Penn Primary Care Urology Update

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Treating Erectile Dysfunction

Since the introduction of Sildenafil one thing is irrefutably true:

Urologists no longer are those that patients see first for treatment of erectile dysfunction and other sexual complaints.

Categories of Sexual Dysfunction

- Erectile dysfunction
- Loss of sexual desire
- Ejaculatory dysfunction
- Orgasmic dysfunction

What is erectile dysfunction?

The inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse.

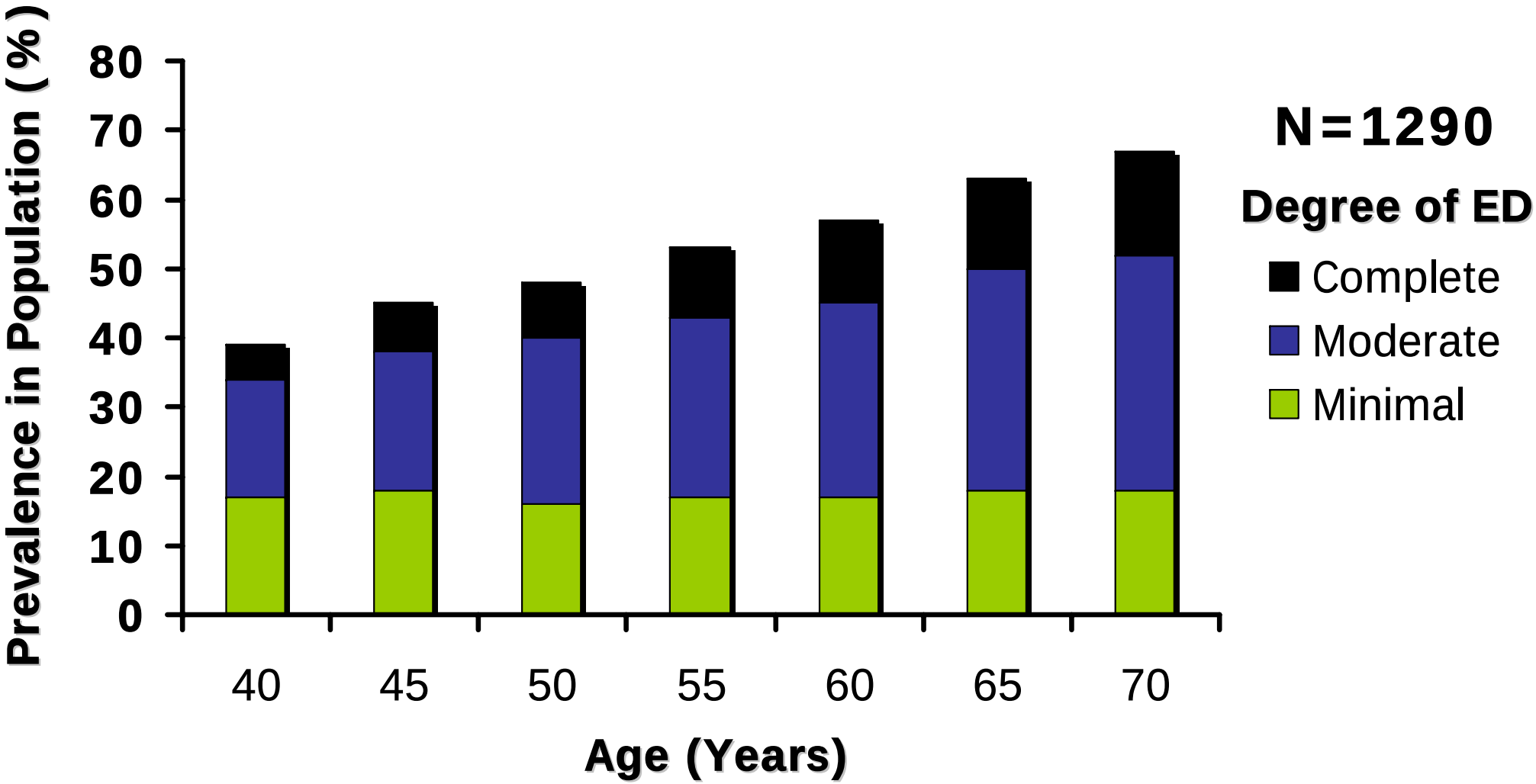
ED is more than just about sex

What is ED really about?

