The Penis and the Heart:
An Intimate Connection

A Pre-emptive Strike: Addressing Cardiovascular Disease Through Preventive Strategies

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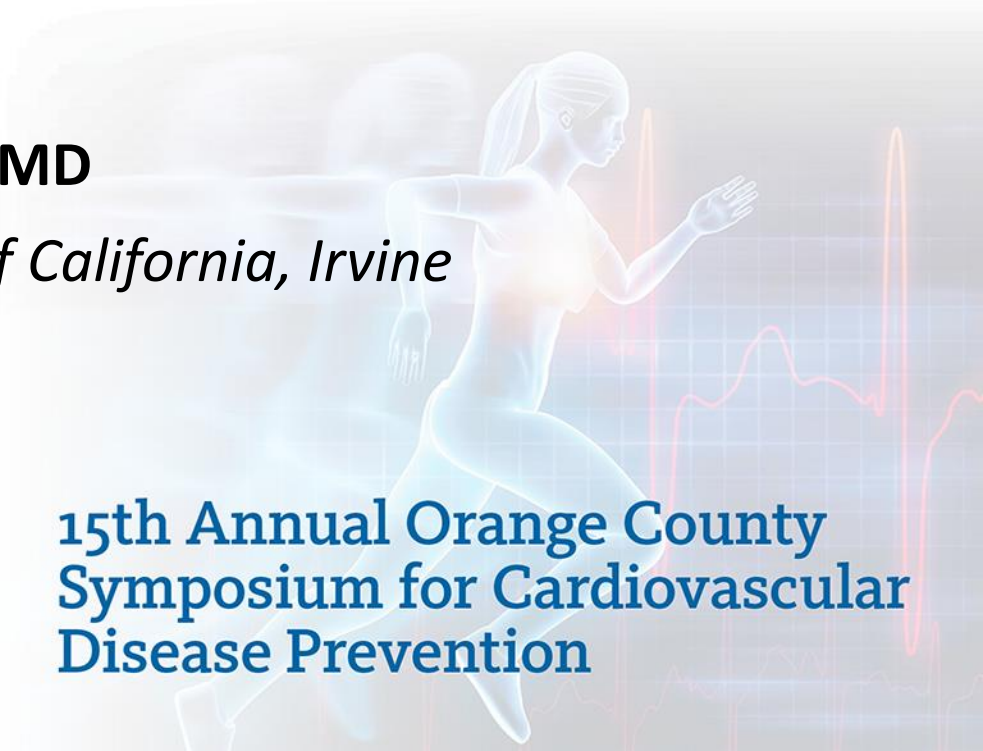


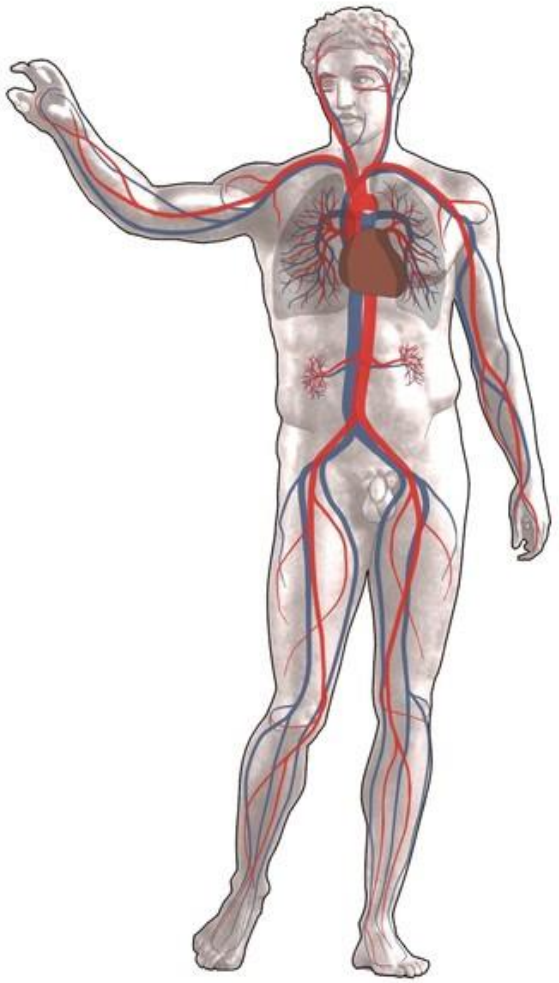
15th Annual Orange County Symposium for Cardiovascular Disease Prevention

Disclosures

- No Disclosures…

The Penis and the Heart: *An Intimate Connection*

- Erectile Dysfunction is common
- Affects nearly 40% of n over 40 years of age



- is frequent in men with established CVD
- co-exists with occult coronary artery disease (CAD)
- is an independent risk factor for future cardiovascular (CV) events both in
  - men with established CVD and
  - in men with no known CVD

Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 year old: longitudinal results from the Massachusetts male aging study. J Urol 2000;163:460 – 463

Vlachopoulos C, et al. Erectile dysfunction in the cardiovascular patient. European Heart Journal (2013) 34, 2034–2046

- **ED is an INDEPENDENT marker of increased risk for CVD**

TABLE 1. Relative Risks for Men With Erectile Dysfunction

	Relative risk	95% Confidence interval	*P* value
Overall	1.48	1.25-1.74	<.001
Coronary heart disease	1.46	1.31-1.63	<.001
Stroke	1.35	1.19-1.54	<.001
All-cause mortality	1.19	1.05-1.34	.005

Adapted from *J Am Coll Cardiol.*[15]

ED and CVD Share Risk Factors

- Age
- Hypercholesterolemia
- Hypertension
- Insulin resistance and diabetes
- Smoking
- Obesity
- Metabolic syndrome
- Sedentary lifestyle
- Depression

Vlachopoulos C, et al. Erectile dysfunction in the cardiovascular patient. European Heart Journal (2013) 34, 2034–2046

CVD RISK IN MEN WITH NO KNOWN CVD

- Erectile dysfunction commonly occurs in the presence of silent CAD, with a time window between ED onset and a CAD event of *2 to 5 years*

- ED is far more predictive of CAD in men 40 to 49 years of age than in older men

Table 1 Differential characteristics of psychogenic vs. organic erectile dysfunction

Characteristic	Predominantly psychogenic ED	Predominantly organic ED
Onset	Acute	Gradual
Circumstances	Situational	Global
Course	Intermittent	Constant
Non-coital erection	Rigid	Poor
Nocturnal/early AM erections	Normal	Inconsistent
Psychosexual problems	Long history	Secondary to ED
Partner problems	At onset	Secondary to ED
Anxiety/fear	Primary	Secondary to ED

Source: Persu *et al.*[7]

- Questionnaires are an integral part of the history

Table 2 The Sexual Health Inventory for Men (SHIM) or IIEF-5 over the past 6 months

1. How did you rate your confidence that you could get and keep an erection?		Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	No sexual activity 0	Almost never or never 1	A few times 2	Sometimes 3	Most times 4	Almost always or always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Did not attempt intercourse 0	Almost never or never 1	A few times 2	Sometimes 3	Most times 4	Almost always or always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did not attempt intercourse 0	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory to you?	Did not attempt intercourse 0	Almost never or never 1	A few times 2	Sometimes 3	Most times 4	Almost always or always 5

The IIEF-5 is administered as a screening instrument for the presence and severity of ED in conjunction with the clinical assessment. The score is the sum of the responses to the five items, so that the overall score may range from 1 to 25; no ED (total score, 22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), and severe ED (1–7).

- Sexual Health Inventory for Men (SHIM)
- values ≤21 being diagnostic of ED
- SHIM can be effectively used by a wide array of medical specialists

