

Men:- Their hearts and private parts

Dr Clive JS Low

Consultant Interventional & General
Cardiologist



Why am I talking to you?

- Full time private. 80 % consulting
- all elective work
- mainly IHD practice
- strong interest in prevention
- Chairman Heart Centre/HC@StG's
JV/Heart Vision
- not too academic/pragmatic (cynical??)

Why am I talking to you?

“A Professor is someone who talks in someone else’s sleep!!”

Mark Twain

The Clinical Conundrum

- What is an individual's cardiovascular risk?
- What is the appropriate risk reduction and CVD surveillance strategy for that patient

The Clinical Conundrum

- Population risk strategies are different to Individual risk strategies
- eg NNT “if you treat 200 patients you will prevent 1 event”
- For an individual death is a binary endpoint!!

Current risk estimation strategy

- NHF table or computer/internet risk estimation
- Based on Framingham or Munster data
- Prospective/Observational
- Good, but lack accuracy for an individual

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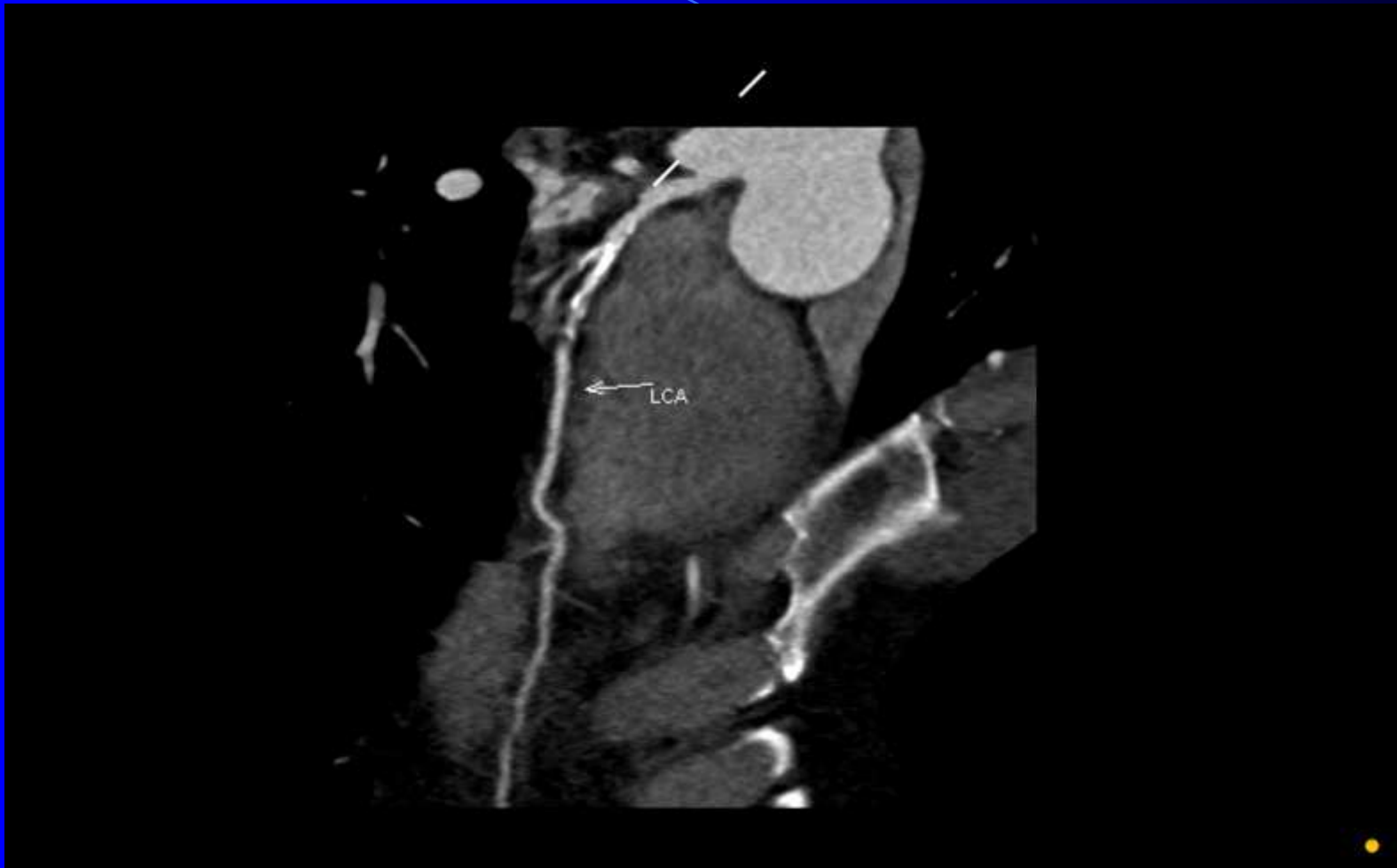
Case 1 – Mr NC aet47

- No angina. Gym 3xwk
- Brother AMI 46. No risk factors. 3vd.
- Normal exam. BP100/58. BMI 24
- TC4.8 TG0.7 HDL1.6 LDL2.9 Lp(a) 764
hsCRP 1.42

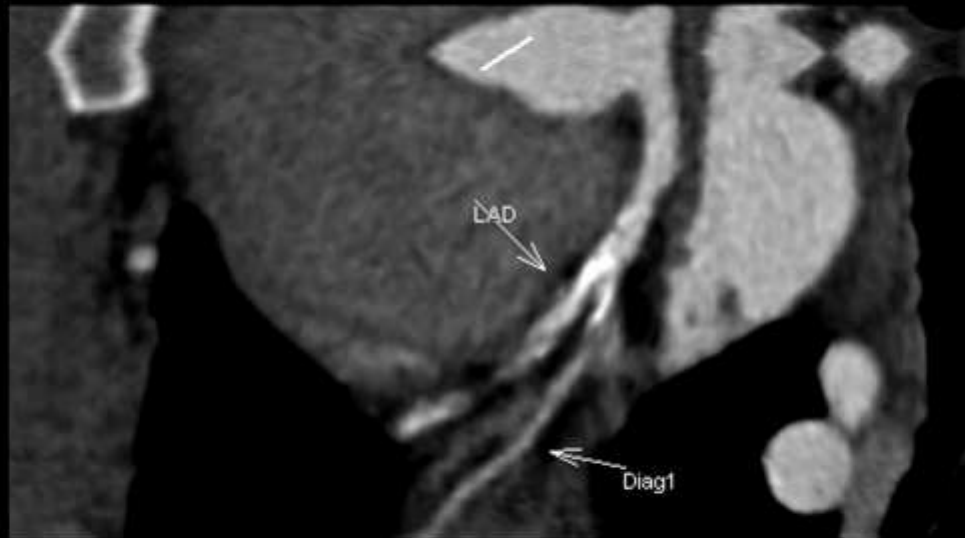
Ex ECG 13'18" Bruce. Max HR 172 (97% PMHR)
No Angina. Normal ECG



Case 1 – Mr NC aet47



Case 1 – Mr NC aet47



Case 1 – Mr NC aet47





Case 1 – Mr NC aet47



Case 1 – Mr NC aet47

- NHF risk estimate 5%/5yrs
 - 2.5% and double it because of family history
- Actual risk greater than 30%/5yrs



What do we do for Case 1

- Throw the book at him
 - Aspirin/Statin/Omega 3/?nicotinic acid PLUS ALL THE LIFESTYLE INTERVENTIONS HE WAS DOING PERFECTLY ALREADY!!!

What do we do for Case 1

Simvastatin reduces 5 yr risk of MI by 25%

Absolute 5yr risk	Relative risk reduction	Absolute 5yr risk with intervention
2.5%	25%	1.9%
30%	25%	22.5%

So is there anything that's easy??

- Low risk patients (<5%/5yr)
 - be good and come back in 5 yrs
- High risk patients (>30%/5yr)
 - use all treatments hard
- Intermediate risk
 - We aren't sure what to do!!

So what's hard about that??

- At least 40% of US population is Intermediate risk!!
- We need tools to reclassify/reassign as many as possible to low or high risk groups so it's easy!!

Which “intermediate” risk patients are really high risk?

-That’s easy – those who have IHD but don’t know it yet!!

- Exercise ECG – positive
- CT coronary calcification
- Abnormal coronary angiogram (CT or invasive)

How good is Ex ECG?

- Meta-analysis 147 studies/ 24074 patients
- Coronary Angiogram and Ex ECG
 - Sensitivity 68 % sd16% (23 – 100%)
 - Specificity 77% sd17% (17-100%)
- Considerable problems with accuracy
 - risk of false positive in low risk patients
 - risk of false negative in high risk patients

•Gianossi, Circulation 1989;80:87-98



What is the definition of a double-blind trial?

Two Orthopaedic Surgeons looking at an ECG!

Which “intermediate” risk patients are really high risk?

-That’s easy – those who have IHD but don’t know it yet!!

-Exercise ECG – positive

-**CT coronary calcification**

-Abnormal coronary angiogram
(CT or invasive)

How good is CT Calcium scoring?

- CTCA score <100
 - <2% chance of abnormal perfusion scan
 - <3% chance of obstructive CAD on angiogram
- Studies > 7600 symptomatic patients
 - Negative predictive value 96-100%

How good is CT Calcium scoring?

- CTCA score >100
 - RR 8 for coronary event in next 4.3 yrs
- CTCA score >300
 - RR 10 for coronary event in next 4.3 yrs
- Additional predictive value over Framingham/
NZ scoring

4 ethnic groups, 6722 adults, mean age 62

•NEJM 2008 March 27; 358:1336



So why not do CT coronary calcium scoring on everyone?

- Radiation exposure
 - ok for over 50's
- Will not show non calcified plaque
 - ?less accurate in young patients
 - will not show “at risk” plaque

Which “intermediate” risk patients are really high risk?

-That’s easy – those who have IHD but don’t know it yet!!

- Exercise ECG – positive
- CT coronary calcification
- Abnormal coronary angiogram (CT or invasive)**

How good is CT Coronary Angiography?

- 64 slice GE
 - Negative predictive value 100%
 - Positive predictive value 85%
- Dual source Siemens (estimate)
 - Negative predictive value 100%
 - Positive predictive value 90+%



•CRG/CDHB unpublished data



But surely you'd have to be
mad to propose screening
invasive coronary
angiography ?

I am mad, and stop calling me Shirley!!

Gratuitous car porn...



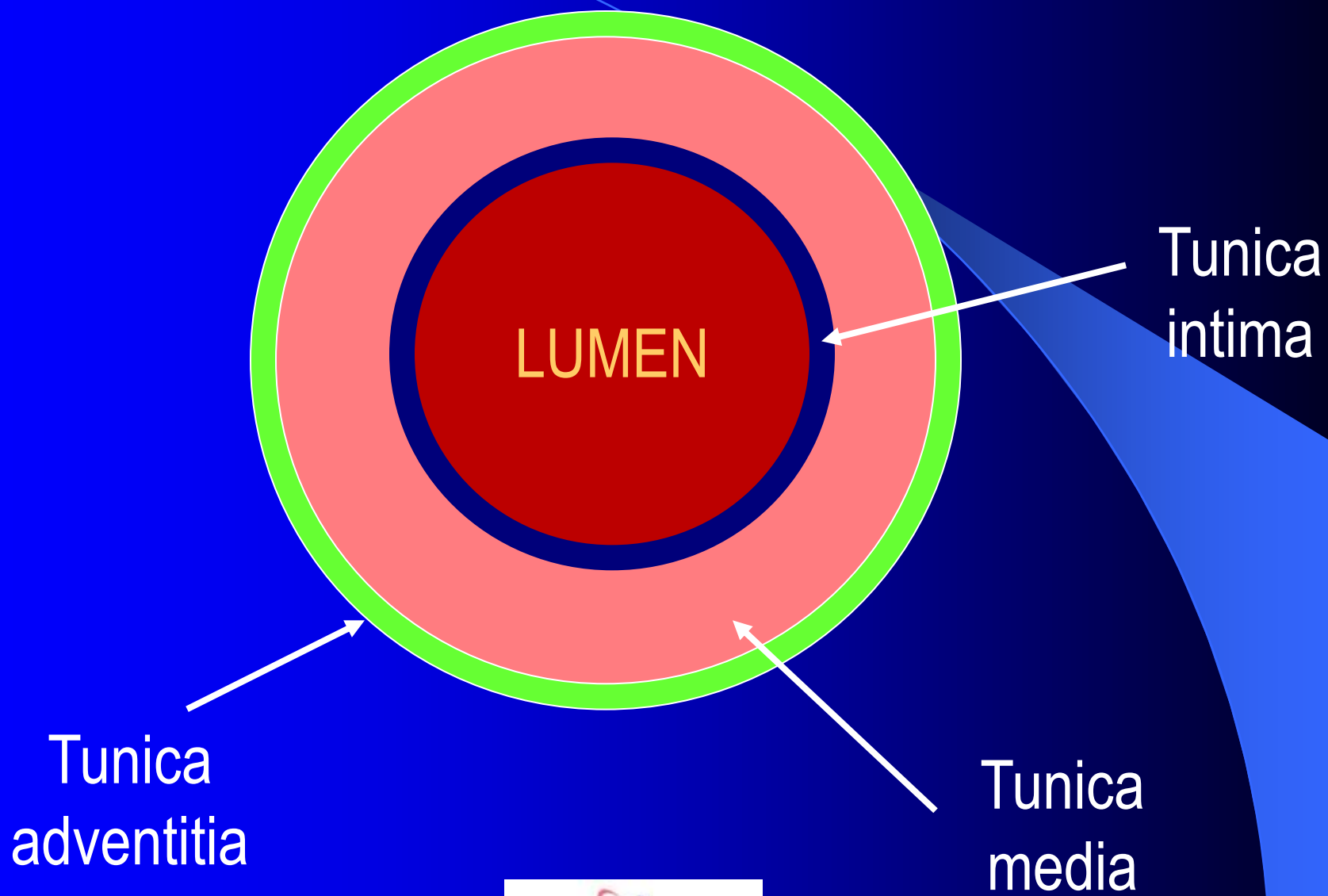
So what about the group where CT is inappropriate?

