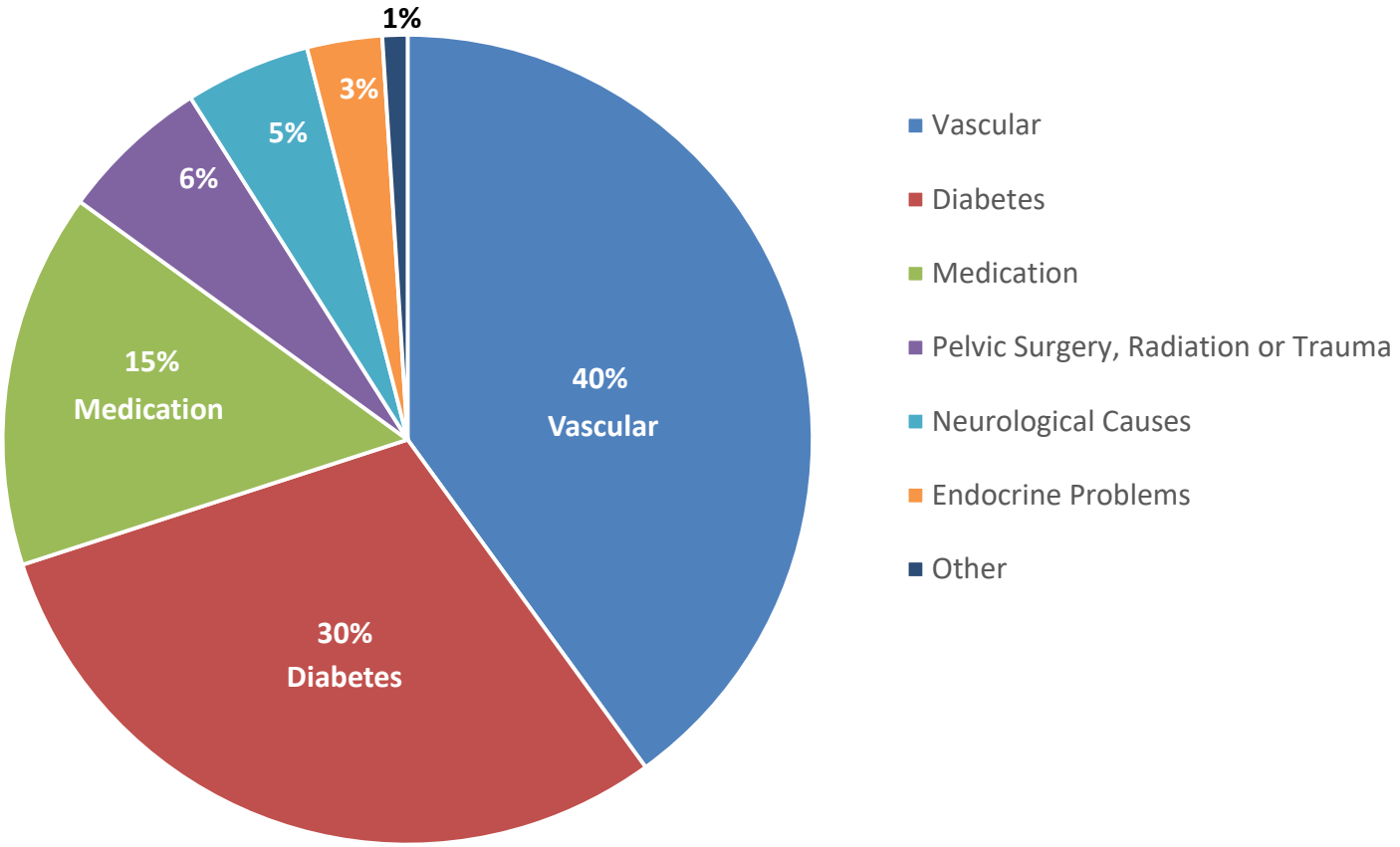


Main causes of ED

Cause	Etiology
Inflammatory	Prostatitis, urethritis
Mechanical	Peyronie's Disease, chordee
Psychological	Depression, performance anxiety, stress, relationship difficulties
Occlusive vascular	Arterial: Hypertension, smoking, hyperlipidemia, DM., peripheral vascular disease Venous: venous occlusion due to anatomical or degenerative changes
Trauma	Pelvic fracture, SC injection, penile trauma
Endocrine	Hypogonadism, hyperprolactinemia, hypo + hyperthyroidism
Neurologic	Parkinson's, multiple sclerosis, spina bifida, pelvic surgery, peripheral neuropathy
Chemical	Anti-HTN, anti-arrhythmics, antidepressants, anxiolytics, anti-androgens, anticonvulsants, alcohol, marijuana, anti-Parkinsonic drugs, LHRH analogues
Extra factors	Prostatectomy, old age, CRF, cirrhosis