ED and CVD share common pathophysiology

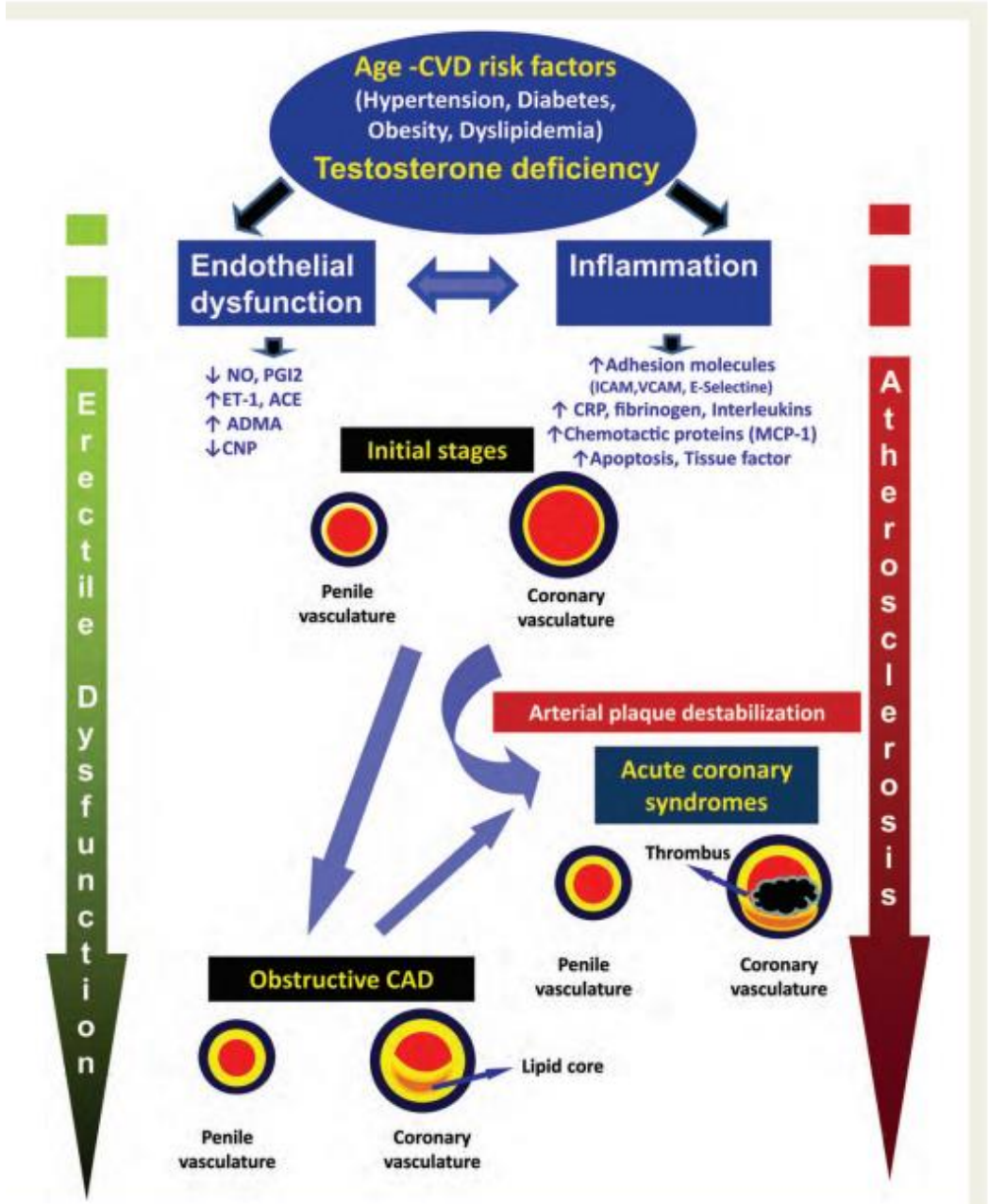


Figure 1 Links between endothelial dysfunction, inflammation, testosterone deficiency, erectile dysfunction, and coronary artery disease. Modified with permission from Vlachopoulos *et al.*[3]

MAYO CLINIC

The Princeton III Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease

Ajay Nehra, MD; Graham Jackson, FRCP, FESC; Martin Miner, MD; Kevin L. Billups, MD; Arthur L. Burnett, MD, MBA; Jacques Buvat, MD; Culley C. Carson, MD; Glenn R. Cunningham, MD; Peter Ganz, MD; Irwin Goldstein, MD; Andre T. Guay, MD; Geoff Hackett, MD; Robert A. Kloner, MD, PhD; John Kostis, MD; Piero Montorsi, MD; Melinda Ramsey, PhD; Raymond Rosen, PhD; Richard Sadovsky, MD; Allen D. Seftel, MD; Ridwan Shabsigh, MD; Charalambos Vlachopoulos, MD; and Frederick C. W. Wu, MD

Abstract

The Princeton Consensus (Expert Panel) Conference is a multispecialty collaborative tradition dedicated to optimizing sexual function and preserving cardiovascular health. The third Princeton Consensus met November 8 to 10, 2010, and had 2 primary objectives. The first objective focused on the evaluation and management of cardiovascular risk in men with erectile dysfunction (ED) and no known cardiovascular disease (CVD), with particular emphasis on identification of men with ED who may require additional cardiologic work-up. The second objective focused on reevaluation and modification of previous recommendations for evaluation of cardiac risk associated with sexual activity in men with known CVD. The Panel's recommendations build on those developed during the first and second Princeton Consensus Conferences, first emphasizing the use of exercise ability and stress testing to ensure that each man's cardiovascular health is consistent with the physical demands of sexual activity before prescribing treatment for ED, and second highlighting the link between ED and CVD, which may be asymptomatic and may benefit from cardiovascular risk reduction.

Nehra A. Wu FC. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012 Aug;87(8):766-78.

Men with ED and no known CVD

History	Lifestyle Factors	Physical Exam	ED Severity, Duration	Diagnostics
Age	Diet	BP	*International Index of Erectile Function score or Sexual Health Inventory of Men*	Resting ECG
Abdominal obesity	Excessive alcohol	Waist circumference		Fasting plasma glucose
HTN	Limited Physical Activity	Body mass index (BMI)		Serum creatinine & albumin to creatinine ratio
HLD	Smoking	Fundal arterial changes		Plasma lipid levels
Prediabetes		Cardiac auscultation		*Total testosterone (before 11 am)*
Symptoms of OSA		Carotid bruits		
Family History of premature CVD		Femoral and pedal artery palpation		

Nehra A. Wu FC. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012 Aug;87(8):766-78.