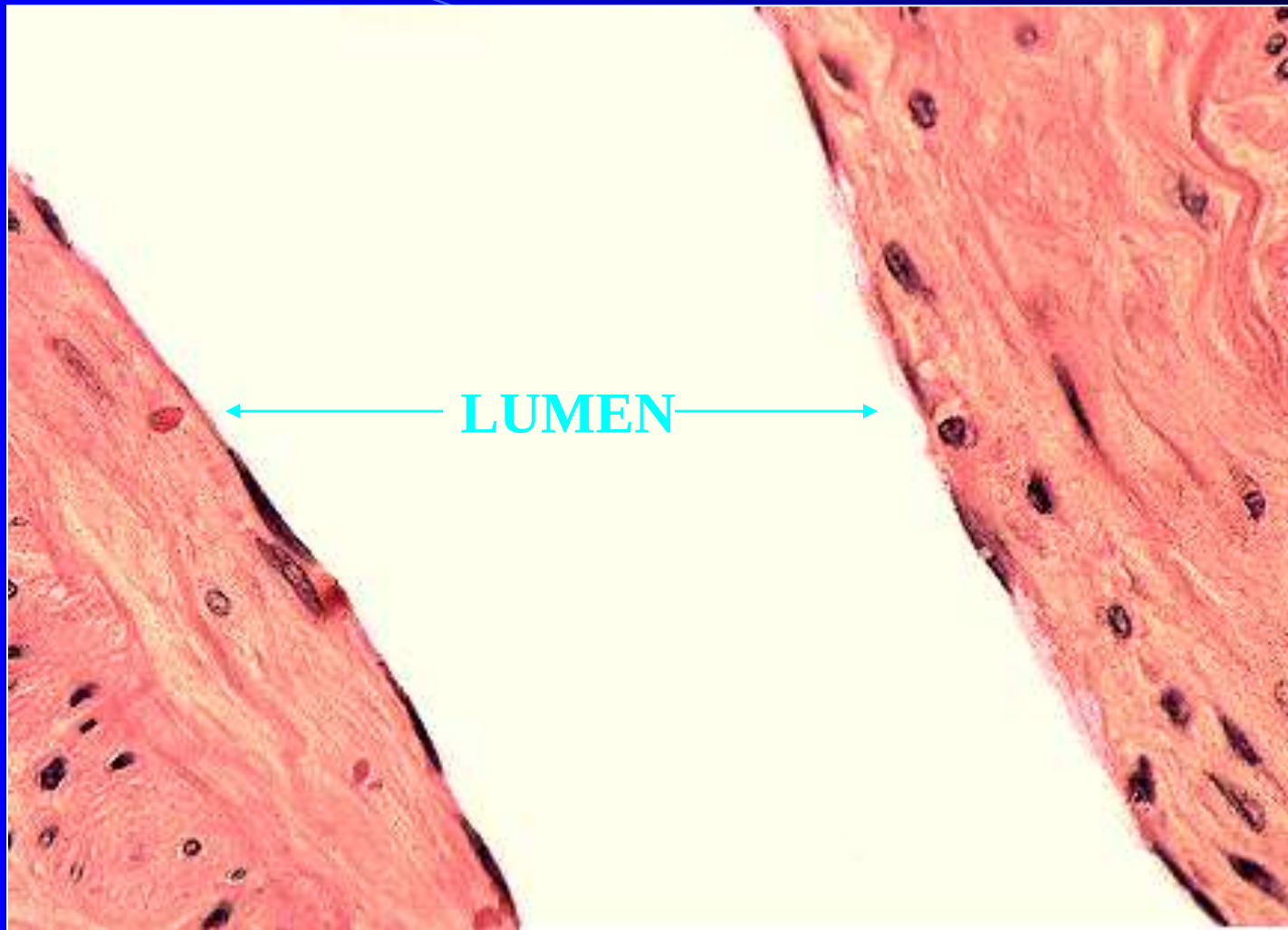
- Back to basics
 - what is the time course of CVD
- Can we detect the beginnings of CVD
 - finally he talks about the endothelium!
 - endothelial function testing/Carotid US IM ratio

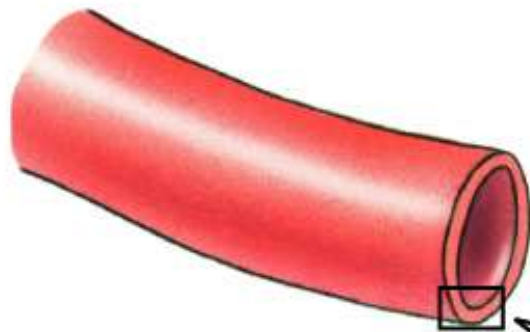
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Off to the internet...

Internet ready –A man who can operate a mouse or computer pointing device with his non-dominant hand.