Main causes of ED



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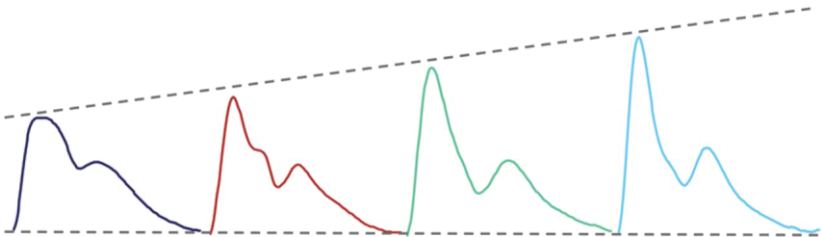
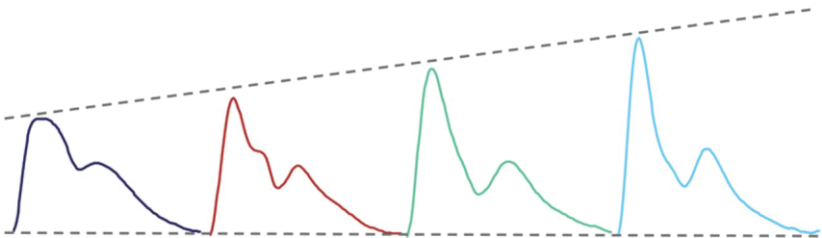


Central hemodynamics

Novel biomarkers

- Arterial stiffness
  - Carotid-femoral pulse wave velocity-cfPWV (IIa/A)
  - Brachial-ankle pulse wave velocity-baPWV (IIb/B)

- Central haemodynamics/wave reflections (IIb/B)
  - Central (aortic) pressure
  - Augmentation pressure (measure of the enhancement of central aortic pressure by the reflected pulse wave)
  - Augmentation Index-AIx (augmentation pressure to PP ratio)



Vlachopoulos C. *Atherosclerosis*;241;(2015):507-532

Recommendation for clinical use

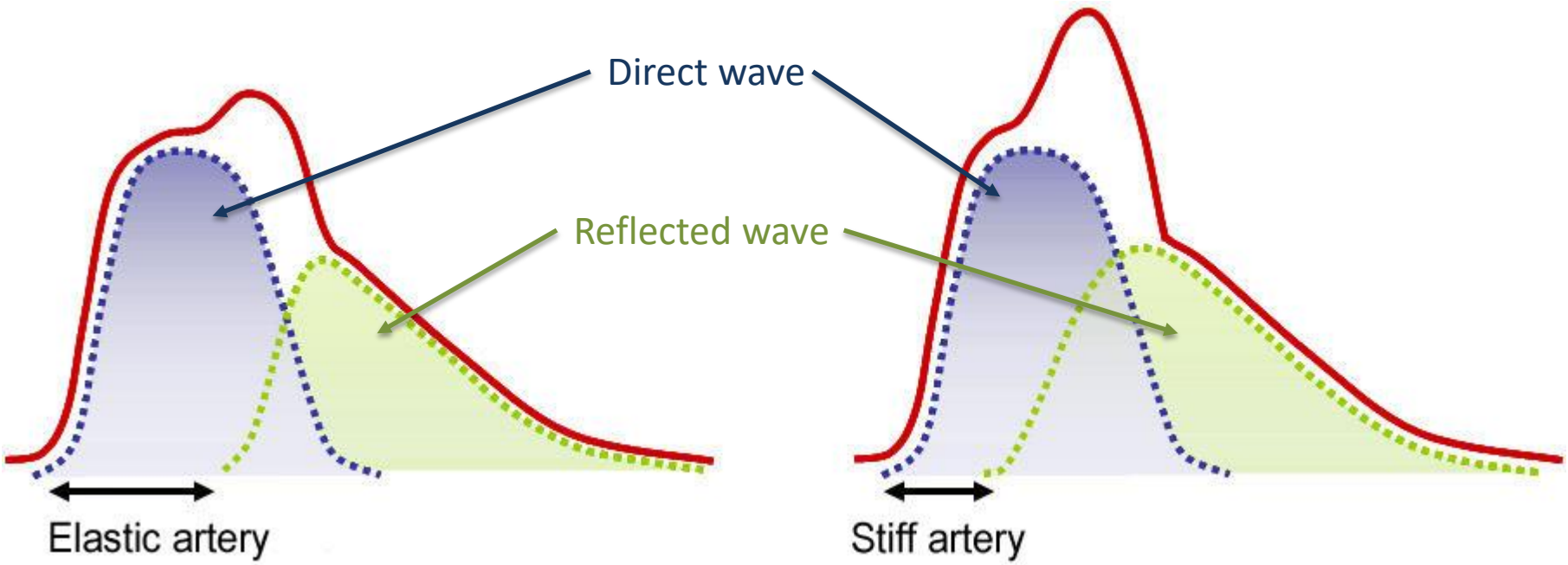
The role of vascular biomarkers for primary and secondary prevention

Table 5
Usefulness of vascular biomarkers for primary and secondary CVD prevention.