Testosterone Replacement and CV Disease

- low testosterone levels are associated with an increase in mortality due to cardiovascular events,
- testosterone replacement therapy did not show a substantial reduction in the incidence of CVDs in men affected by ED

ORIGINAL ARTICLE

Cardiovascular Safety of Testosterone-Replacement Therapy

A. Michael Lincoff, M.D., Shalender Bhasin, M.B., B.S., Panagiotis Flevaris, M.D., Ph.D., Lisa M. Mitchell, R.N., B.S.N., Shehzad Basaria, M.D., William E. Boden, M.D., Glenn R. Cunningham, M.D., Christopher B. Granger, M.D., Mohit Khera, M.D., M.P.H., Ian M. Thompson, Jr., M.D., Qiuqing Wang, M.S., Kathy Wolski, M.P.H., et al., for the TRAVERSE Study Investigators*

Article Figures/Media Metrics

July 13, 2023
N Engl J Med 2023; 389:107-117
DOI: 10.1056/NEJMoa2215025
Chinese Translation 中文翻译

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Abstract

BACKGROUND The cardiovascular safety of testosterone-replacement therapy in middle-aged and older men with hypogonadism has not been determined.

METHODS In a multicenter, randomized, double-blind, placebo-controlled, noninferiority trial, we enrolled 5246 men 45 to 80 years of age who had preexisting or a high risk of cardiovascular disease and who reported symptoms of hypogonadism and had two fasting

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Corona, G.G.; Rastrelli, G.; Di Pasquale, G.; Sforza, A.; Mannucci, E.; Maggi, M. Endogenous Testosterone Levels and Cardiovascular Risk: Meta-Analysis of Observational Studies. *J. Sex. Med.* **2018**, *15*, 1260–1271

July 13, 2023. N Engl J Med 2023; 389:107-117

ED in CVD

regardless of the clinical presentation, the advanced coronary and ⋮ with known CVD: ED increased the risk of all-cause mortality by

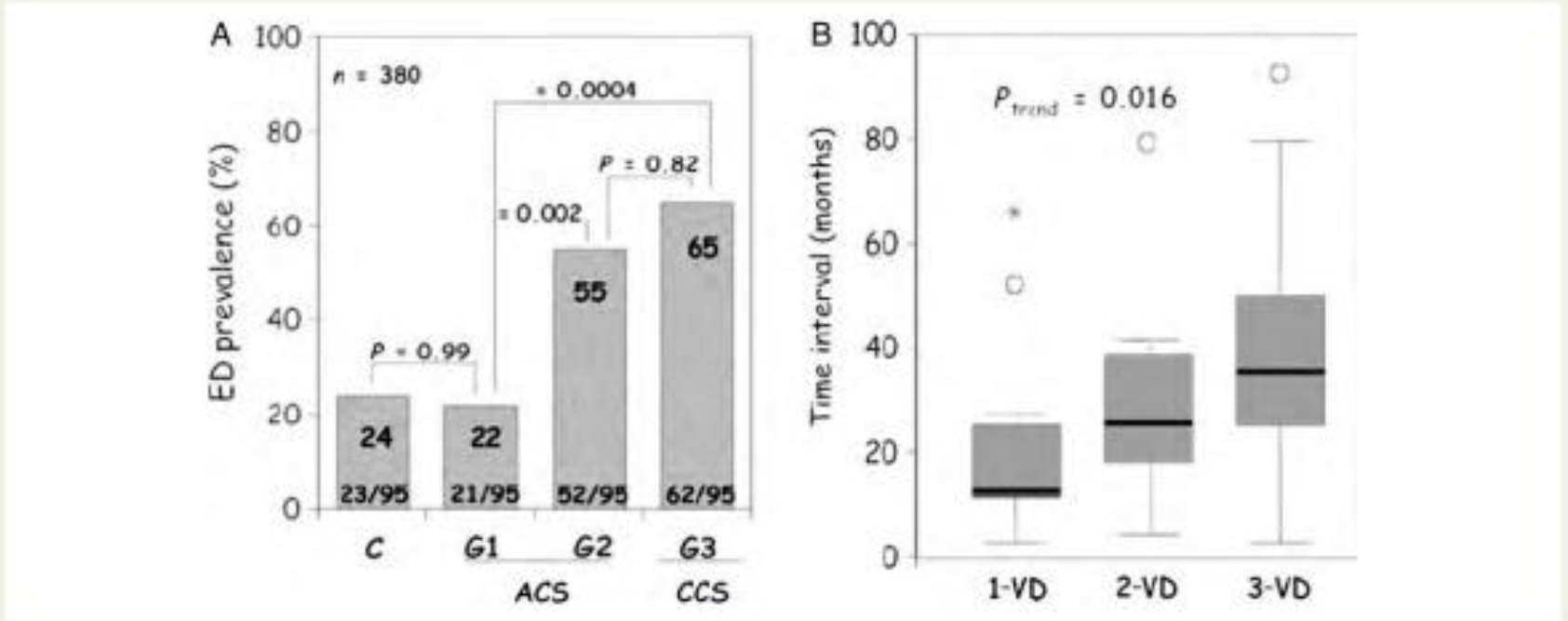


Figure 3 Relation between erectile dysfunction prevalence and type of coronary syndrome (*A*). Time interval (months) between erectile dysfunction and coronary artery disease symptom onset in chronic coronary syndrome according to the number of vessels involved (*B*). ACS, acute coronary syndrome; CCS, chronic coronary syndrome, G1: ACS and 1-VD; G2: ACS and 2-,3-VD; G3: CCS. VD, vessel disease; C: the control group with normal coronary angiography. With permission from Montorsi *et al.*[15]