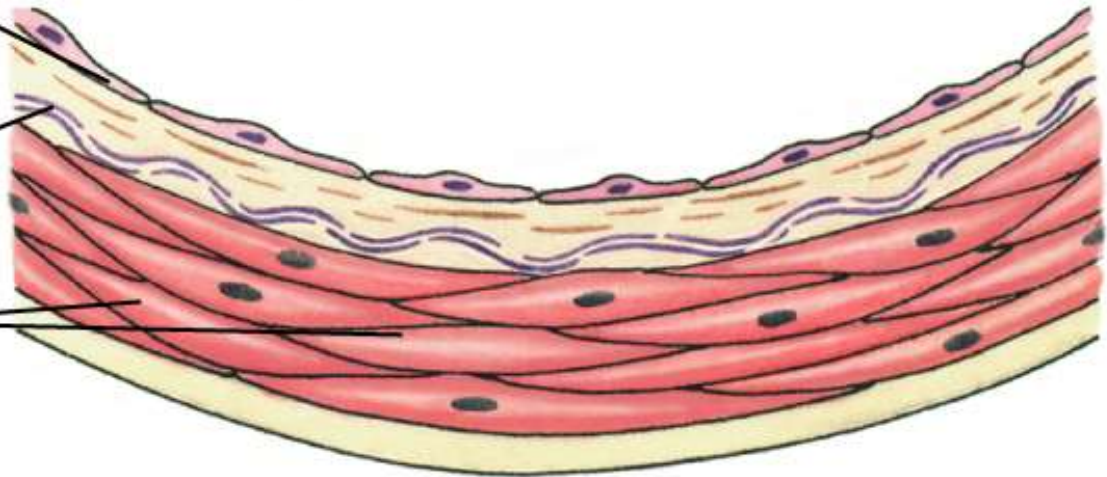


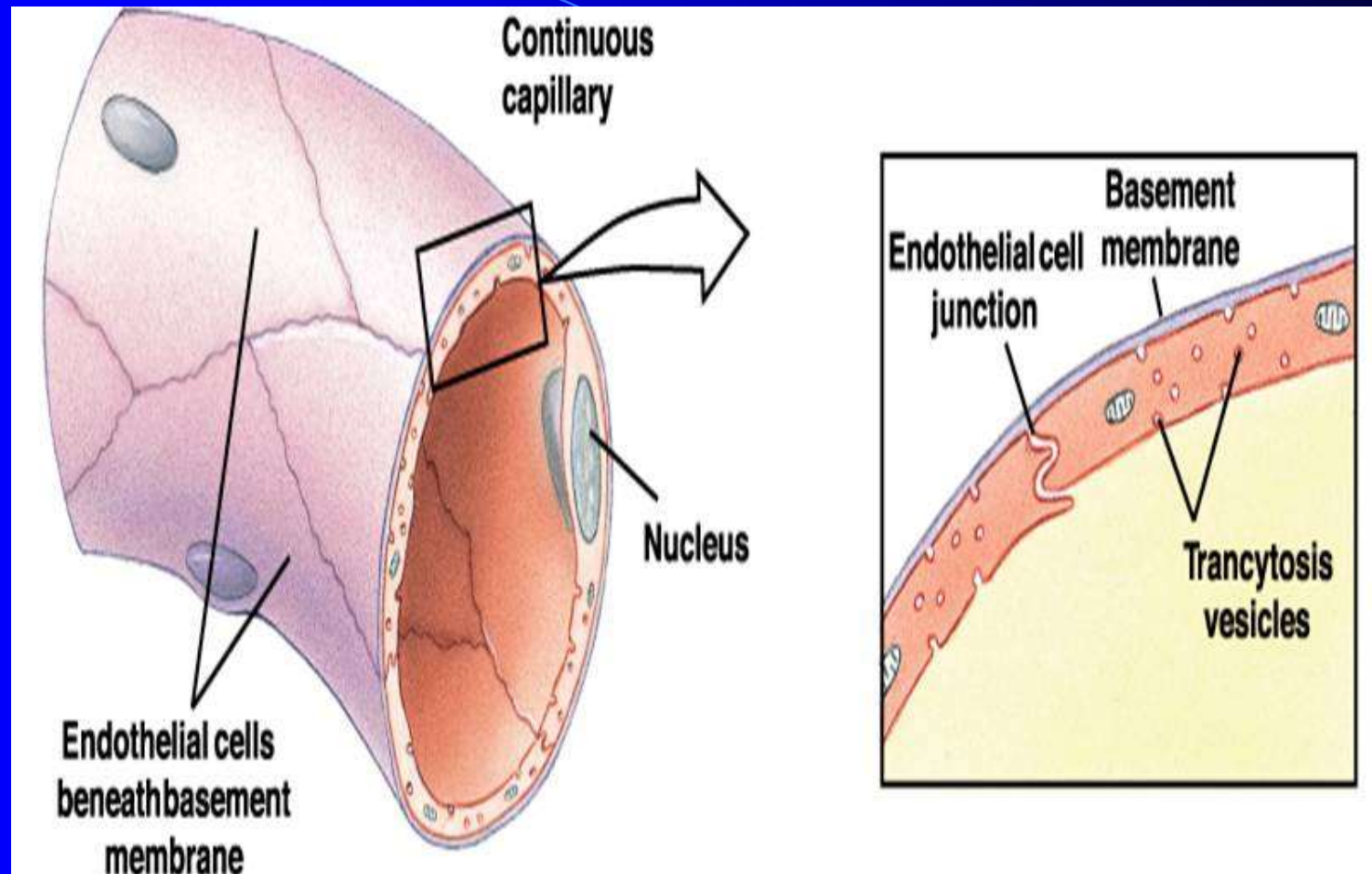
Normal arterial wall

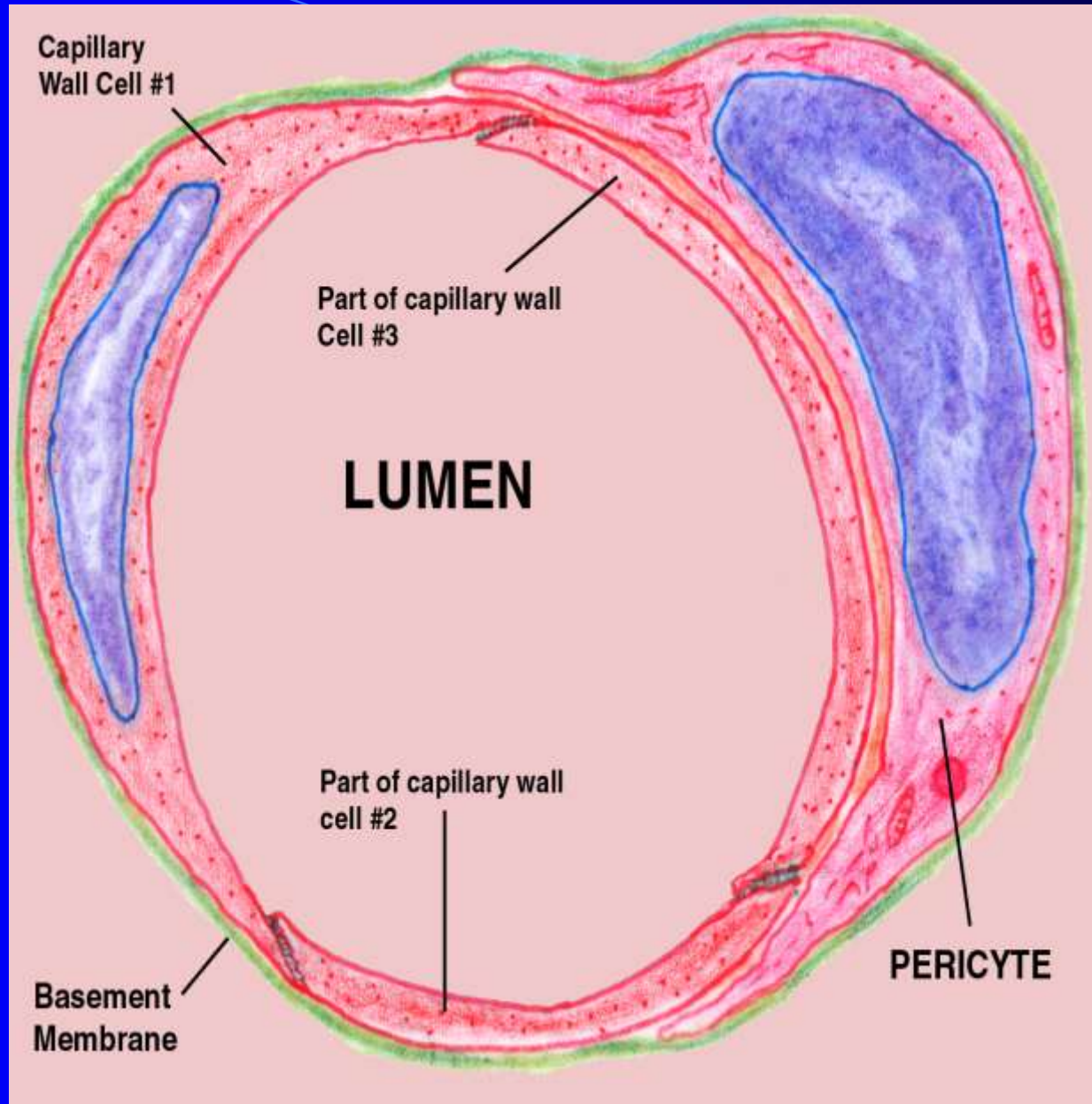
Endothelial cells

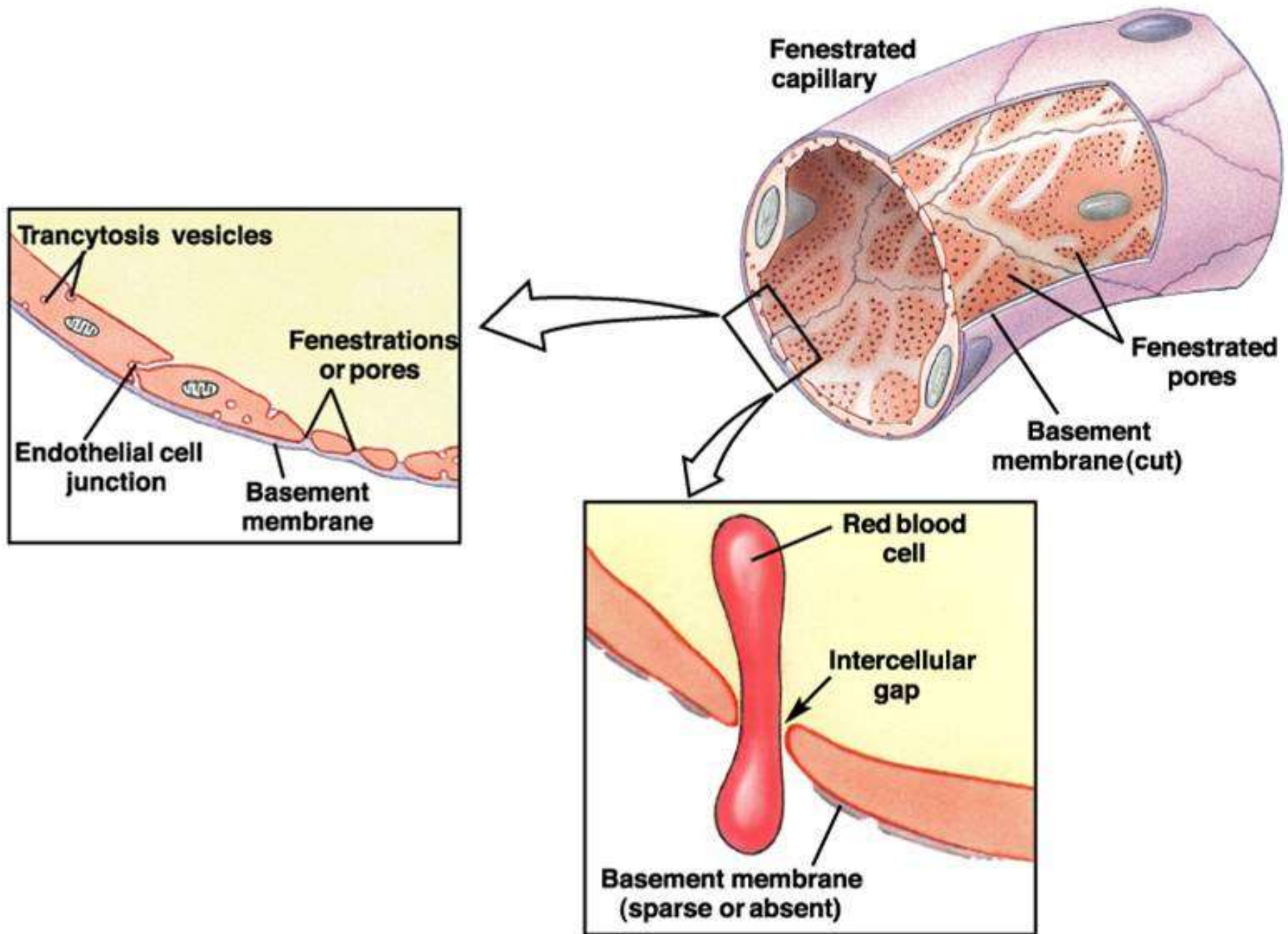
**Elastic connective
tissue**

**Smooth
muscle cells**

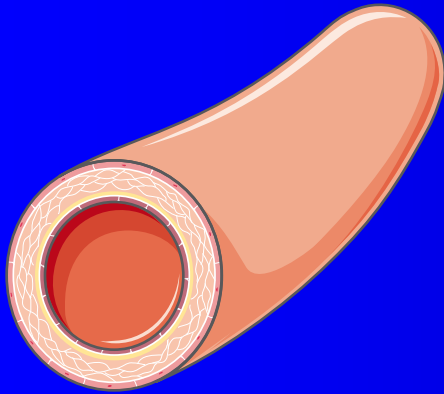




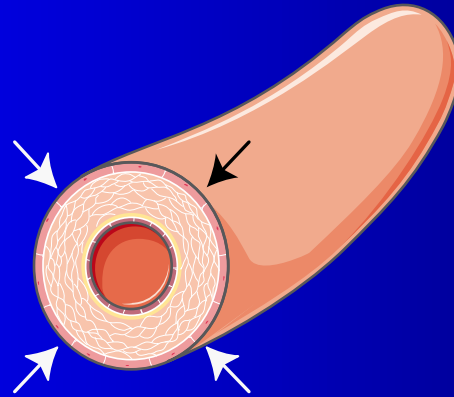




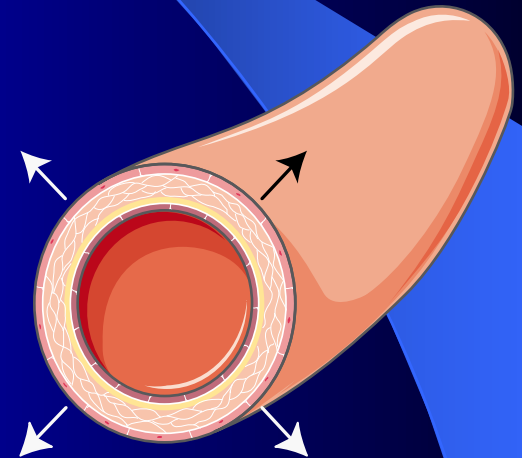
Vasoconstriction and dilatation



Normal



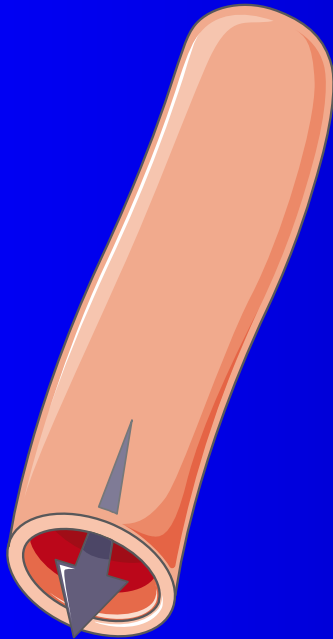
Vasoconstriction



Vasodilatation

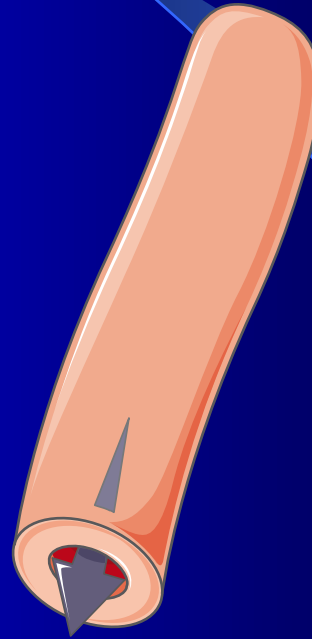
Vasoconstriction and dilatation

↓ Resistance to flow



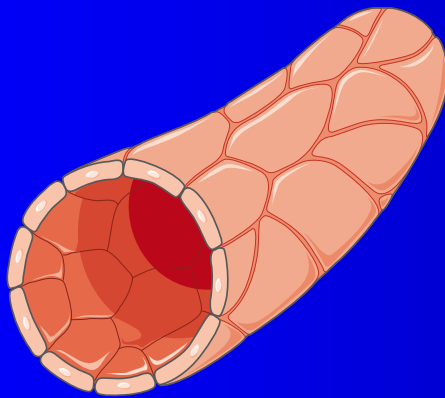
Vasodilatation

↑ Resistance to flow

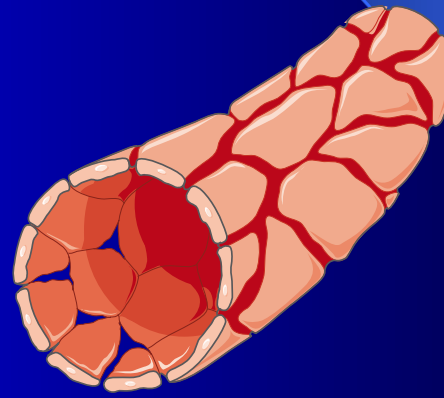


Vasoconstriction