	Recommendation	Level of evidence	Comments
Carotid ultrasonography	IIa	A	Moderate usefulness for risk stratification. Concomitant identification of plaque presence.
Ankle-brachial index	IIa	A	Useful for risk stratification, especially women.
Arterial stiffness			
Carotid-femoral pulse wave velocity	IIa	A	Useful for risk stratification.
Brachial-ankle pulse wave velocity	IIb	B	
Central haemodynamics/Wave reflections	IIb	B	
Endothelial function			
Flow mediated dilatation	III	B	Requires skilled, trained operator. Reactive hyperaemia is stressful. Methodological problems are not resolved. Added value is not proven.
Endothelial peripheral arterial tonometry	III	C	Reactive hyperaemia is stressful. Added value is not proven.
Circulating biomarkers related to vascular wall biology			
High sensitivity C- reactive protein	IIb	B	

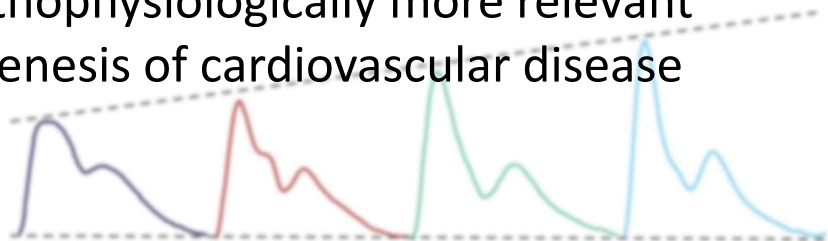
Vlachopoulos et al. Atherosclerosis 2015, European Society of Cardiology - Position Paper

Central pressures and Augmentation index



- Central pressures **do not** correspond to brachial pressures due to pressure pulse amplification of a varying degree when moving from the aorta to the periphery

- Central (aortic, carotid) pressures are pathophysiologically more relevant than peripheral pressures for the pathogenesis of cardiovascular disease



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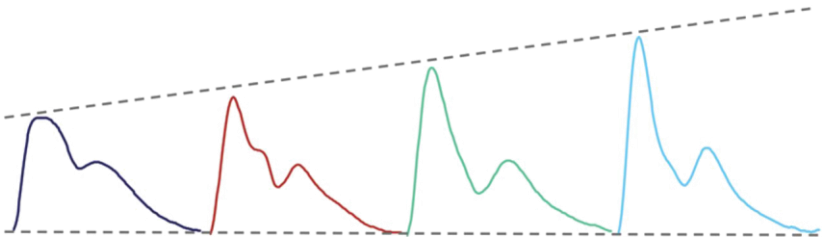


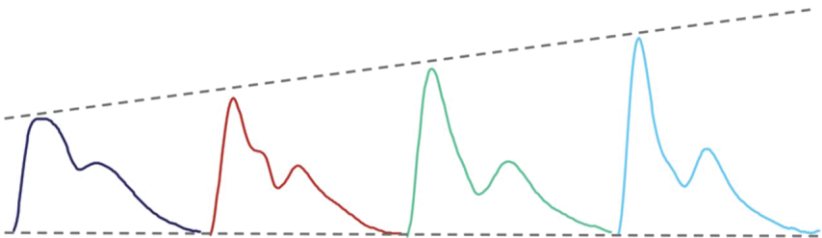
Study Protocol

Background

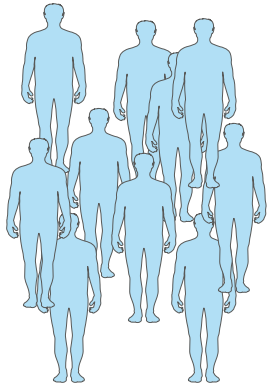
- Established and novel biomarkers are particularly useful in primary or secondary prevention, and since ED is primarily a vascular disease, arterial biomarkers are particularly appealing

- Central (aortic) blood pressures (BP) more accurately reflect loading conditions of vital organs and thus, should better related to target organ damage and cardiovascular events than peripheral pressures.

- The purpose of the present study was to investigate whether central hemodynamics predict major adverse cardiovascular events (MACEs) in patients with erectile dysfunction (ED) beyond traditional risk factors.