- Quality of erections?
- Quality of life/partner issues?
- Co-morbidities?

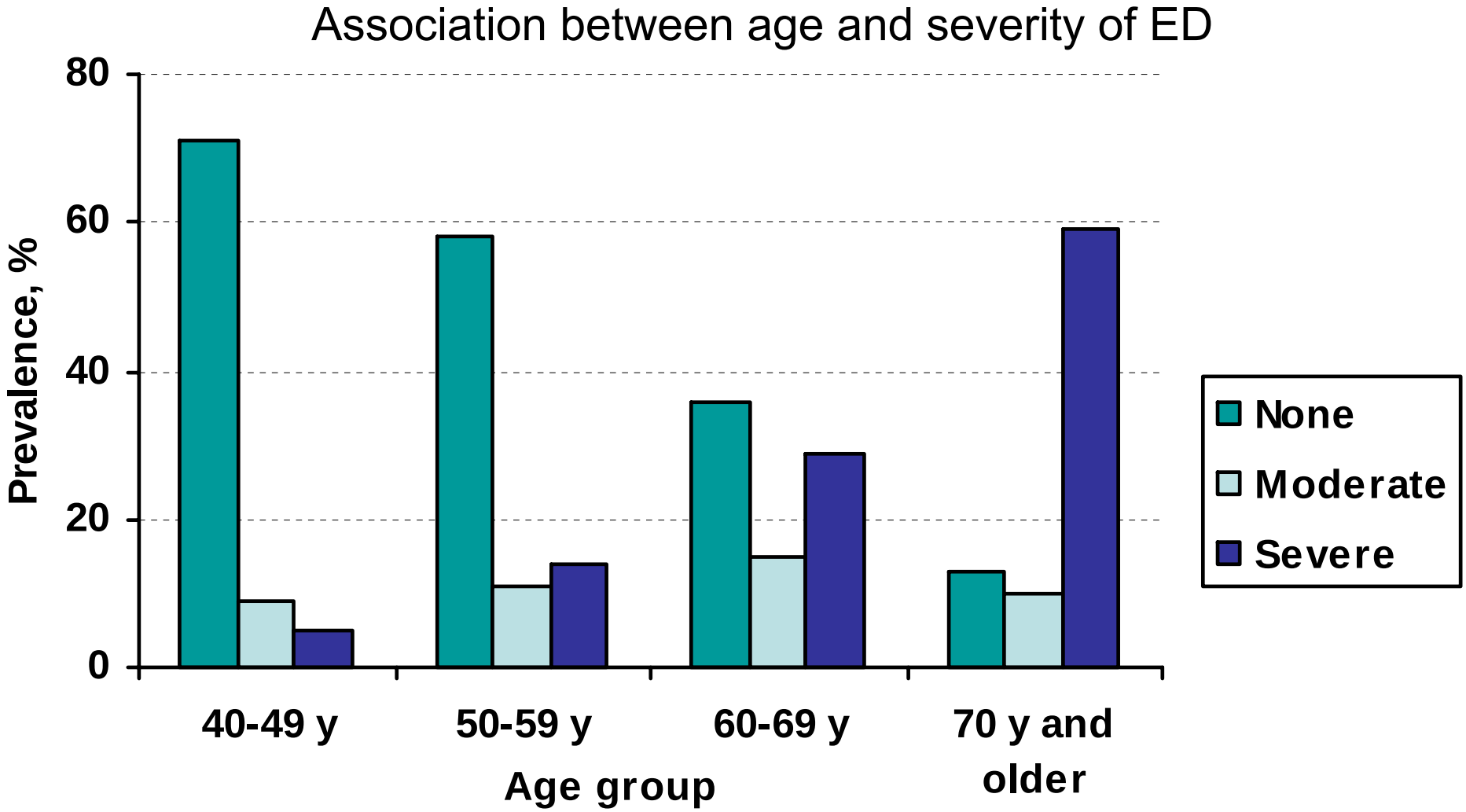
ED Prevalence Increases With Age

Increase in prevalence with age is mostly due to rising rates of moderate and complete ED



Feldman et al. *J Urol*. 1994;151:54-61.