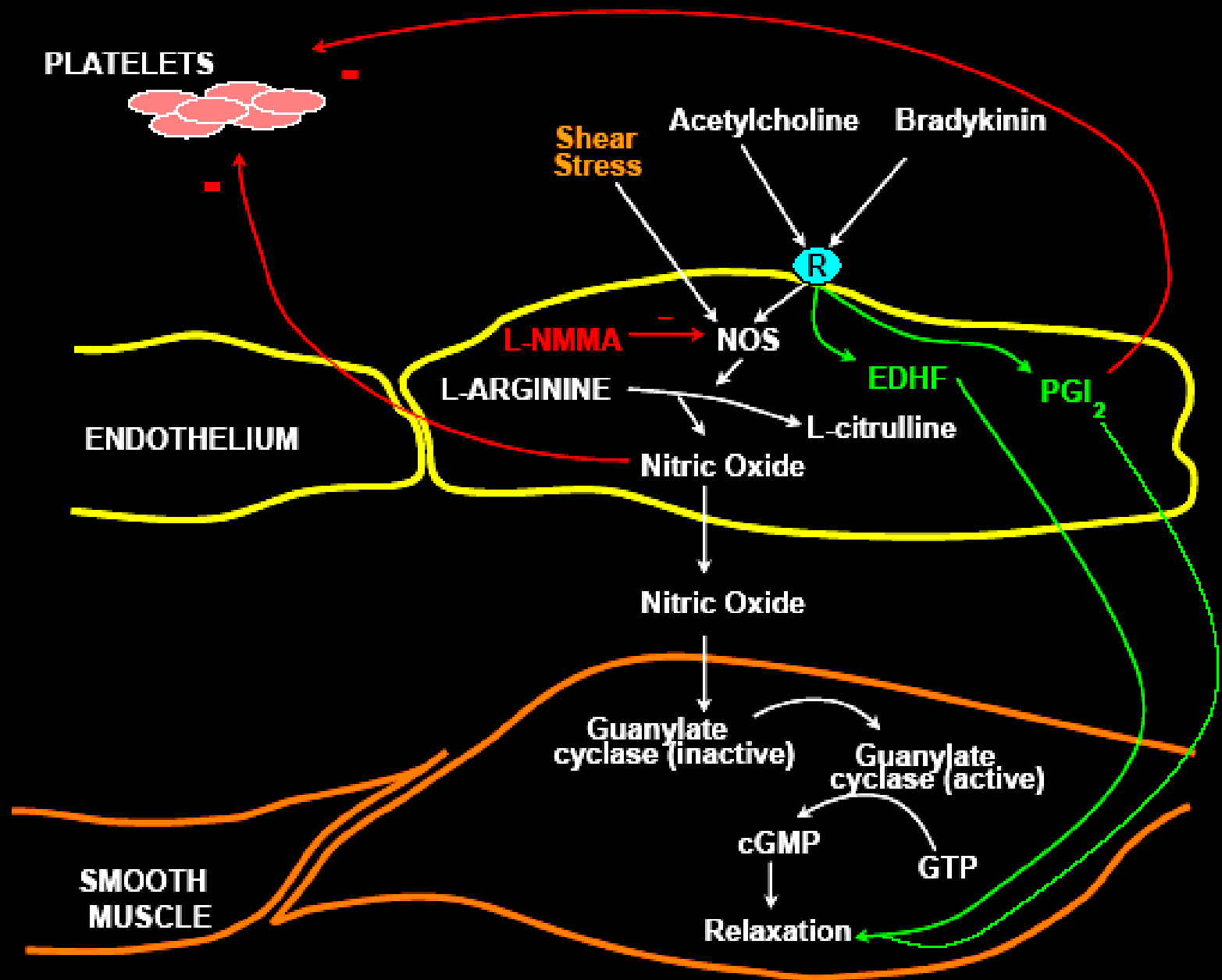
Endothelial Apoptosis



Normal



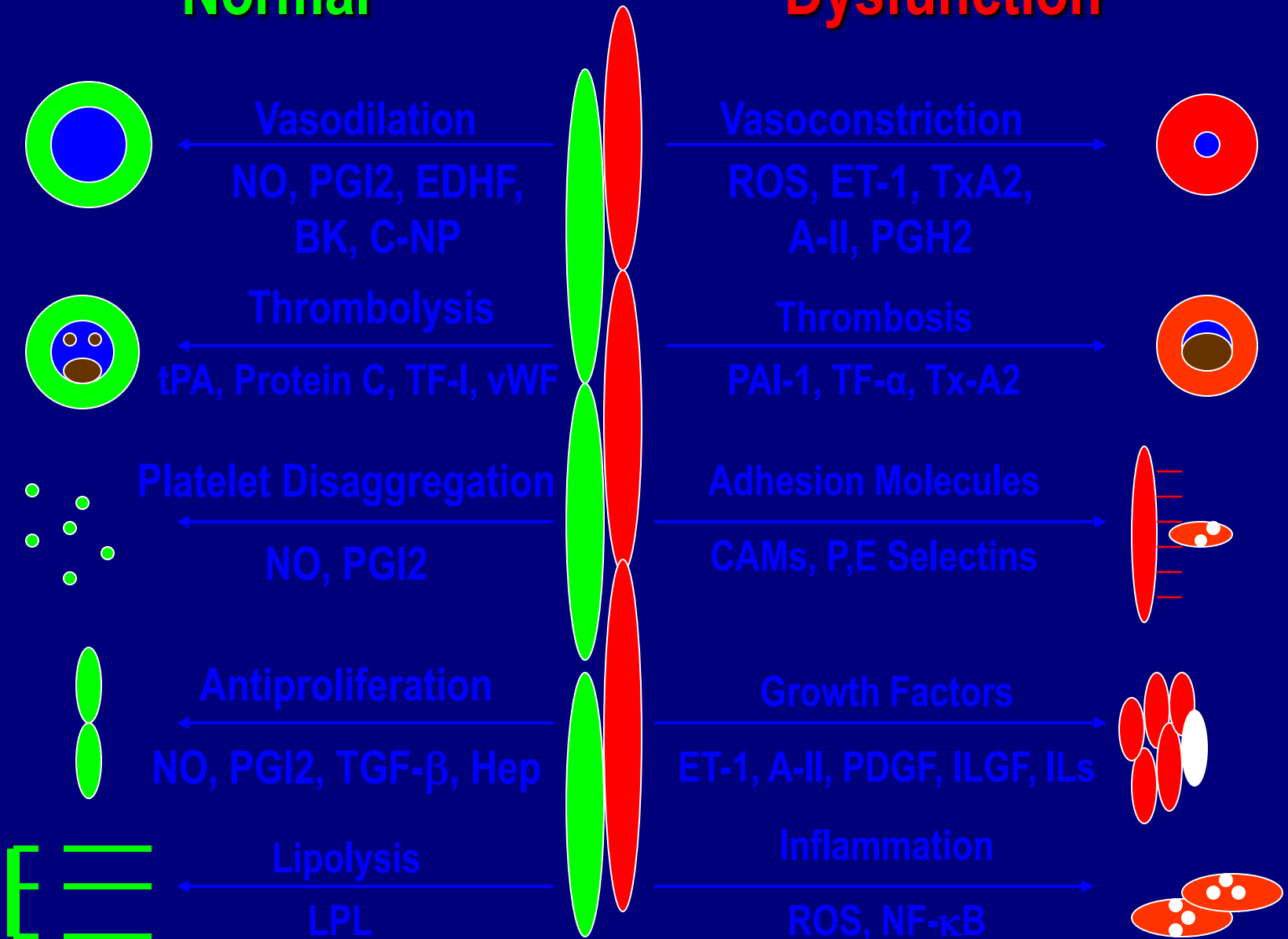
Apoptosed



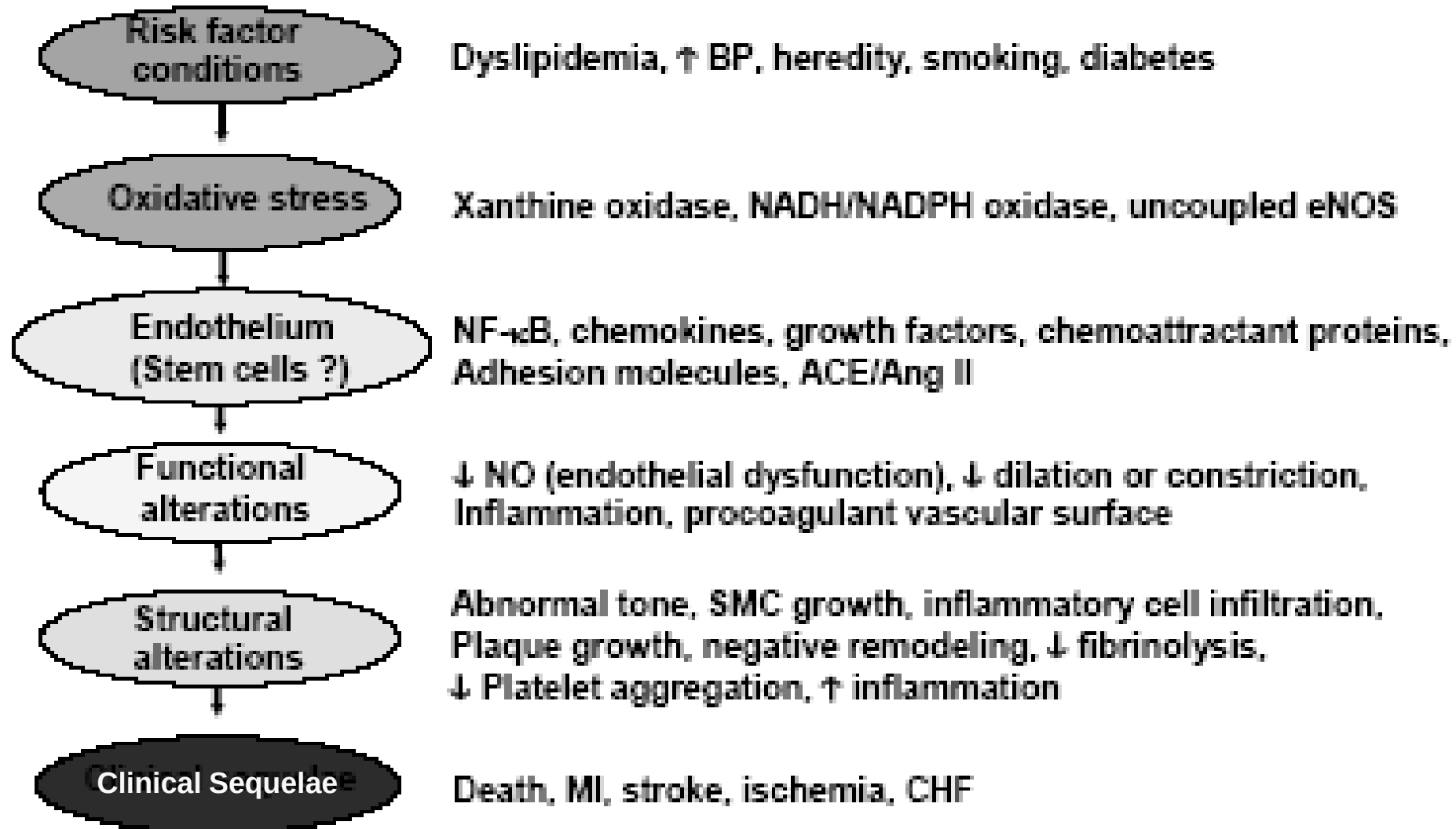
Regulatory Functions of the Endothelium

Normal

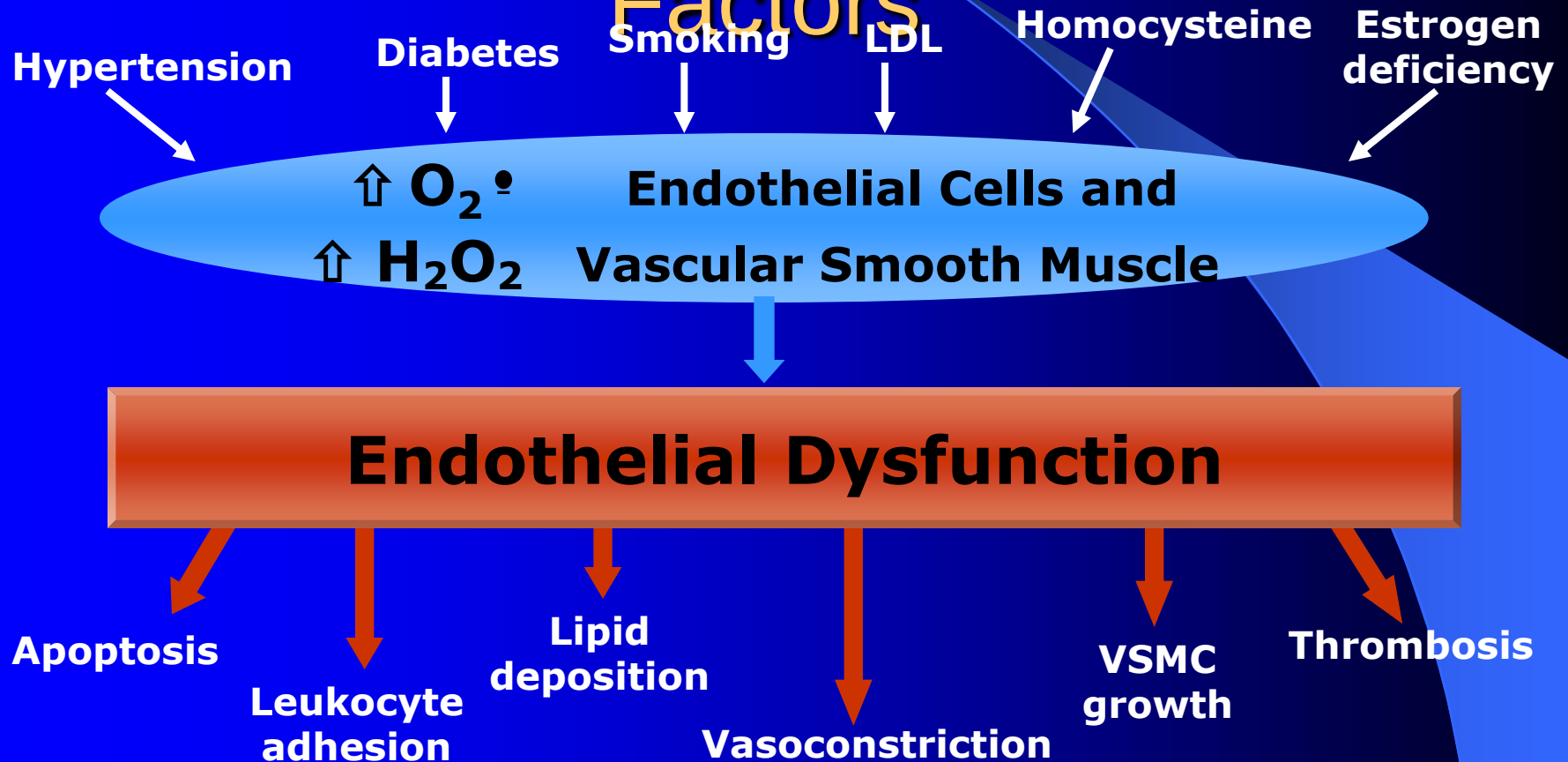
Dysfunction



Pathophysiology of vascular disease



Oxidative Stress: Endothelial Dysfunction and CAD/Renal Risk Factors



Clinical Methods for Assessing Endothelium - Dependent Dilation

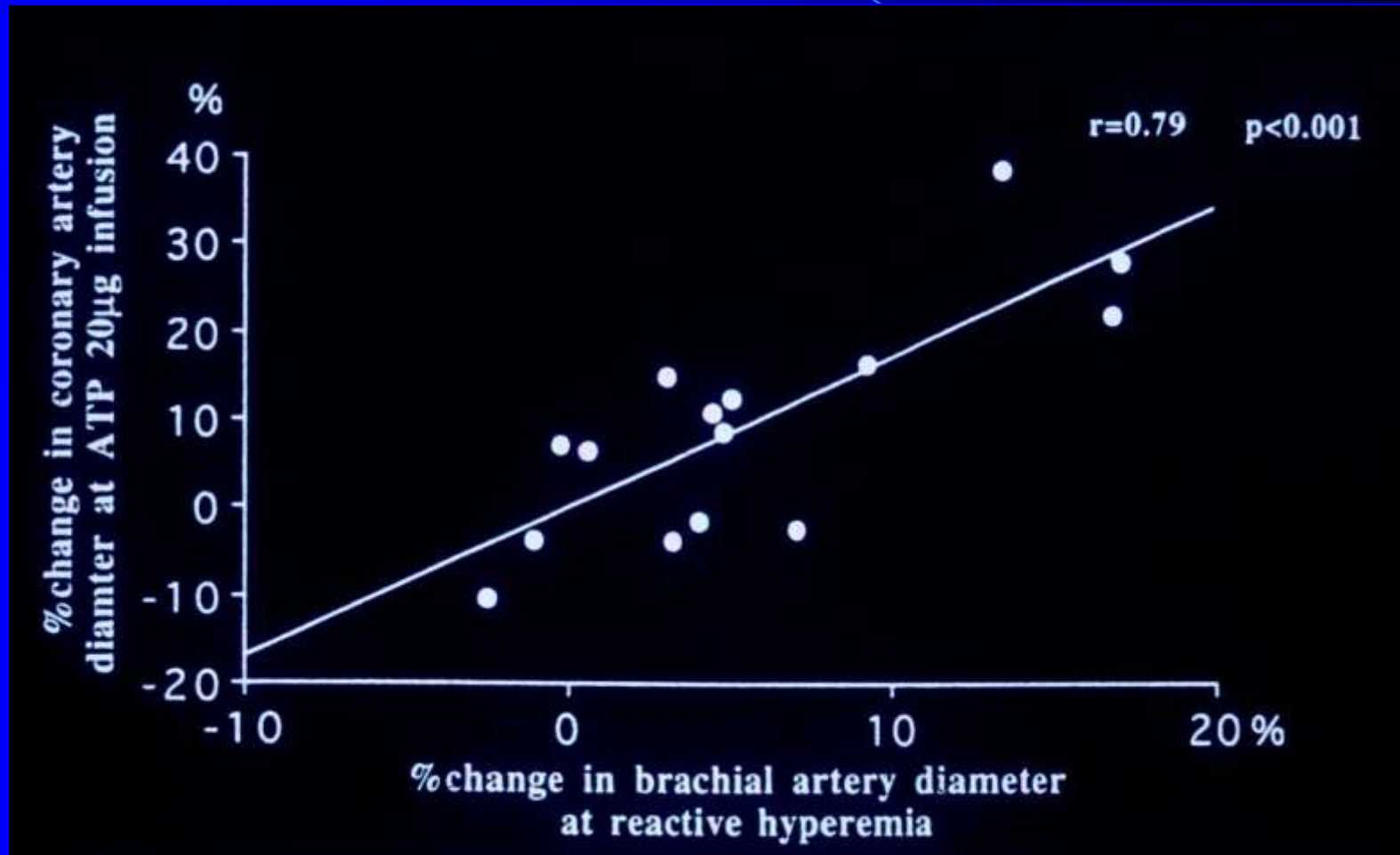
Coronary Arteries

- Epicardial Artery Diameter Δ with ACh
- CBF Δ with ACh
- Epicardial Artery Diameter Δ with Adenosine

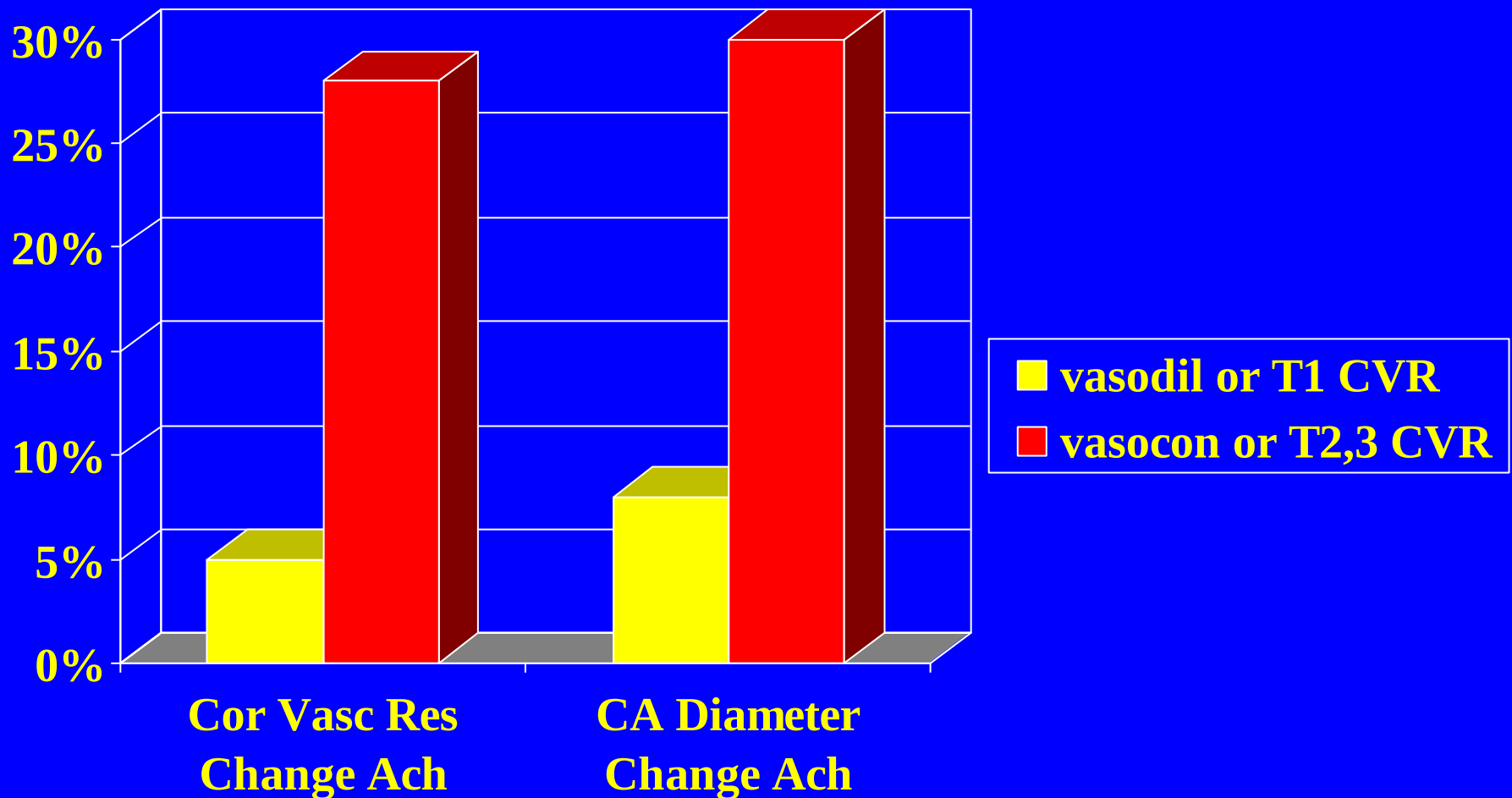
Forearm

- Brachial Artery Diameter Δ with Arterial Occlusion FMD
- Forearm Blood Flow with ACh