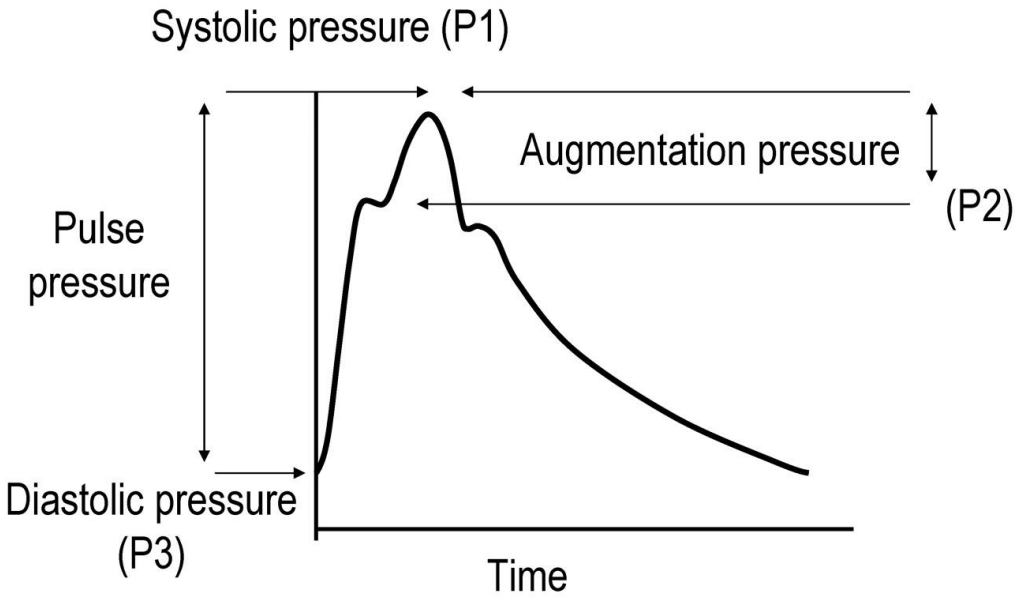


Study Protocol



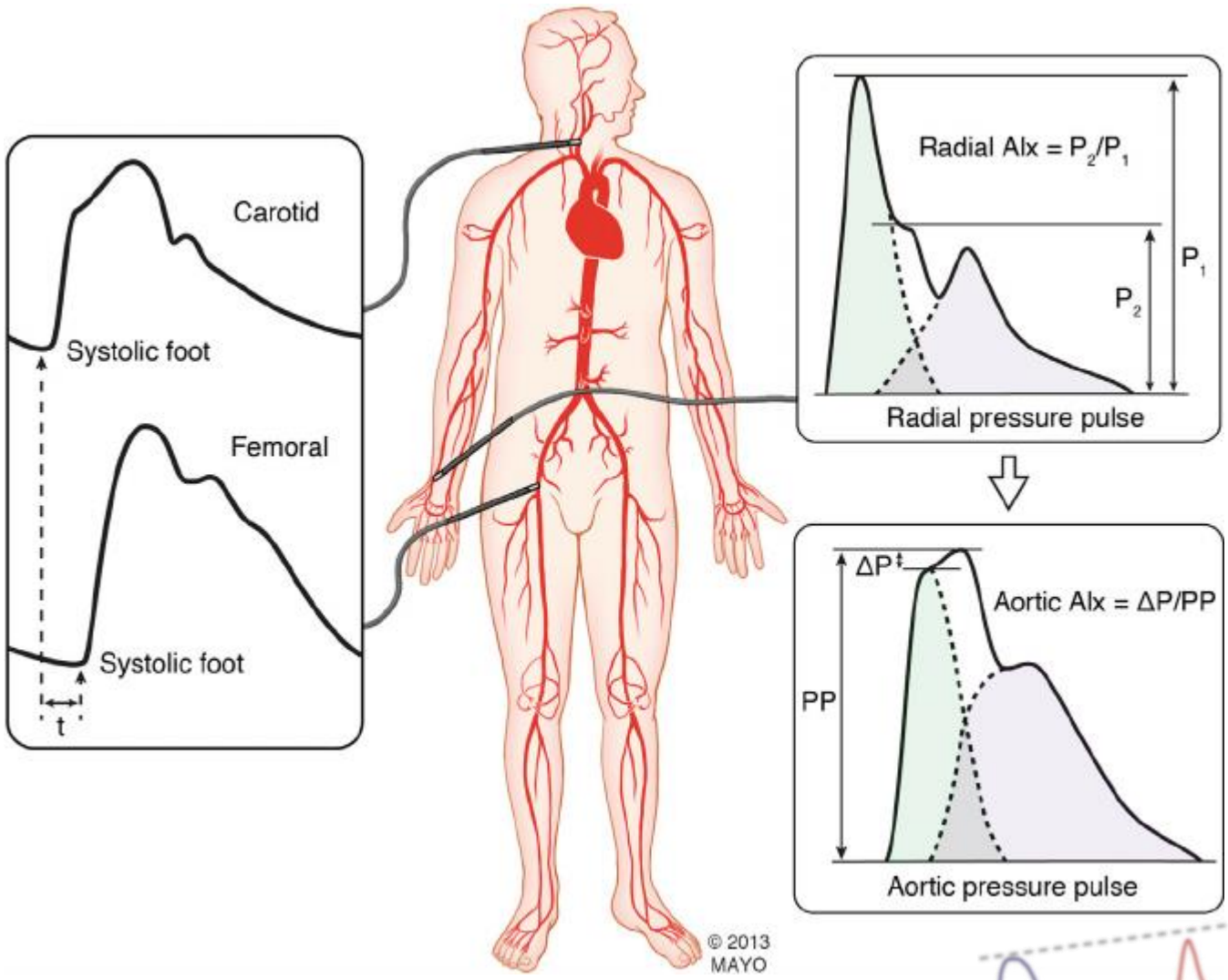
398 ED pts (mean age 56 yrs)

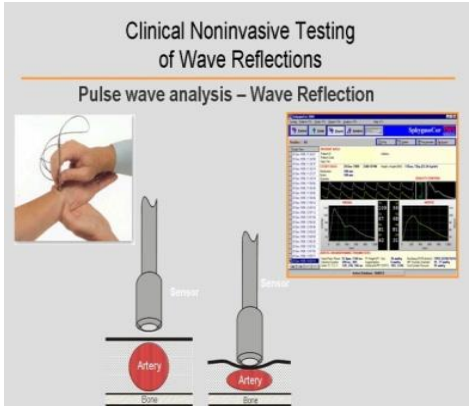
Sexual Health Inventory for Men (SHIM) Questionnaire
1. How do you rate your confidence that you could get and keep an erection?
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
4. During sexual intercourse how difficult was it to maintain your erection to completion of intercourse?
5. When you attempted sexual intercourse, how often was it satisfactory for you?
ASSESMENT OF ED