ED in patients with no known CVD

- ED as their first and sole clinical manifestation of subclinical CAD

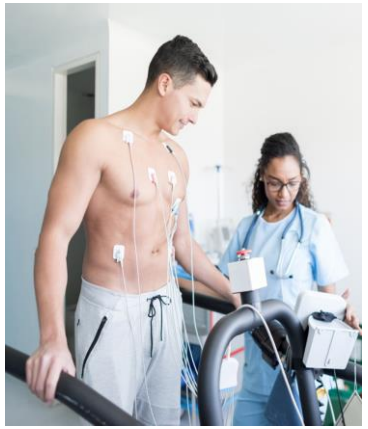
Table 3. Management of a patient with CVD or without known CVD

A. Patients without established CVD or diabetes

Low SCORE /FRS	Moderate SCORE/FRS	High or Very high SCORE/FRS
Exercise ability Lifestyle advice or intervention Treatment of RFs PDE5i	Exercise ability or stress test (in higher scores) Lifestyle intervention Consider drug intervention if RF uncontrolled PDE5i	Cardiologist referral Stress test Lifestyle intervention RF drug intervention PDE5i Tth‡
if biomarker abnormal and/or hypogonadism	*if biomarker abnormal and/or hypogonadism*	
Exercise ability or stress test Lifestyle intervention RF drug intervention PDE5i Tth‡	Stress test Lifestyle intervention RF drug intervention PDE5i Tth‡	

B. Patients with established CVD or diabetes

Low risk*	Indeterminate risk**		High risk***
	Low risk (negative stress test)	High risk (positive stress test)	
Exercise ability or stress test Lifestyle intervention RF drug intervention PDE5i Tth‡	Lifestyle intervention RF drug intervention PDE5i Tth‡	Deferral of sexual activity Cardiologist referral	Deferral of sexual activity Cardiologist referral



Exercise Ability and Sexual Activity Risk Stratification

- *Risk refers to the likelihood of mortal or morbid events during or shortly after sexual activity*

- Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing 2 flights of stairs in 10 seconds
- Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.
  - Equates to approximately 4-5 METS
- Sexual activity between couples in longstanding relationships equates to approximately 3 METS

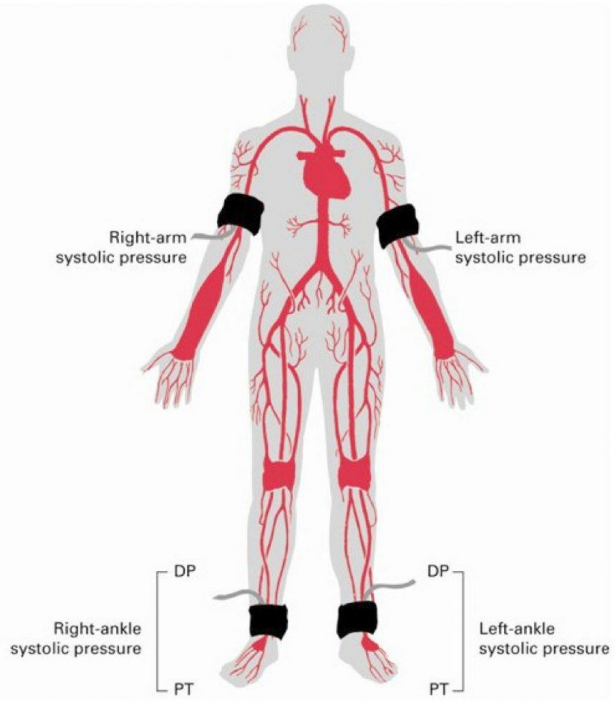
Cardiac Evaluation in Asymptomatic Individuals