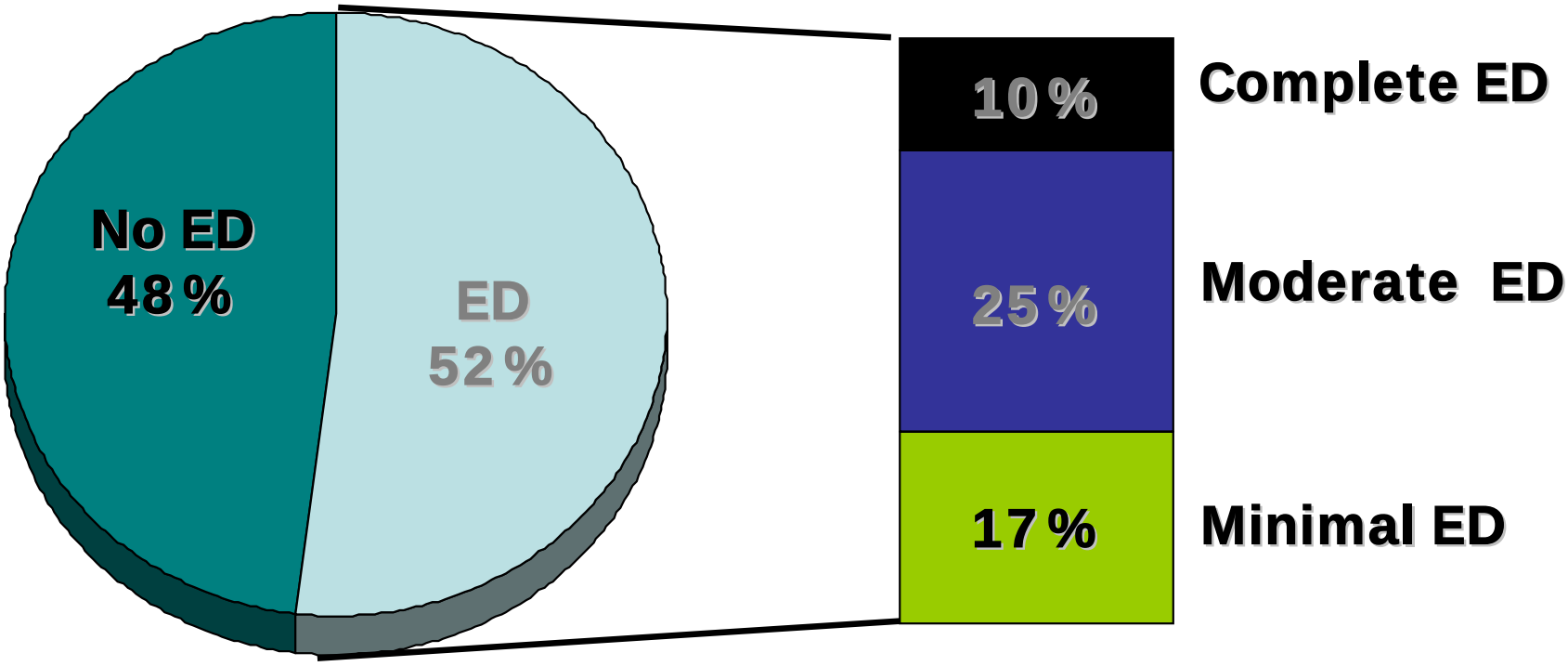
Severity of ED Increases With Age



Grover et al. *Arch Intern Med.* 2006;166:213-219.

ED Prevalence and Severity

Over half of 40- to 70-year-old men (N=1290) have some degree of ED



Feldman et al. *J Urol*. 1994;151:54-61.