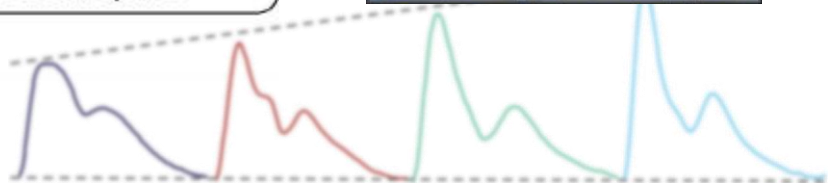


Augmentation Index (AIx) was defined as augmented pressure (AP=maximum systolic pressure - pressure at the inflection point) divided by pulse pressure and expressed as percentage $\left(\frac{\mathbf{AP}}{\mathbf{PP}}\%\right)$. Higher values of AIx indicate increased arterial stiffening and wave reflections and vice-versa.

Study Protocol







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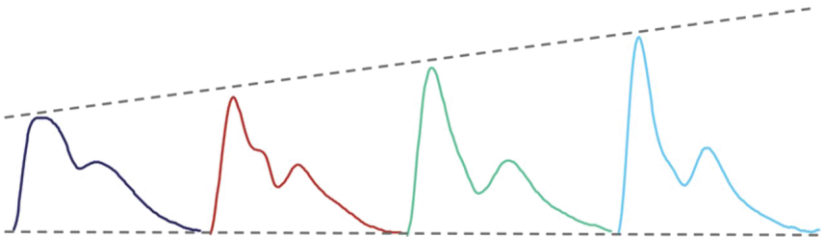
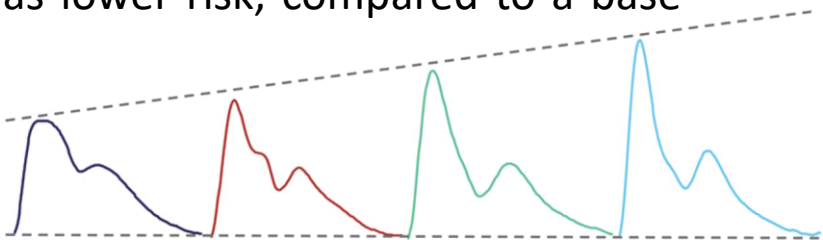


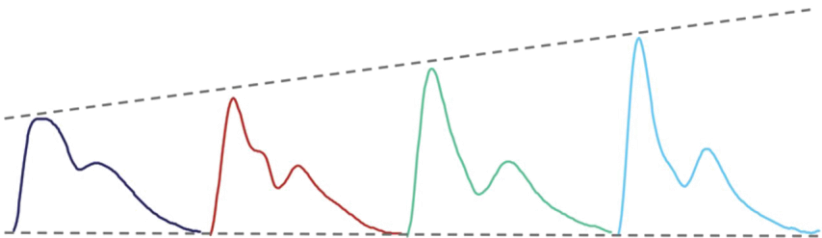
Statistical analysis & results

- Differences in normal variables: *Student t-test*
- Differences in non-normal variables: *Mann-Whitney U test*
- Frequency comparison: *Pearson chi-square test*
- Free of MACE survival among tertiles estimation: *Kaplan-Meier curves and Mantel log-rank test for comparison*
- Central pressures: relative risks (RRs) calculation per 10-mmHg difference & risk estimates were adjusted for age and risk factors
- AIx: RRs calculation per absolute 10% difference & risk estimates were adjusted for peripheral pressure
- Subject reclassification: further assessment with *net reclassification improvement (NRI)*, so that case subjects will not be categorized as higher-risk and control subjects will not be categorized as lower-risk, compared to a base model



Statistical analysis & results

- The mean follow-up time was **6.5 years** (range 1-11), during which **29** (7.2%) subjects developed MACE (24 nonfatal, 5 fatal)
- Of those with CAD events (**n=20**), 2 were fatal, 4 were myocardial infarction with survival beyond one day and 14 were documented angina pectoris or coronary revascularization
- Other MACE events were cerebrovascular events (**n=6**), and new onset of peripheral arterial disease (**n=3**, 1 fatal)



Statistical analysis & results

Baseline clinical characteristics of patients with a MACE and subjects without MACE