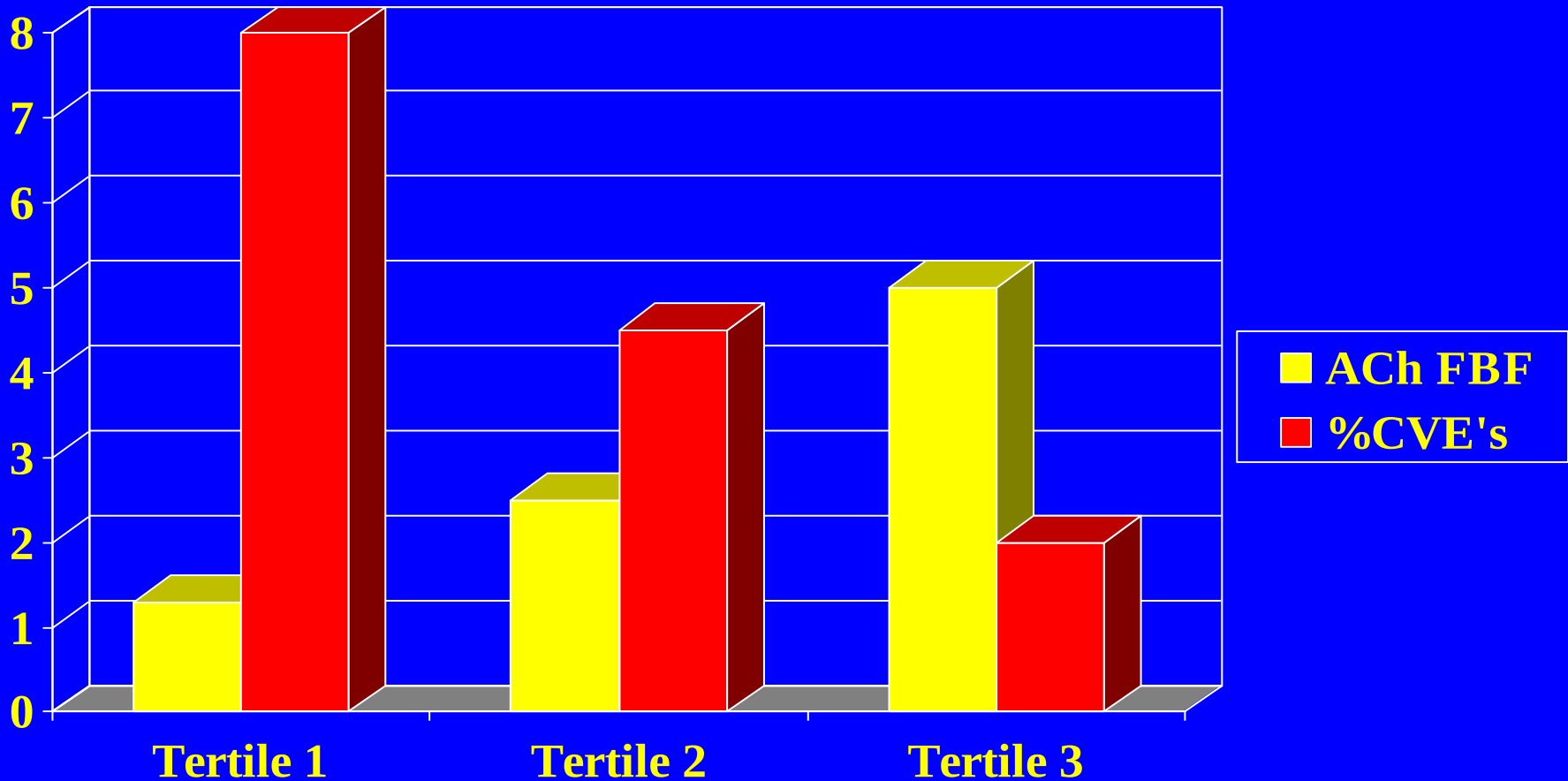
Comparison of Brachial and Coronary Flow-Mediated Vasodilation



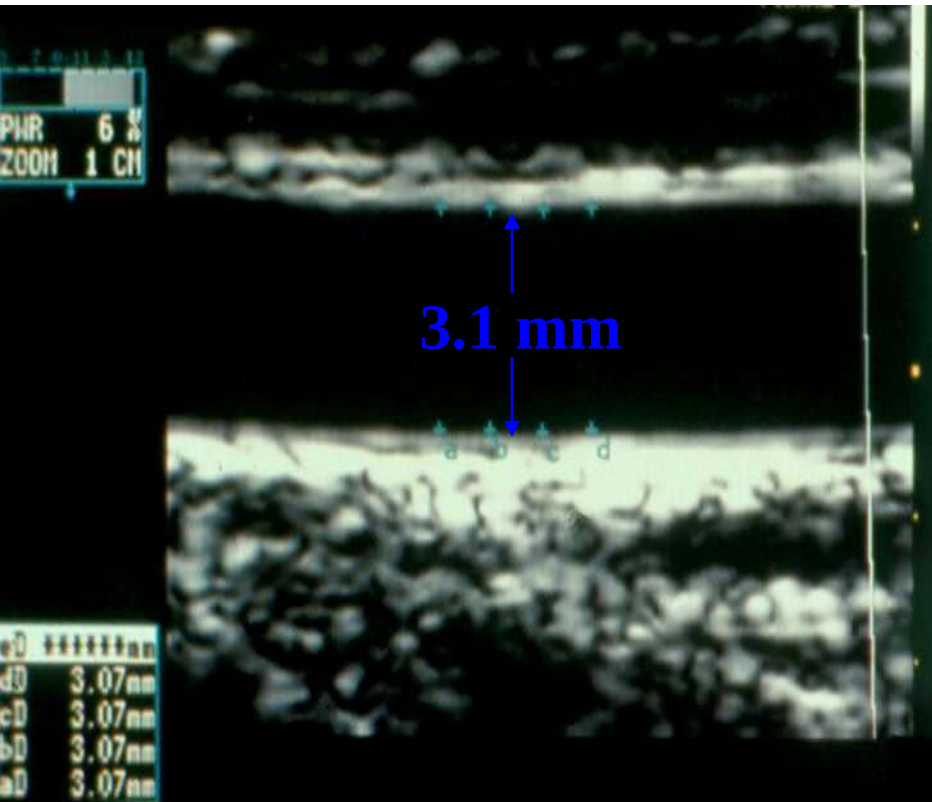
CVE's over 4 Years in 176 Subjects without CAD as per CVR and CA Diameters Changes with ACh



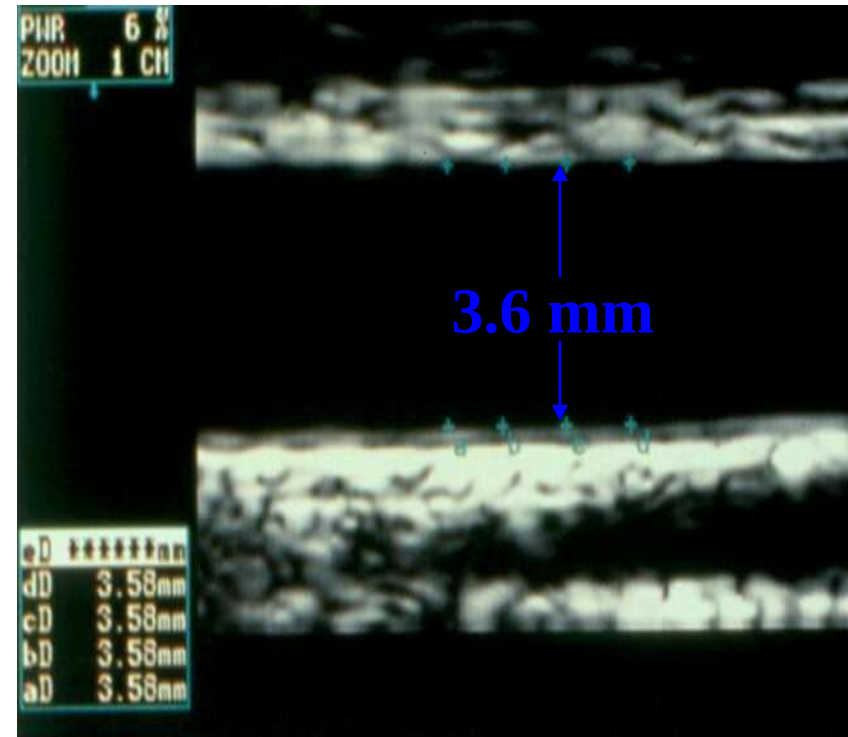
Effect of ACh-Induced Forearm Vasodilation on CVE's (%) in 225 Never Treated HTN cases



Brachial Artery Flow-Mediated Vasodilation



Baseline



5 Minutes

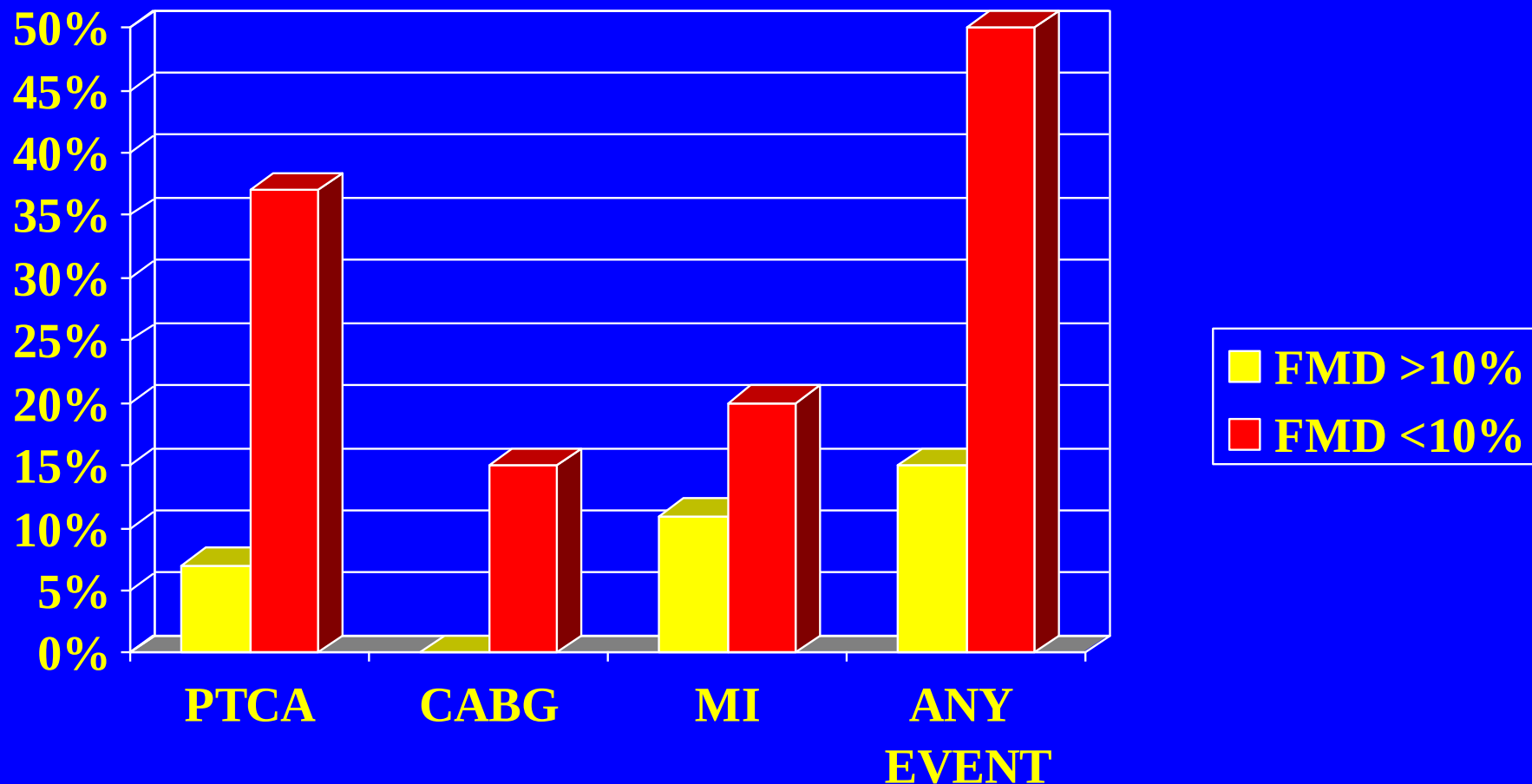
Post-

Occlusion

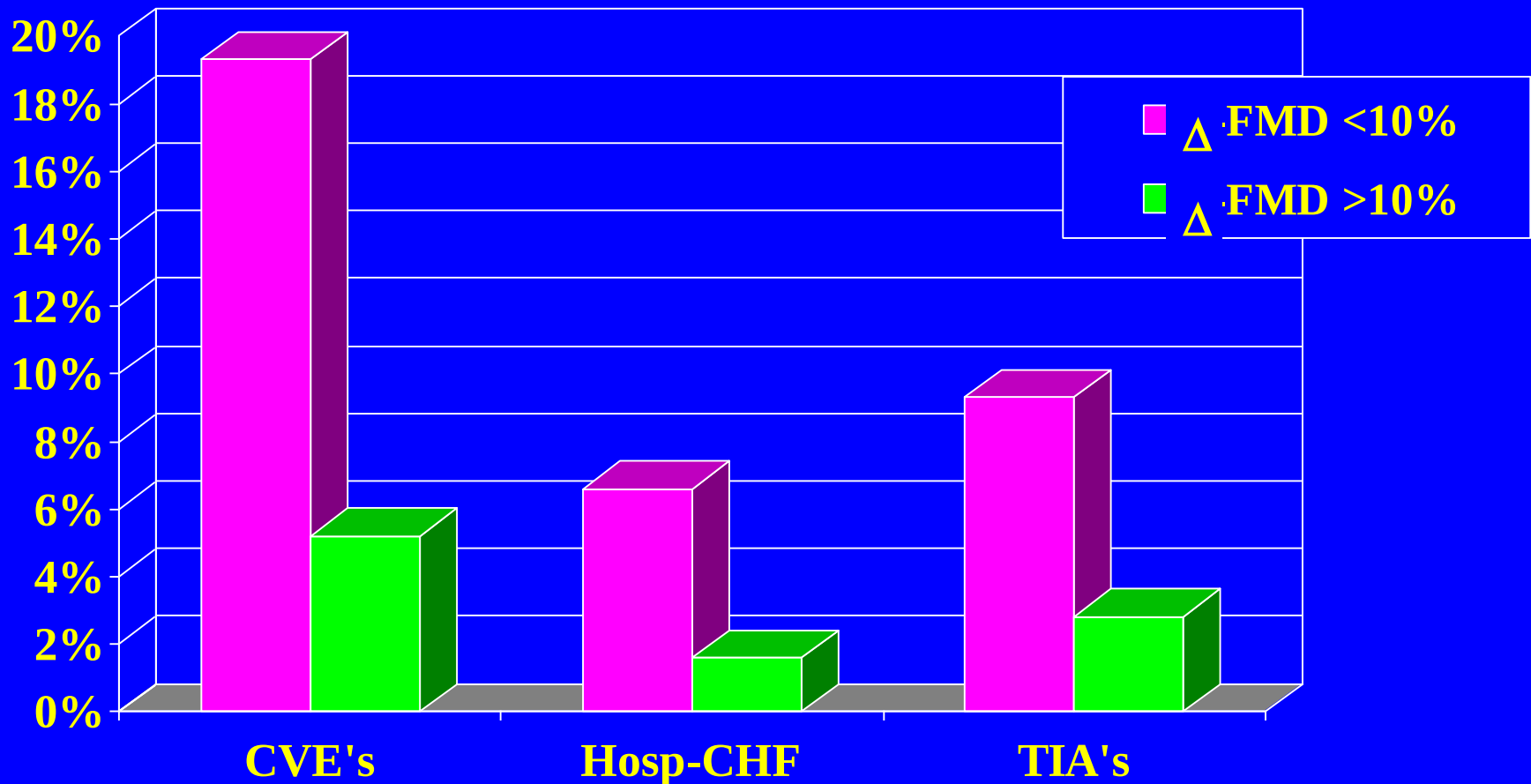
Blood Pressure Cuff
Occlusion – 1 Minute
Release

Can Endothelial Dysfunction help in Diagnosis of CVD ??