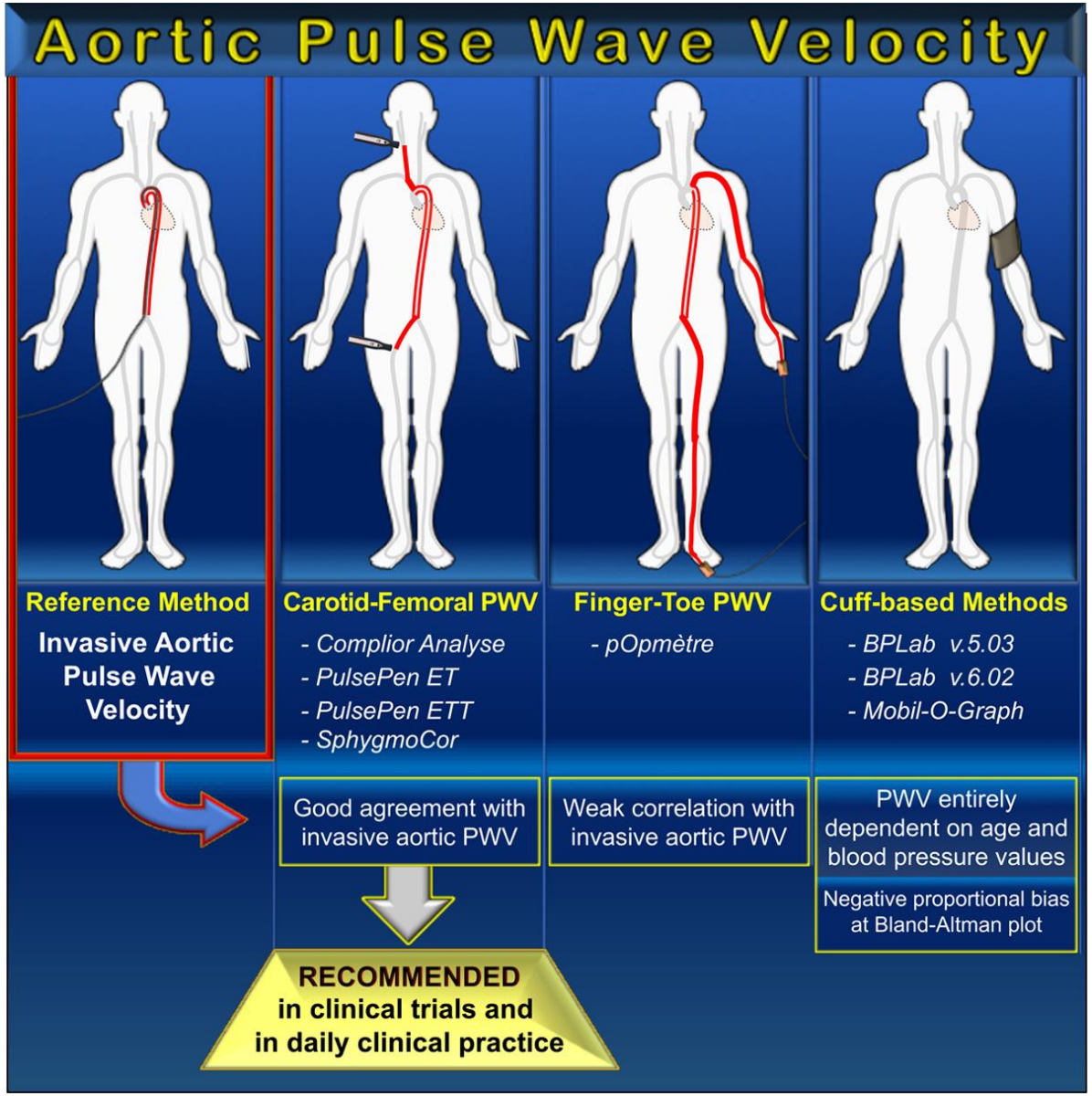
- Biomarkers
- hsCRP

Table 4 Prognostic markers of cardiovascular disease in the patient with erectile dysfunction

Biomarkers	Association with vasculogenic ED	Overall CVD predictive value	Association with CV prevalence in ED	CVD predictive value in ED	Response to treatment	Availability	Cost
Testosterone	+++	++	+	+	+	++++	+
High sensitivity C-reactive protein	++	+++	+	–	+	++++	+
Fibrinogen, IL-6	+++	++	+	–	+	++	++
IMT	+++	+++	+	–	+	++	++
Aortic stiffness	++	+++	+	–/+	+	++	++
ABI	++	+++	+	–	–	+++	+
CCTA	++	+++	+	–	–	+	+++
CAC	++	++	+	–	–	+	+++
Endothelial Dysfunction	+++	++	+	–	++	++	++
Albuminuria	+	+++	+	+	–	++++	+
Penile Doppler	++++	–	+	+	++	+	+++

ABI, ankle-brachial index; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; CVD, cardiovascular disease; ED, erectile dysfunction; IL-6,