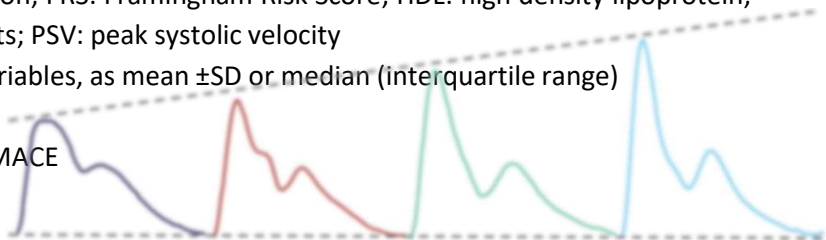
	MACE (n=29)	No MACE (n=369)	*P value
Age (years)	61±6	55±10	<0.001
BMI (Kgr/m^2)	27.8±2.7	28.7±4.2	0.23
Total cholesterol, mg/dl	209±34	207±36	0.85
HDL cholesterol, mg/dl	44±8	45±9	0.86
Triglycerides, mg/dl	111 (75-136)	109 (80-131)	0.98
Glucose, mg/dl	107 (86–117)	105 (84–115)	0.54
hsCRP, mg/l	1.9 (1.5-2.4)	1.7 (1.3-2.0)	0.43
Total testosterone, ng/ml	4.0 ±0.8	4.5±1.2	<0.05
Hypertension, n (%)	24 (83)	170 (48)	<0.001
Hypercholesterolemia, n (%)	16 (55)	212(60)	0.39
Diabetes, n (%)	6 (21)	61(17)	0.37
Smoking, n (%)	16 (55)	187 (53)	0.48
Drug Therapy, n (%)			
Antihypertenive therapy	20 (69)	156 (42)	0.005
Statins	11 (38)	114 (31)	0.47
IIEF-5	12.6±3	13.2±4	0.46
†PSV (cm/s)	29±10	33±9	0.03

BMI: body-mass index; BP: blood pressure; CV: cardiovascular; ED: erectile dysfunction; FRS: Framingham Risk Score; HDL: high density lipoprotein; hsCRP: high sensitivity C-reactive protein; MACE: major adverce cardiovascular events; PSV: peak systolic velocity

Categorical variables are presented as absolute (relative) frequencies; continuous variables, as mean ±SD or median (interquartile range)

†PSV was measured in 278 ED patietns (25 with MACE and 253 w/o MACE)

*P value: refers to differences between patients with a MACE and subjects without MACE



Statistical analysis & results

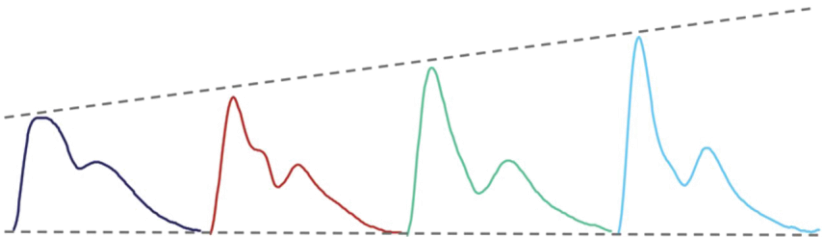
Peripheral and Central BP characteristics of patients with a MACE and subjects without MACE

	MACE (n=29)	No MACE (n=369)	*P value
Heart rate (bpm)	69±8	70±7	0.54
Brachial Systolic BP, mmHg	140±17	131±17	0.008
Brachial Diastolic BP, mmHg	84±7	82±8	0.25
Brachial Pulse Pressure, mmHg	56±13	49±13	<0.001
Mean Pressure, mmHg	103±10	100±10	0.27
Aortic Systolic BP, mmHg	130±16	121±16	0.006
Aortic Diastolic BP, mmHg	84±7	83±8	0.57
Aortic Pulse Pressure, mmHg	56±13	48±13	<0.001
Augmentation Index (%)	30±10	24±10	<0.001

BP: blood pressure; MACE: major adverse cardiovascular events;

Continuous variables, as mean ±SD

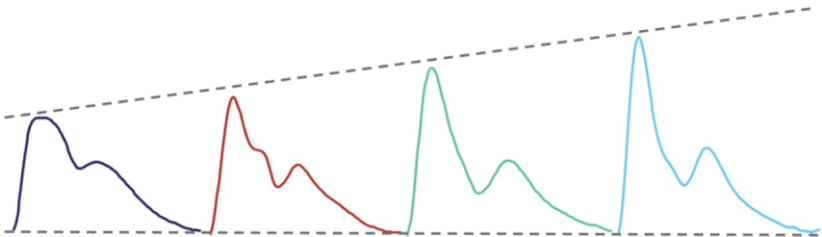
*P value: refers to differences between patients with a MACE and subjects without MACE



Statistical analysis & results

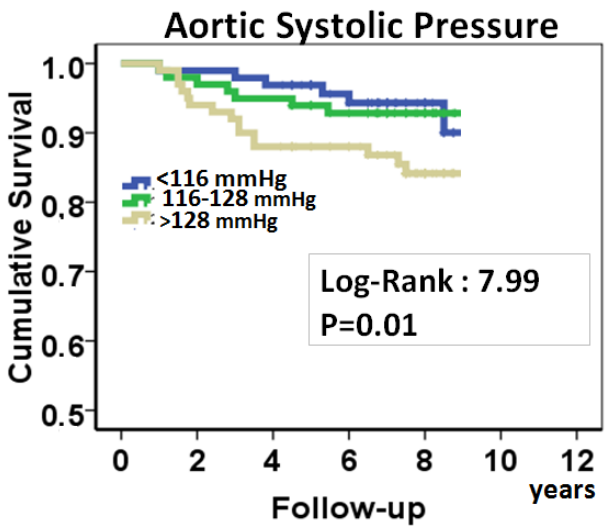
Outcome and prognostic impact of central hemodynamics