CHD Events over 5 Years in 76 CAD Patients According to Brachial Artery FMD



5-Year Outcome in 350 Postmenopausal Hypertensive Women with controlled BP (<140/90) Change in BAFMD



Assessment of Coronary Vascular Function

Endothelium-dependent probes:

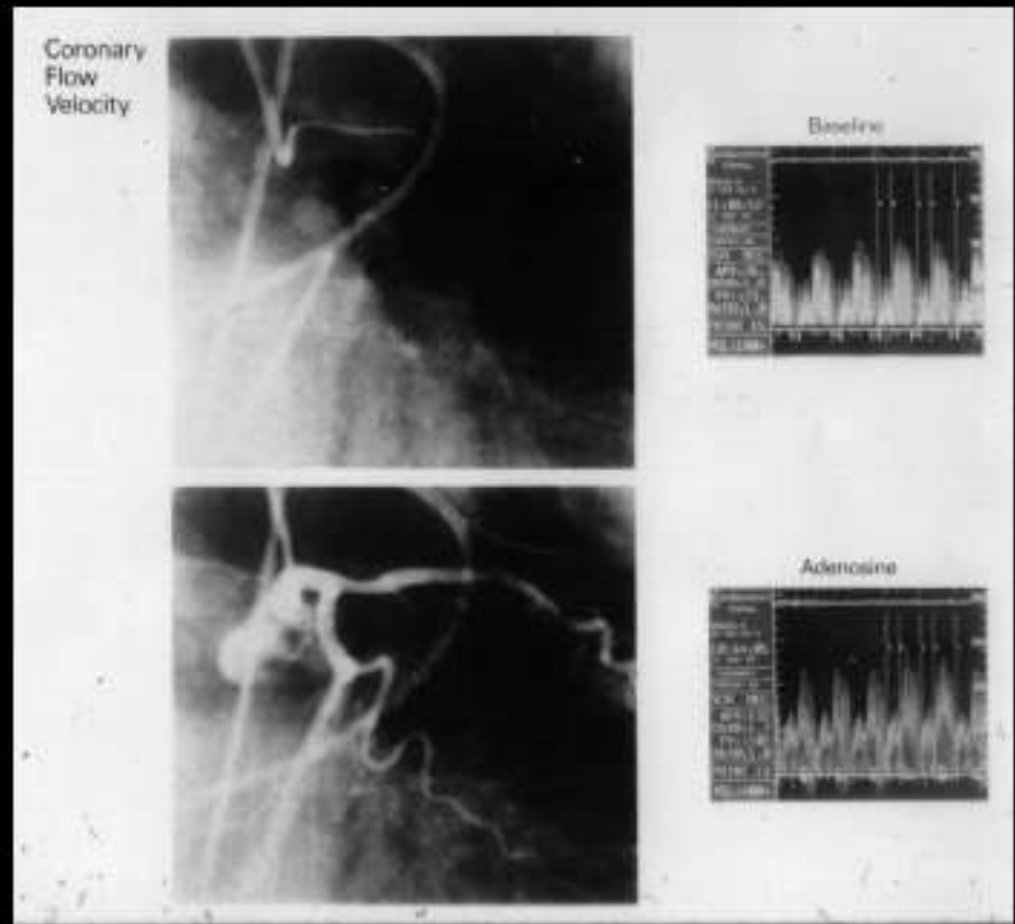
- Acetylcholine,
- Bradykinin,
- Substance P,
- L-NMMA,
- Shear Stress

Endothelium-independent probes:

- Sodium nitroprusside,
- Adenosine

Measurements:

- Coronary blood flow and resistance
- Epicardial Diameter



Normal Endothelial Function

Baseline



Acetylcholine



Endothelial Dysfunction

Acetylcholine



Nitroprusside



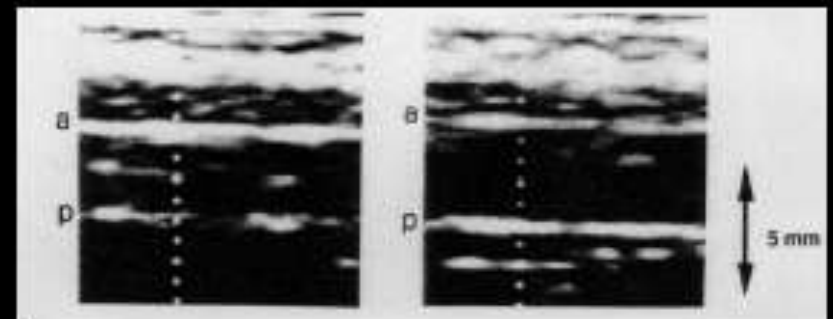
Brachial artery reactivity

- Flow-mediated vasodilation (FMD)
 - Endothelium-dependent
 - Baseline measurements
 - Reactive Hyperemia
- Sublingual Nitroglycerin response (NTG)
 - Endothelium-independent



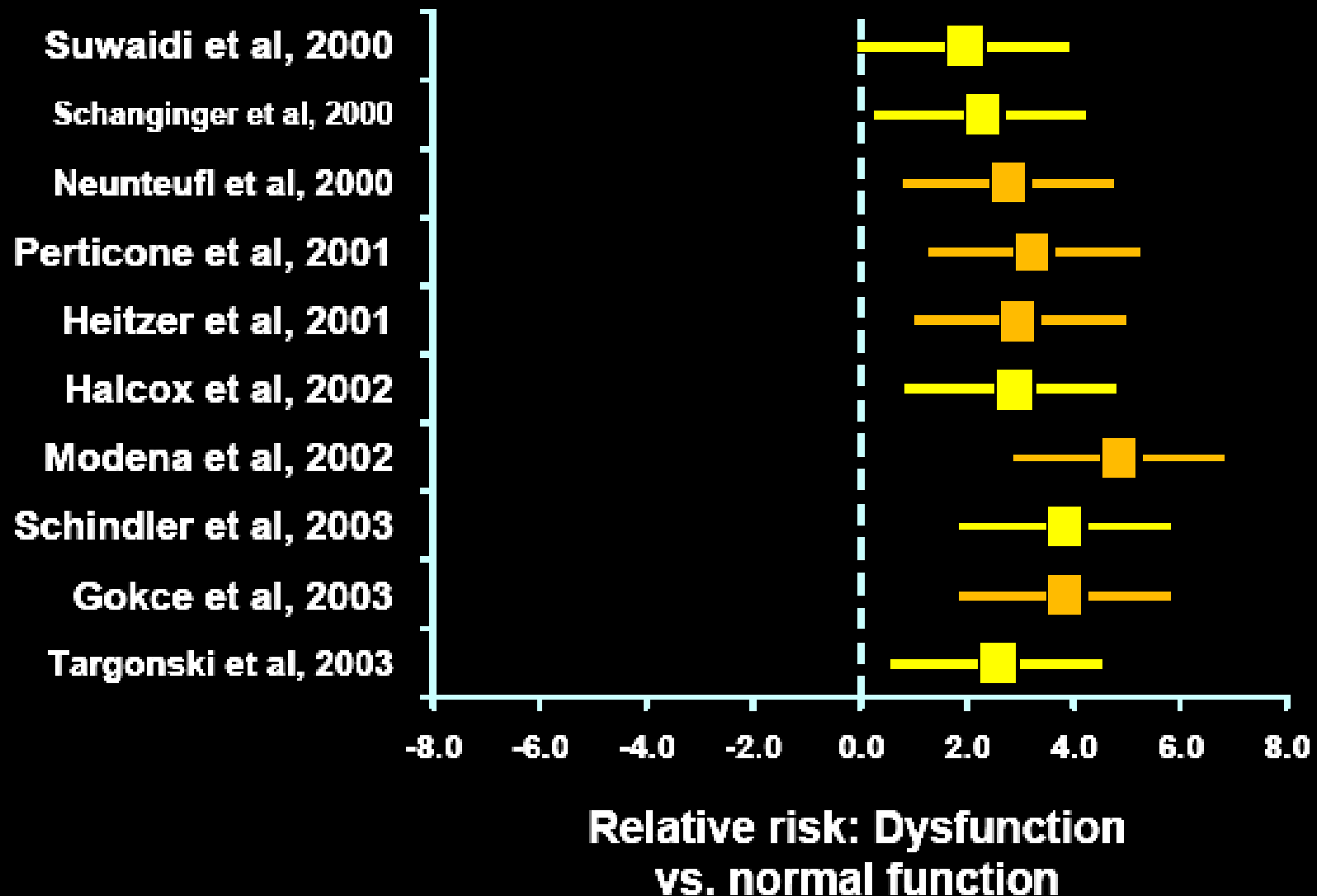
Rest

**Reactive
Hyperemia**



Can Endothelial Dysfunction predict prognosis of CVD ??

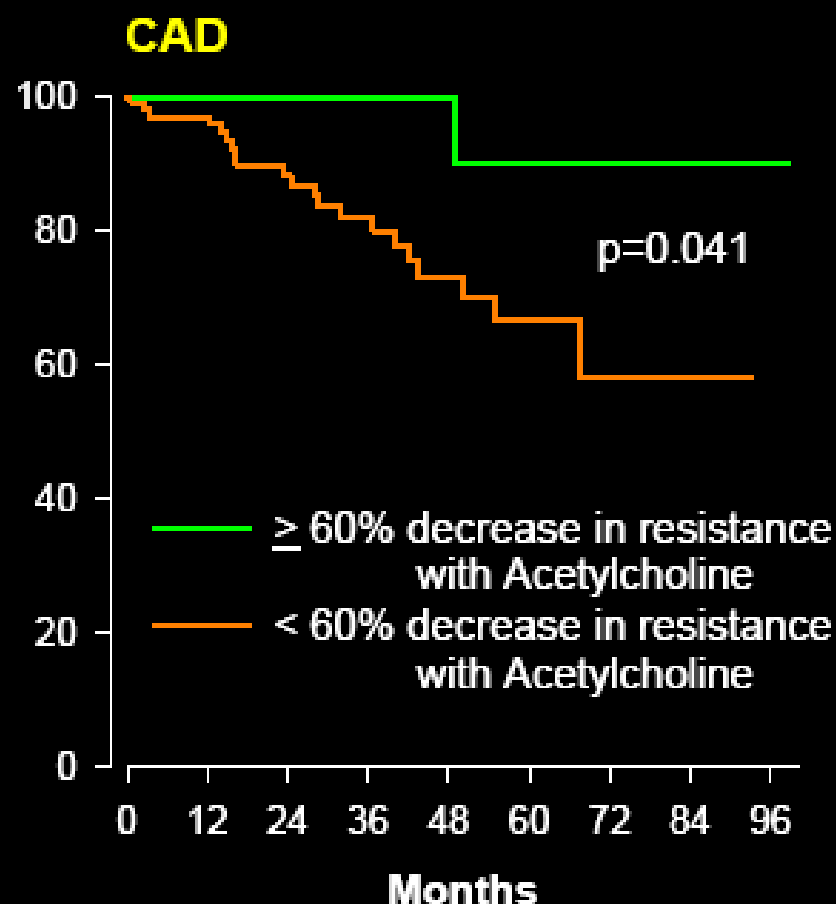
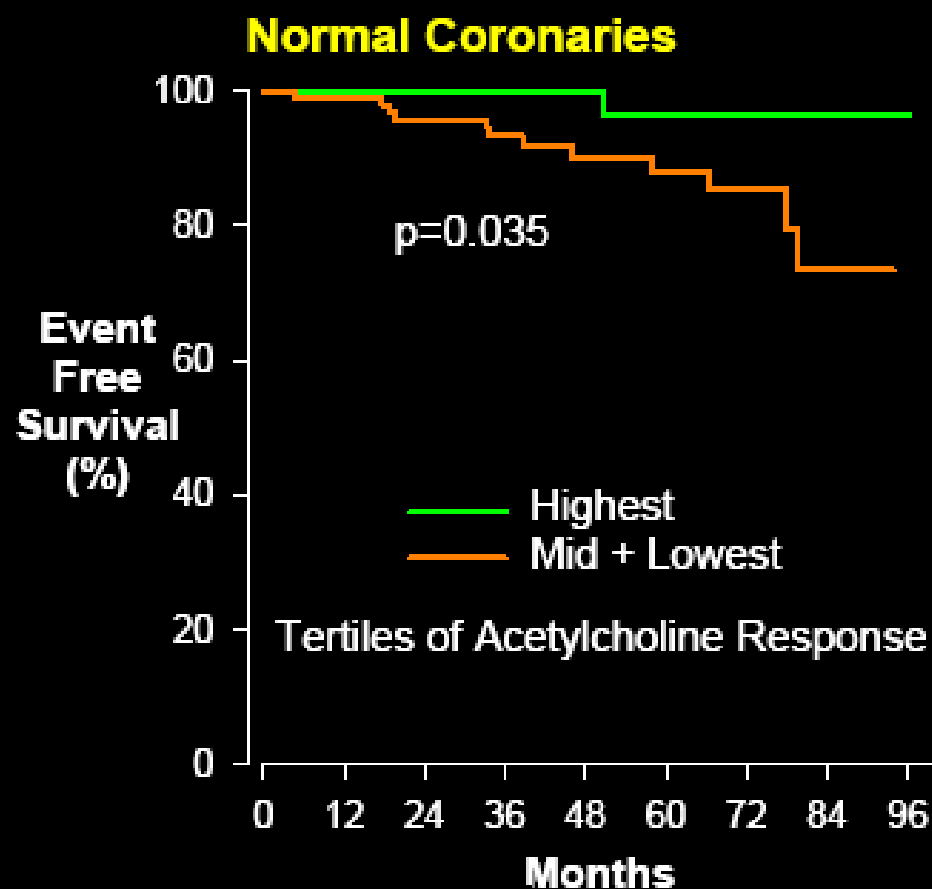
Prediction of future cardiovascular events by measurement of endothelial function



Event-Free Survival According to Coronary Vascular Function

308 patients undergoing catheterization with and without CAD/follow-up 44±2 months

Events: Death, CVA, Myocardial infarction, Unstable angina



What is the Rx. for Endothelial Dysfunction?

- Control of all the known CV risk factors
- Diet and physical activity are vital in Rx of ED
- Main focus on the big six – DM, HTN, Lipids, Obesity, Smoking, Sedentary life style
- Statins are the first line treatment for ED

Erectile Dysfunction – Today's concept

Penis is the barometer
of Endothelial Health

Erectile Dysfunction is a
mirror of Cardiovascular Risk

ED = ED



It's a mid-life problem!

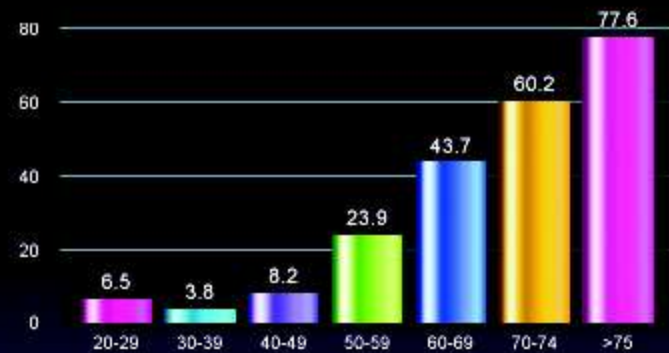


ED is a remarkably common condition.

ED in a substantial majority of men is due to underlying vascular causes.