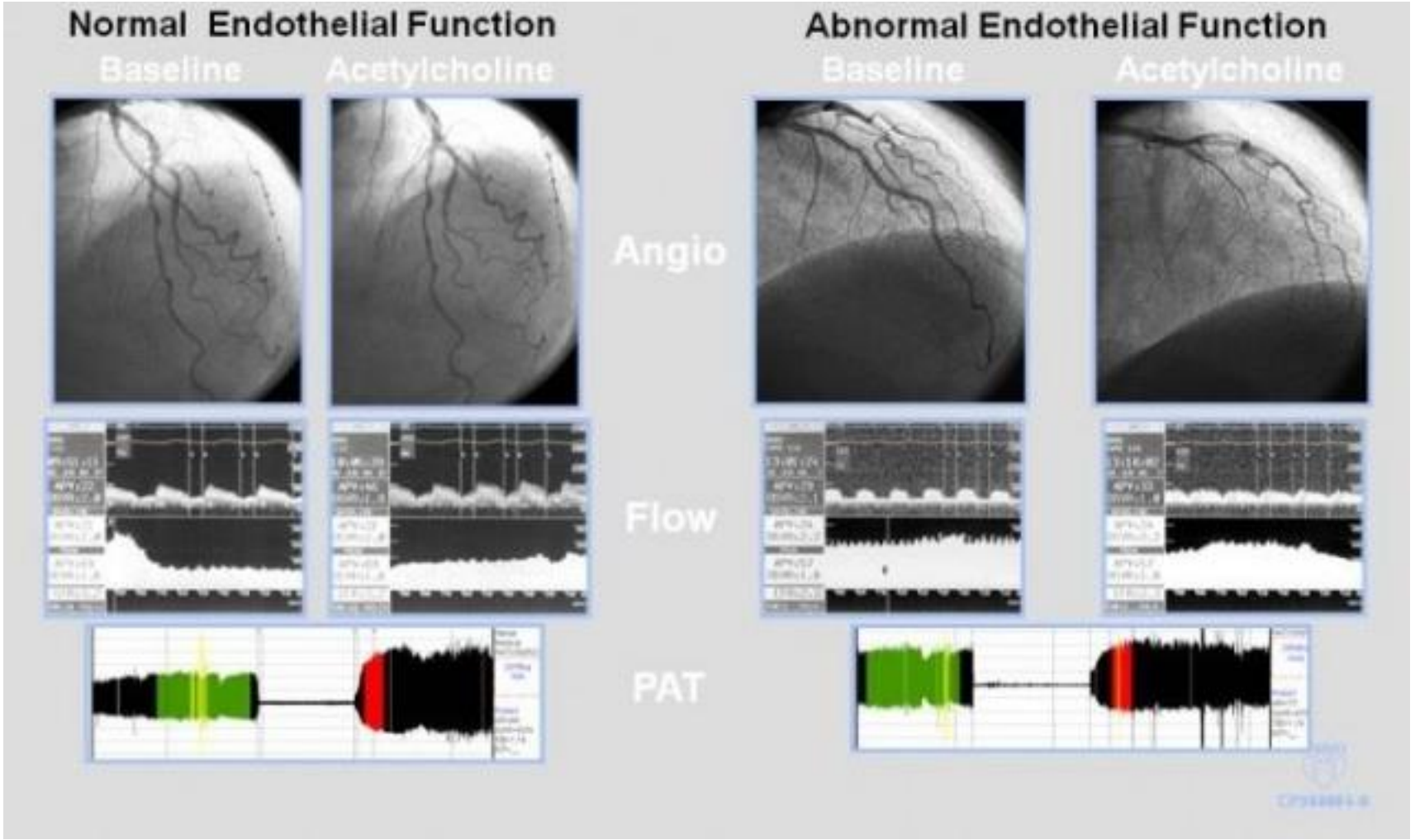


Paolo Salvi. Hypertension. Noninvasive Estimation of Aortic Stiffness Through Different Approaches, Volume: 74, Issue: 1, Pages: 117-129, DOI: (10.1161/HYPERTENSIONAHA.119.12853)

Endothelial Dysfunction

- earliest detectable stage of cardiovascular disease.
- it is treatable, and unlike the atherosclerotic plaque that it causes
- it is even reversible

Endothelial Function Testing



Coronary Function Testing in the Cardiac Cath Lab

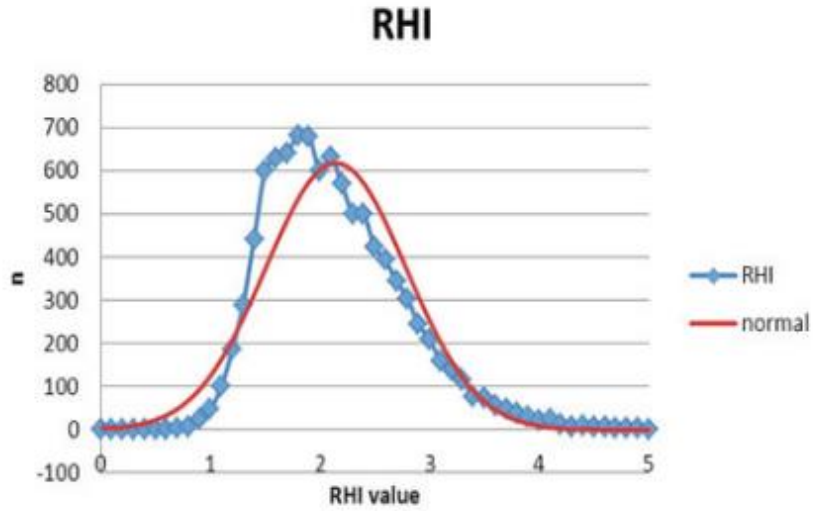
Peripheral Endothelial Function Testing in the Clinic