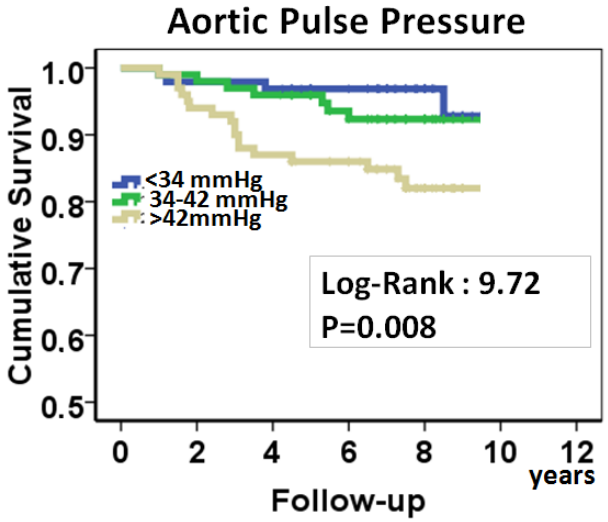
- The whole population was divided into tertiles according to the brachial and aortic BP level, AIx and AP.

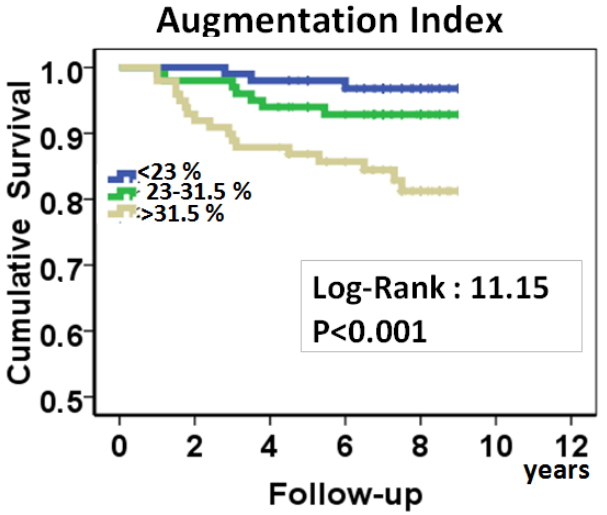


Statistical analysis & results

Kaplan-Meier curves for MACE by tertile group of Ao systolic / Ao pulse pressure and AIx



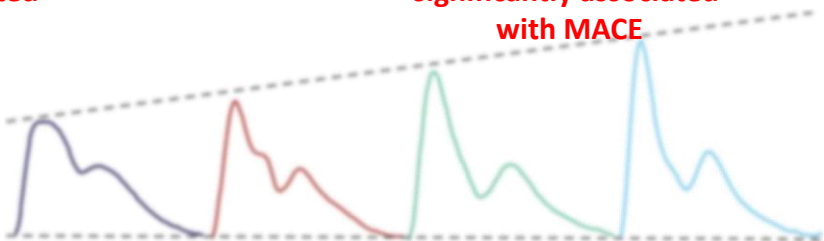




significantly associated with MACE

significantly associated with MACE

significantly associated with MACE



Statistical analysis & results

Adjusted HRs for MACEs

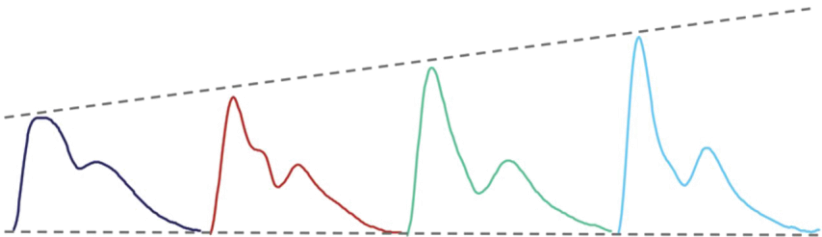
(for age, cholesterol, smoking history & additionaly for systolic pressure for AIx)

Parameters	HR (95% CI)	Significance (P)
Aortic Systolic BP	1.062 (95% CI 1.016–1.117)	0.047
Aortic Diastolic BP	1.012 (95% CI 0.970–1.050)	0.54
Aortic PP	1.117 (95% CI 1.038–1.153)	0.025
Brachial Systolic BP	1.034 (95% CI 1.004–1.106	0.20
Brachial PP	1.072 (95% CI 1.024–1.138)	0.036
AIx	1.191 (95% CI 1.056–1.372)	0.01

10mmHg difference

10% absolute increase

AIx: augmentation index; BP: blood pressure; PP: pulse pressure



Statistical analysis & results

MACE by tertiles of Ao Systolic pressure

	1st tertile <116 mmHg	2nd tertile 116-128 mmHg	3rd tertile >128 mmHg
HR (95% CI) for MACE			
Unadjusted	1 (REF)	1.14 (0.35 -3.40)	†2.55 (0.95-6.29)
Adjusted for age, cholesterol, smoking	1 (REF)	0.95 (0.27-2.78)	1.87 (0.70-4.79)