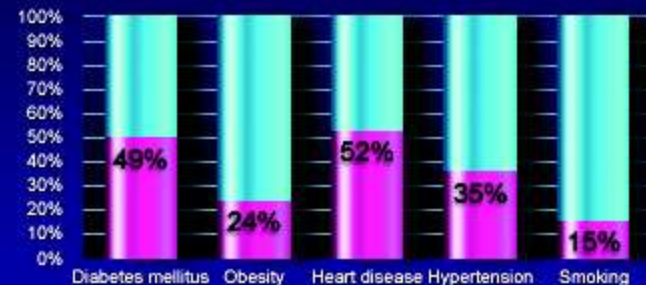
ED is highly prevalent in men with vascular risk factors for CVD.

The Prevalence of ED



n=2536, ED 18.5 %

Associations Between ED and Various Comorbid States



Christopher S Saigal, Hunter Wessells, Jennifer Pace, Matt Schonlau, Timothy J Wilt. Predictors and prevalence of erectile dysfunction in a racially diverse population. Arch Intern Med. 2006;166:207-212

Erectile dysfunction is a big problem

You could cut off a yard,
and you'd still have enough
for a baseball bat!!

Mark Twain

Risk Factors of ED

Traditional

Age
High LDL cholesterol
Low HDL cholesterol
Hypertension
Diabetes
Smoking

1

Underlying

Obesity
Sedentary lifestyle
Atherogenic diet

2

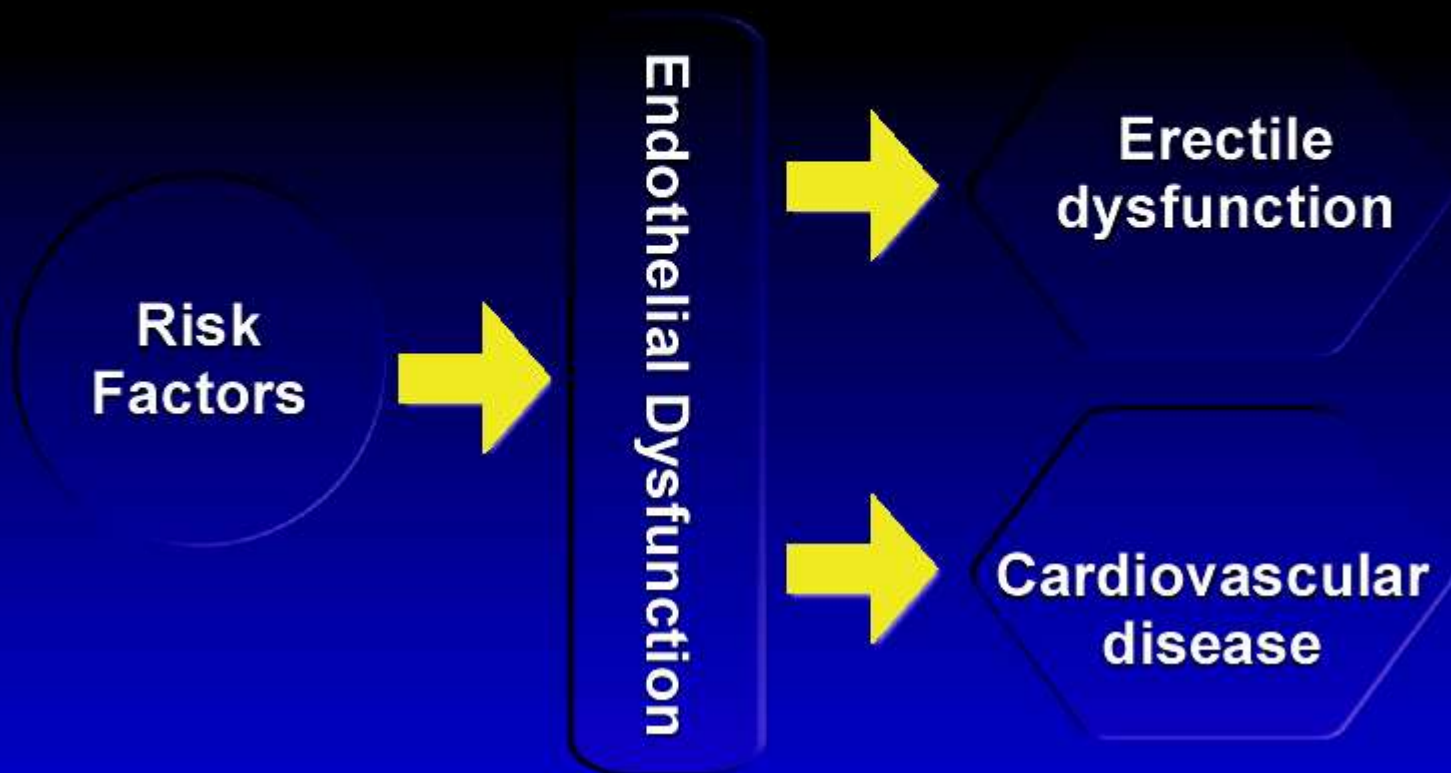
Emerging

insulin resistance/
metabolic syndrome

3

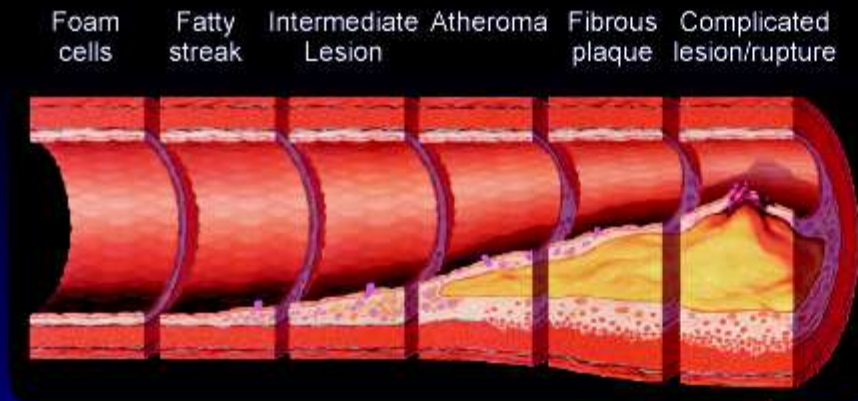
Friday, January 1, 2010

Endothelial Dysfunction is the common dominator



Friday, January 1, 2010

Atherosclerosis timeline



The mechanism of atherosclerosis involves a complex interplay between the effects of lipid accumulation, inflammation and smooth muscle cell growth.

Central to this interplay is **endothelial dysfunction**, which predisposes to the initiation, progression and the development of complications of atherosclerosis.

It is associated with the formation of plaques in the arterial system that can either rupture or grow to occlude the blood vessel



Adapted from Pepine CJ. Am J Cardiol. 1988;82 (suppl 10A):23S-27S.

Development and progression of ED

Functional vascular ED

①

Impaired endothelial
and neurogenic
relaxations

Impaired
vasodilatation

Impaired
relaxation

Structural vascular ED

②

Atherosclerosis

Arterial stenosis

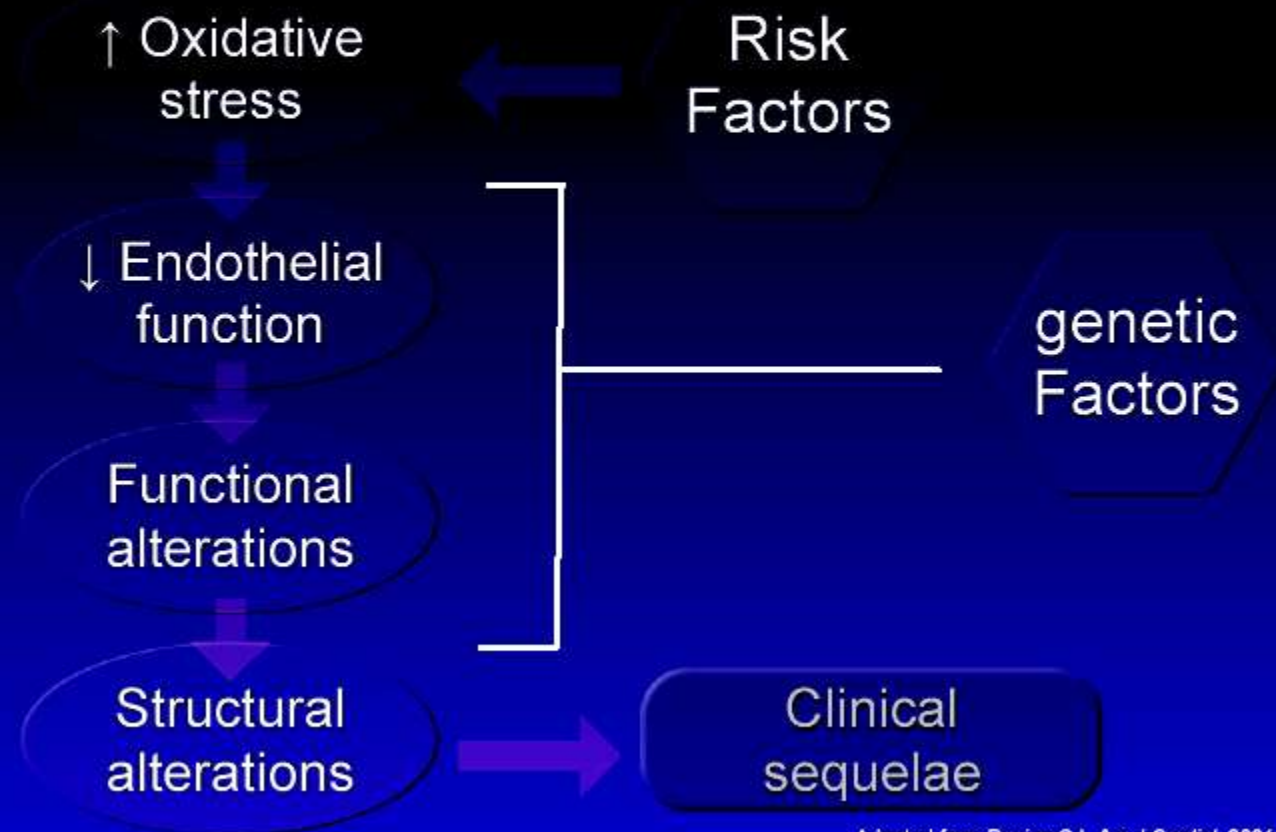
SM atrophy /
fibrosis

Risk
Factors

Reduced Inflow

Increased Outflow

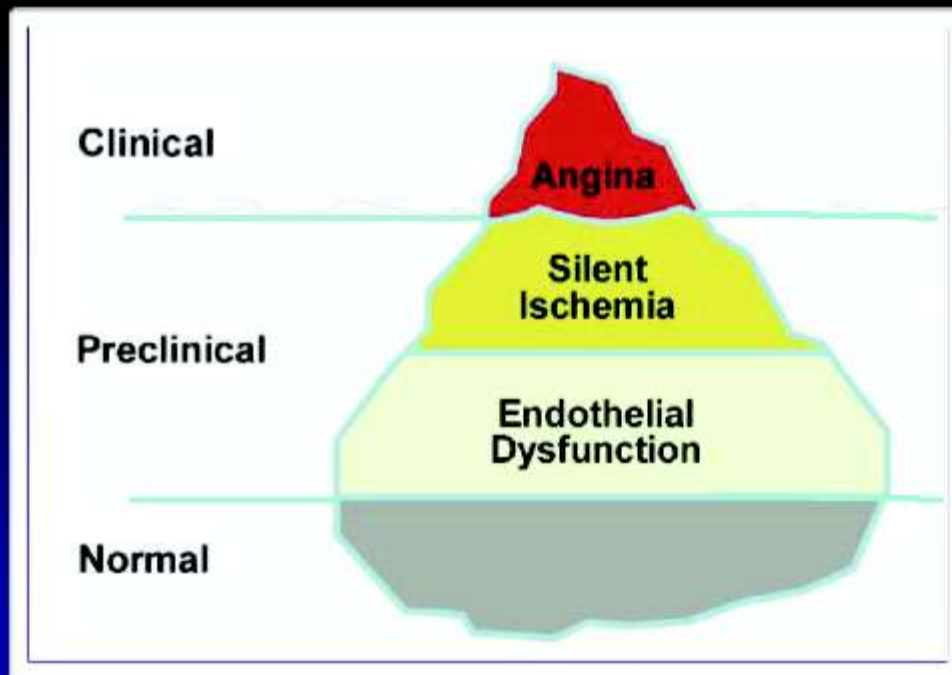
Development and progression of CVD



Adapted from Pepine CJ. *Am J Cardiol.* 2001;88(suppl):5K-9K.

Friday, January 1, 2010

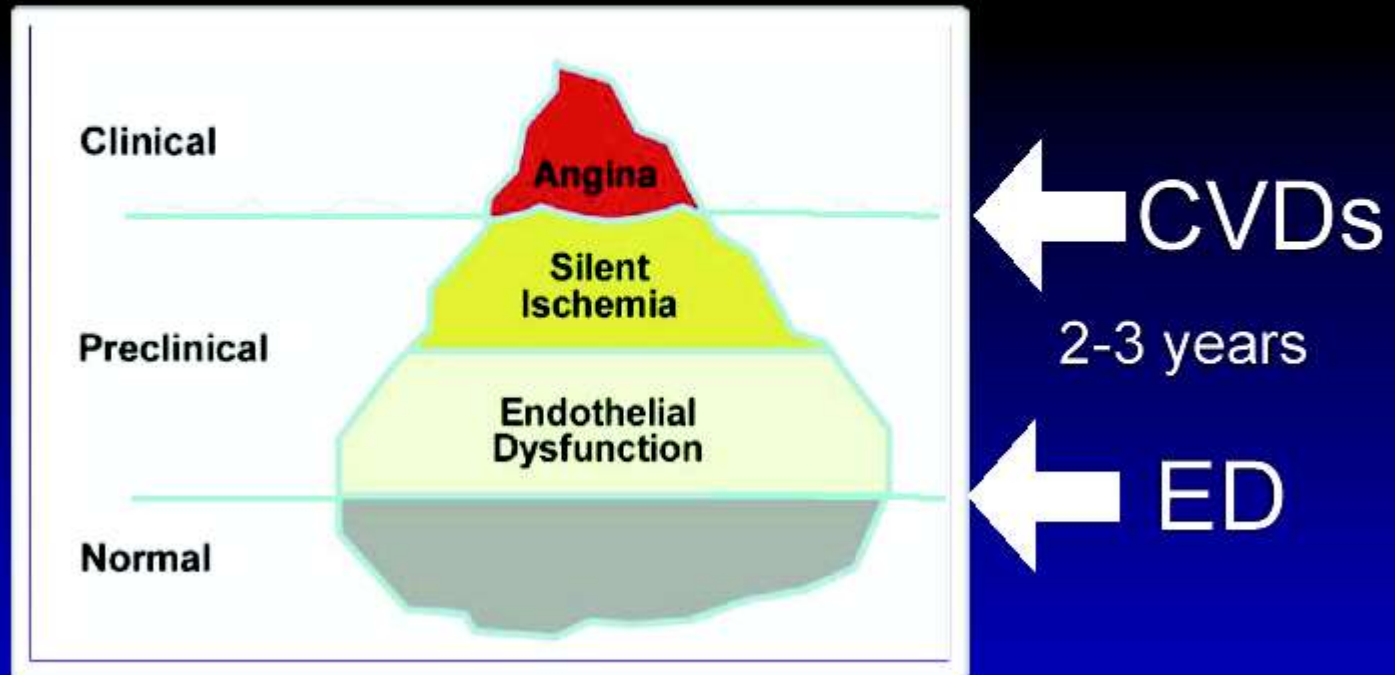
Clinical spectrum of coronary artery disease



DeBusk, Erectile Dysfunction Therapy in Special Populations and Applications: Coronary Artery Disease. Am J Cardiol 2005;96: 62M-66M

Friday, January 1, 2010

Clinical spectrum of coronary artery disease

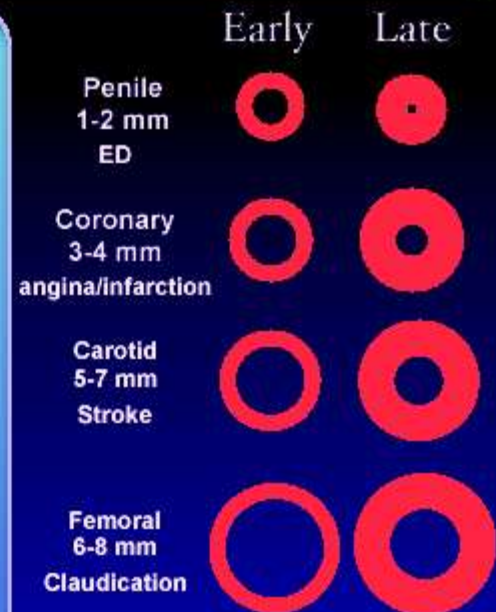


DeBusk, Erectile Dysfunction Therapy in Special Populations and Applications: Coronary Artery Disease. Am J Cardiol 2005;96: 62M-66M

Friday, January 1, 2010

Why ED occurs before other vascular diseases?