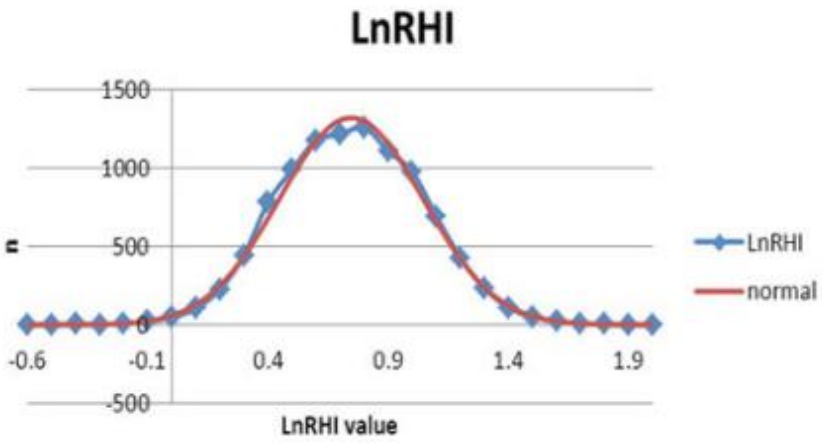
https://web.archive.org/web/20220316194340/https://www.itamar-medical.com/endothelial-dysfunction/

Reactive Hyperemia

- Developed in 1992 scientists
- research technique for assessing endothelial dysfunction using high resolution US imaging of the brachial artery
- **reactive hyperemia procedure**
- requires 5 min occlusion and release of the brachial artery blood flow using a blood pressure cuff, and manually measuring the diameter of the brachial artery using a high-frequency ultrasound imaging probe.
- If the brachial artery diameter increases in less than 5% it indicates endothelial dysfunction and a sign of cardiovascular disease
- If the brachial artery diameter increases more than 10% it is a clear indication for healthy endothelial function.
  - The healthier the artery – the larger the reactive hyperemic response.

Non-Invasive Measure of Endothelial Function





Endothelial Dysfunction and Erectile Dysfunction

HEALTHY ENDOTHELIUM

- Selective permeable barrier
- Antioxidant effects
- Anticoagulant effects
- Fibrinolytic effects
- Blood flow and vascular resistances modulator
- Hormonal and metabolic activities regulator

RISK FACTORS:

- Turbulent blood flow
- Ageing
- Smoking
- Vascular injury
- Chronic inflammatory state
- Diabetes mellitus
- Hypertension
- Hypercholesterolemia and homocystinemia
- Infections and complement activation
- Sedentary lifestyle
- Alcohol abuse
- Obesity or metabolic syndrome

FUNCTIONAL CHANGES-ENDOTHELIAL DYSFUNCTION

- Altered NO response
- Vasoconstriction
- Procoagulant state
- Antifibrinolytic effects
- Increased expression of adhesion molecules
- Release of pro inflammatory factors
- Altered expression of cytokines, chemokines and growth factors
- ROS production
- Leukocyte infiltration

STRUCTURAL CHANGES

- Atherothrombotic plaque formation, inflammation

Lifestyle and pharmacological treatment:

Treatment Options

- Lifestyle modifications: diet, exercise, smoking cessation
- Medications: PDE5 inhibitors (Viagra, Cialis)
- Addressing underlying cardiovascular conditions

Lifestyle Modifications

Diet
•**Fruits and vegetables**
•**Two or more 3.5 ounce servings of fish per week**
•**Fiber-rich whole grains**
•**Less than 1,500 mg of sodium/day**
•**Limit added sugars or beverages**
•**Limit saturated fat <6% of total calories**
•**Mediterranean Diet –lower risk by 30%**

Exercise
At least 150 min per week (2 hours 30 mins) of moderate intensity exercise, or
At least 75 min of vigorous activity per week
Strengthen muscles and bones at least 2 days per week
Heart rate goal: 220 – age x 50-85%
Manage Stress

Treatment Options

Cardiovascular Conditions

Managing hypertension, diabetes, and coronary artery disease

Collaboration between urologists and cardiologists

Psychological Aspects

Importance of open communication with a healthcare provider

Address the psychological impact of ED

Drugs that effect the ED and the CV system

- Treatment for ED should not negatively affect cardiovascular health.
  - PDE5i (sildenafil, etc) should be avoided within 24 hours of nitrate use
- Conversely, potential effects on erectile function of agents used to treat cardiovascular risk factors should be considered
  - β–blockers
  - Antihypertensives

Thank You