†P<0.05 for 3rd tertile vs 1st tertile

MACE by tertiles of Ao Pulse Pressure

	1st tertile <34 mmHg	2nd tertile 34-42 mmHg	3rd tertile >42 mmHg
HR (95% CI) for MACE			
Unadjusted	1 (REF)	1.49 (0.43 -5.30)	¶ 4.04 (1.36-10.5)
Adjusted for age, cholesterol, smoking	1 (REF)	1.62 (0.46-5.73)	†2.76 (0.90-8.56)

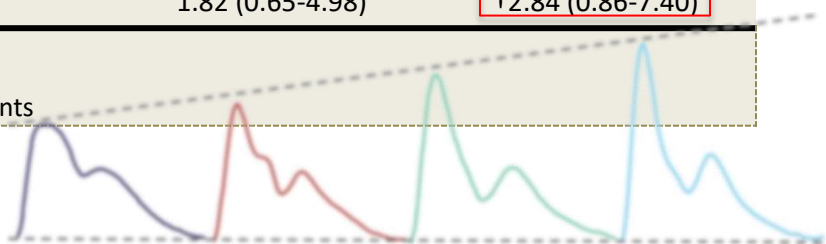
¶ P<0.01, †P<0.05 for 3rd tertile vs 1st tertile

MACE by tertiles of Augmentation Index

	1st tertile <23 %	2nd tertile 23-31.5 %	3rd tertile >31.5 %
HR (95% CI) for MACE			
Unadjusted	1 (REF)	1.69 (0.37-4.96)	¶ 3.95 (1.47-12.5)
Adjusted for age, SP, heart rate, cholesterol, smoking	1 (REF)	1.82 (0.65-4.98)	†2.84 (0.86-7.40)

¶ P<0.01, †P<0.05 for 3rd tertile vs 1st tertile

AIx: augmentation index; SP: systolic pressure; MACE: major adverse cardiovascular events



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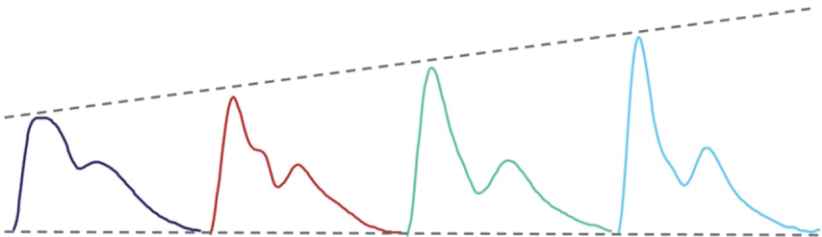
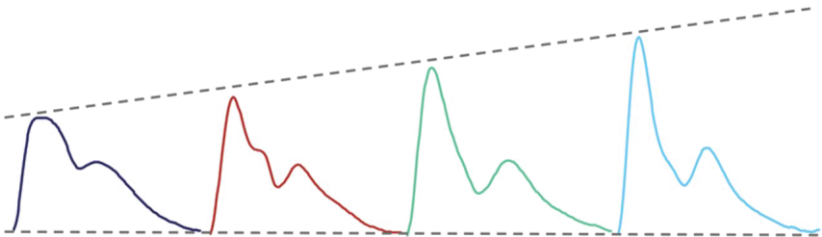


Discussion

- Clinical implications
- Central hemodynamics and CV risk
- Mechanisms
- Limitations



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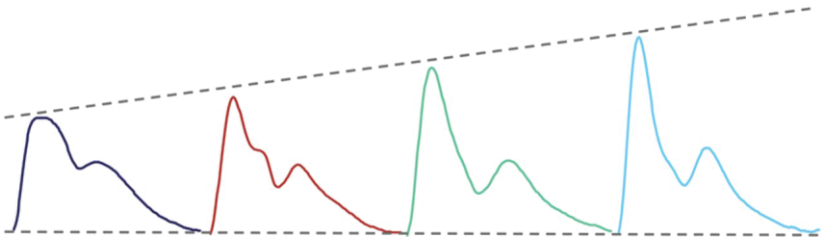
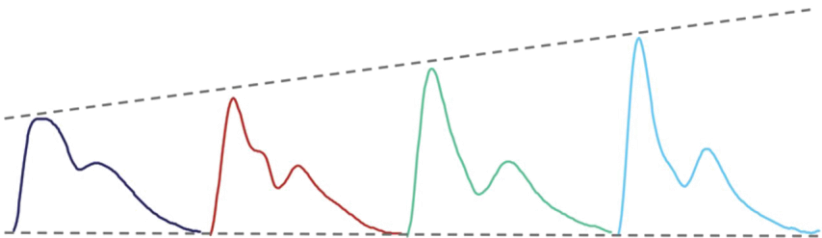


Conclusions

- Aortic systolic and pulse pressure and aortic augmentation index independently of age and risk factors predicted MACEs
- The adjusted relationship between AIx/aortic pulse pressure and incident MACEs was consistent
- Central pressures and wave reflection indices fulfill important criteria for a biomarker to enter the clinical arena as regards investigation of ED patients without known CVD



Thank you for your attention!

Tak for din opmærksomhed!

Σας ευχαριστώ για την προσοχή σας!