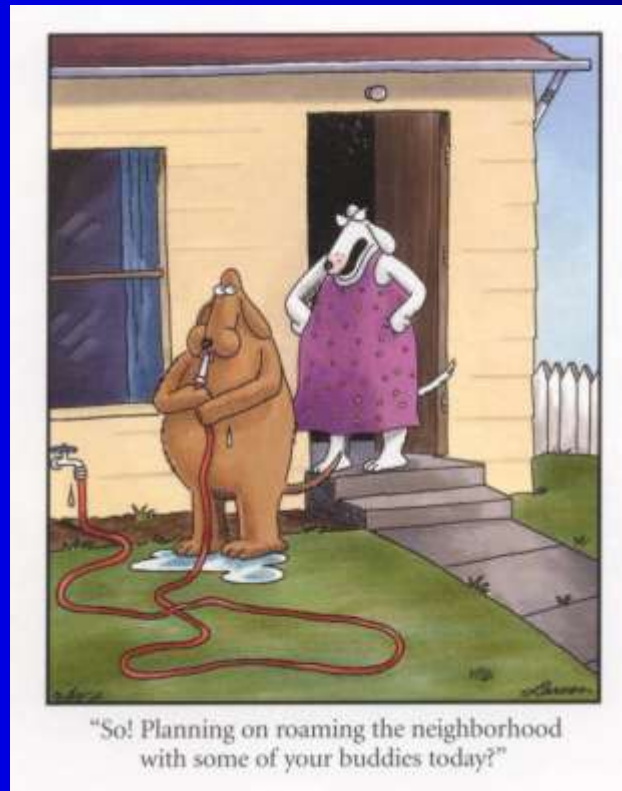
- The small diameter of the cavernosal arteries.
- The penis is a vascular organ, sensitive to changes in oxidative stress and NO levels.
- The high content of endothelium and smooth muscle on a per gram tissue basis (compared to other organs).



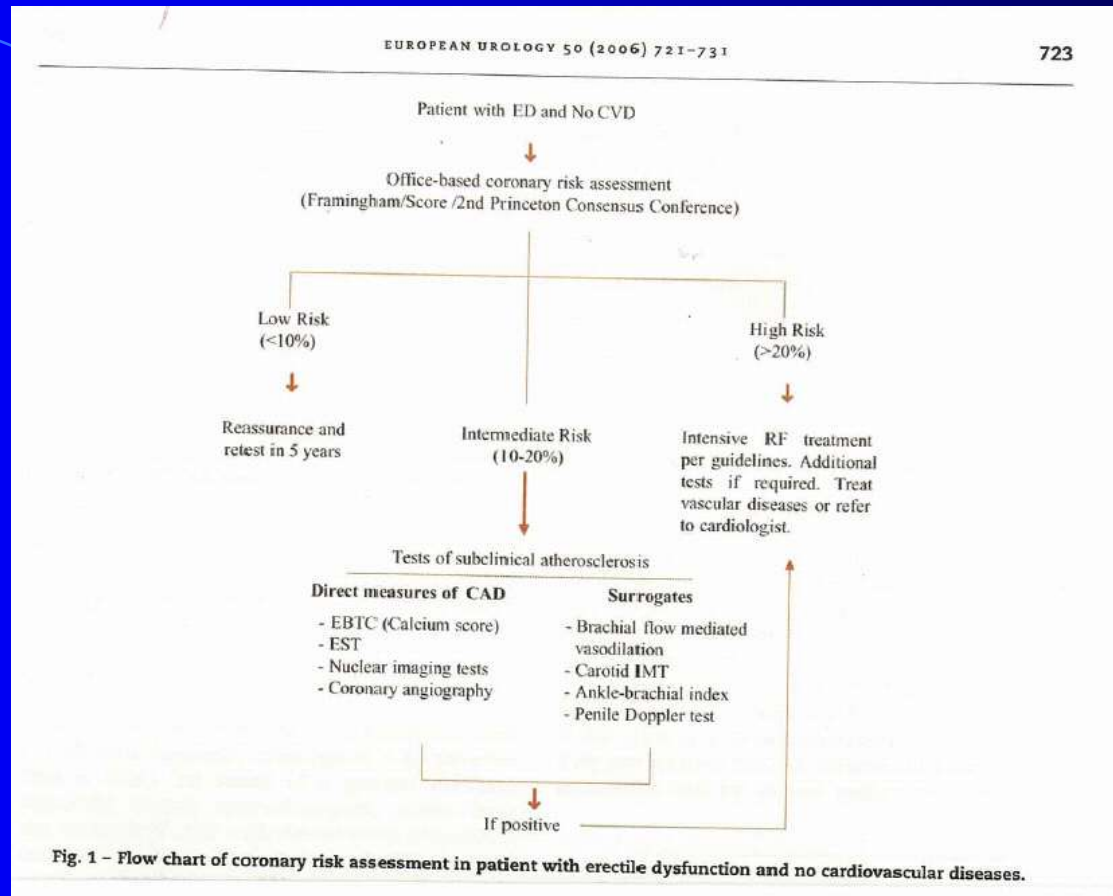
Montorsi et al. The Artery Size Hypothesis: A Macrovascular Link Between Erectile Dysfunction and Coronary Artery Disease. Curr Opin Urol. Am J Cardiol 2005;96:19M-23M.

WHO view on therapy for ED

- The first choice is oral therapy...!!!



Conclusion – What to do



Conclusion – What to do (Intermediate risk)



If you are Scottish
(and not bashful)
Ask if patient has
Erectile dysfunction
-cheap and cheerful
measure of higher
Vascular disease/risk

Conclusion – What to do (Intermediate risk)

Consider further investigation

- Exercise ECG
- Coronary CT
 - Calcium score
 - Angiography
- Brachial FMR
- Carotid IMT

Conclusion – What about erectile dysfunction

- Remember it may be a marker of vascular disease/risk
- confidently treat with PDE5 inhibitor
- in treating with a PDE5 inhibitor you may be “reviving” the vascular Tree elsewhere!!

Disclosure

- This symposium is sponsored by Eli Lilly
- I have received honoraria for speaking for Eli Lilly, MSD, Pfizer.
- I have not received any consulting fees or educational or research grants, or donations from pharmaceutical companies
- Some slides sourced from other authors

I'm off – enjoy your evening





Cardiovascular risk of sexual intercourse

1965 Ueno Japan

- autopsy series of 8275 non-violent sudden deaths
- prior sexual activity relevant in 67 (0.8%)
- 36 cardiac (coronary atheroma in 9 (NB Japan))

Cardiovascular risk of sexual intercourse

Sudden Death related to sexual activity
(during & for 2hrs after – autopsy)

-0.6% (34/5559) to 1.7% (30/1722) of sudden deaths

-80-90% male

-75-77% during extra-marital sex

-50% MI in one study

Cardiovascular risk of sexual intercourse

1965 Ueno Japan Contd

- average age male death 45
(average age of sexual partner 33!)
- high proportion of extra marital relationships & heavy food and alcohol intake before event.

Cardiovascular risk of sexual intercourse

1996 ONSET study. European

- trigger for MI in 1774 patients (age 20-92 yrs)

- 0.9% of MIs related to sexual activity

- RR not increased for men taking regular exercise

- RR lower for women

Cardiovascular risk of sexual intercourse

1996 ONSET study. European

-Muller's later comment – weekly intercourse increases MI risk from 1%/yr to 1.01%/yr for a sedentary 50 yr old man with no risk factors

Cardiovascular risk of sexual intercourse

2000 SHEEP study. Stockholm not Sydney!

- Stockholm Heart Epidemiology Programme

- Patients aged 45 – 70yrs

- 1.3% of MI after sexual activity

- RR 2.1 if regular exercise

- RR 4.4 if sedentary

Risk of MI with sexual intercourse

DMIOS study

- RR 2.5 – similar with or without previous MI
 - Sedentary men RR 3.0
 - “Active” men RR 1.2

SHEEP study

- RR 2.1
 - Sedentary men RR 4.4
 - “Active” men RR 0.7

Energy requirements of sexual intercourse

- Variable!!

- Mean peak heart rate 104-185 bpm

- Peak systolic BP 150-180 mmHg

- 2 mets, up to 6 or 7 mets at orgasm

Risk of myocardial ischaemia with sexual intercourse

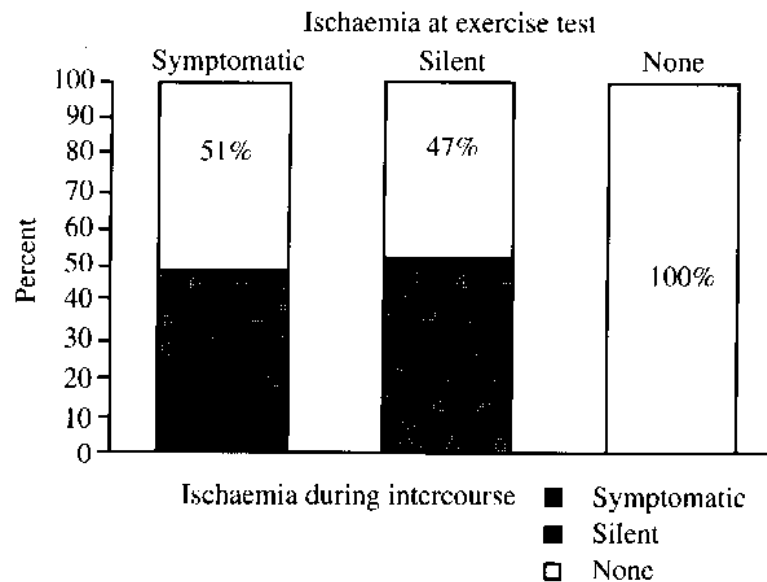


Figure 2 Ischaemia during intercourse in patients with and without ischaemia at exercise test. (Data from Drory *et al.*^[21].)

Effect of sildenafil on myocardial ischaemia

Table 1 *Effect of sildenafil versus placebo on time to limiting angina in evaluable patients*

Findings	Mean time to limiting angina		<i>P</i>
	Sildenafil (n = 56)	Placebo (n = 52)	
Baseline test (s)	372.9	396.3	0.0401
Change from baseline (s)	36.3	18.3	
Change from baseline (%)	9.8	4.7	
Treatment test (adjusted for covariates; s)	423.6	403.7	

Data from Fox *et al.*^[21] and Jackson *et al.*^[22].

ED and Rx after MI/IHD



A doctor was preparing to examine an elderly lady. He noticed that she was a little nervous, so he began to tell her a story as he put on his surgical gloves. "Do you know how they make these gloves?" he asked.

"No," she replied, "How?"

"Well, in the glove factory there's a large tank of latex. The workers, who are lined up according to hand size, walk up to the tank, dip their hands in, and then walk around until the latex dries right onto their hands! Then they peel off the gloves and start the process all over again."

Seeing that he wasn't getting the laugh he had hoped for, the doctor began the exam without further delay. Five minutes later, the woman began to giggle.

"I'm sorry," she said, blushing. "It just occurred to me how they must make condoms!"

**BANK HOLIDAY (EIRE, SCOTLAND, AUSTRALIA—NSW, ACT)
PICNIC DAY (AUSTRALIA—NT)**

Cardiovascular risk of sexual intercourse with PDE5I in patients with IHD

224 men with IHD

- 83% hypertension
- 14% CABG
- 19% previous MI
- 2% had emergent cardiovascular event with sildenafil vs 1% placebo

Cardiovascular risk of sexual intercourse with PDE5I in patients with IHD

US FDA investigation

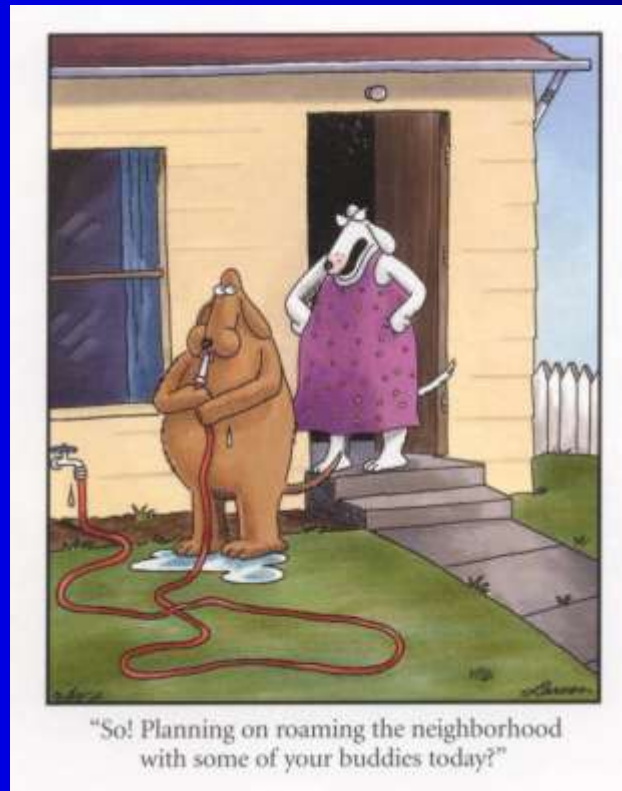
- 6 million sildenafil prescriptions dispensed
- 77 reported deaths from CVD in recipients
- 19 took or had GTN in their possession

Cardiovascular risk of sexual intercourse with PDE5I in patients with IHD

- 2002 Vardenafil safety study (Levitra)
 - 850 men 18yrs + (mean 57 yrs)
 - severe hypertension, unstable angina or MI <6 months excluded
 - 26 week randomised trial
 - Only ONE MI – in placebo group!

WHO view on therapy for ED

- The first choice is oral therapy...!!!



Resuming sexual activity after MI

- If clinically well and no angina, intercourse is safe at 7 days
 - usual partner
 - avoid excess alcohol/large meal before
- If ED is present PDE5I use should be deferred (?90 days)
 - consider drugs as cause of ED
 - talk to the patient!