Association of ED with Other Conditions

ED Prevalence in 40- to 70-year-old men

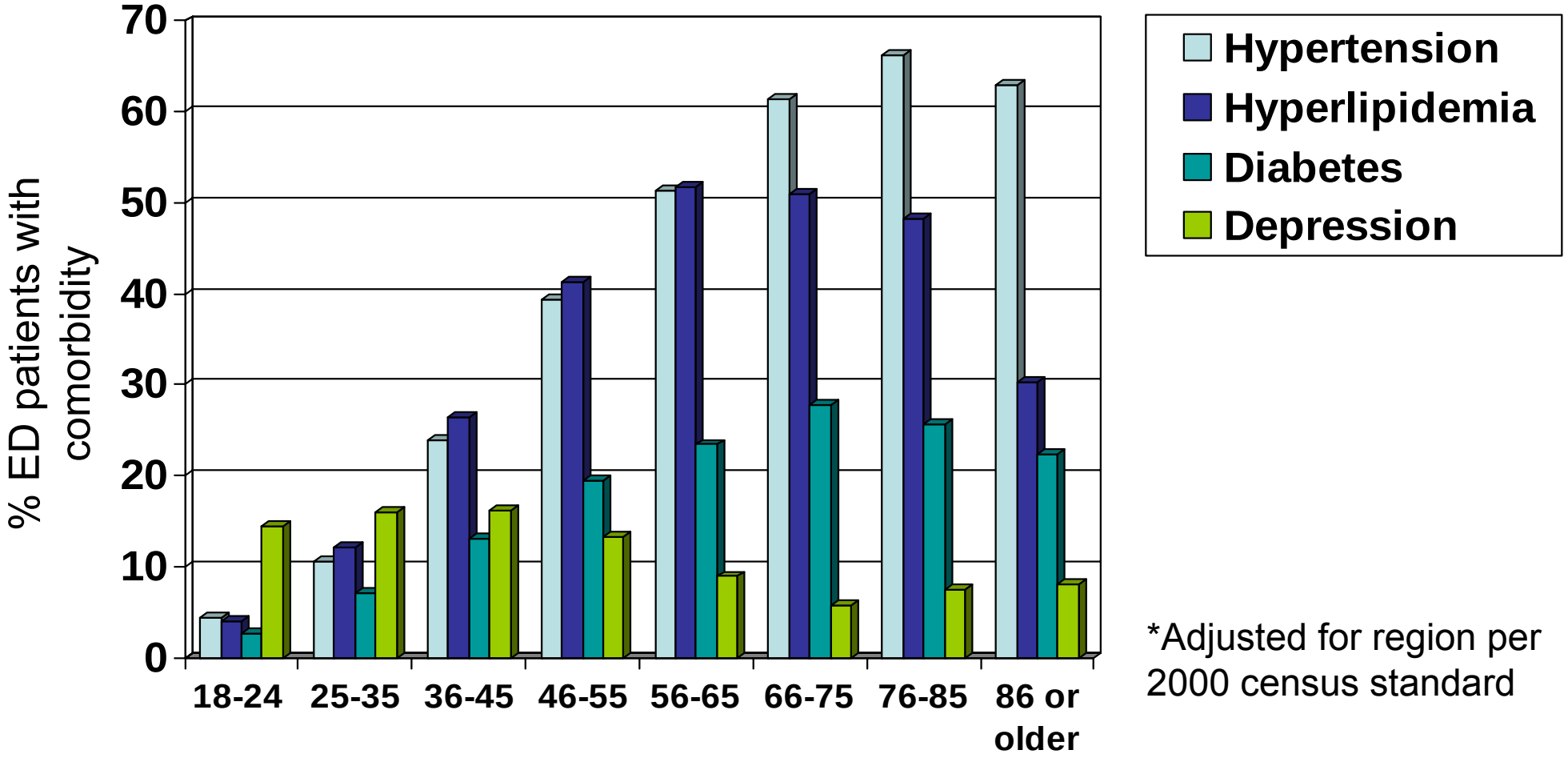
Risk Factor for ED	Complete ED (%)	Moderate to Complete ED (%)
Heart disease (smoker)	**56**	**78**
Depression (severe)	**41**	**90**
Diabetes	**28**	**56**
Hypertension (smoker)	**20**	**40**
HDL-C <30 mg/dL (56-70 y)	**8*** **16†**	**33*** **48†**
General male population	9.6	35

*40-55 years old. †56-70 years old.

Feldman et al. *J Urol.* 1994;151:54-61.

ED Shares Common Risk With Other Conditions

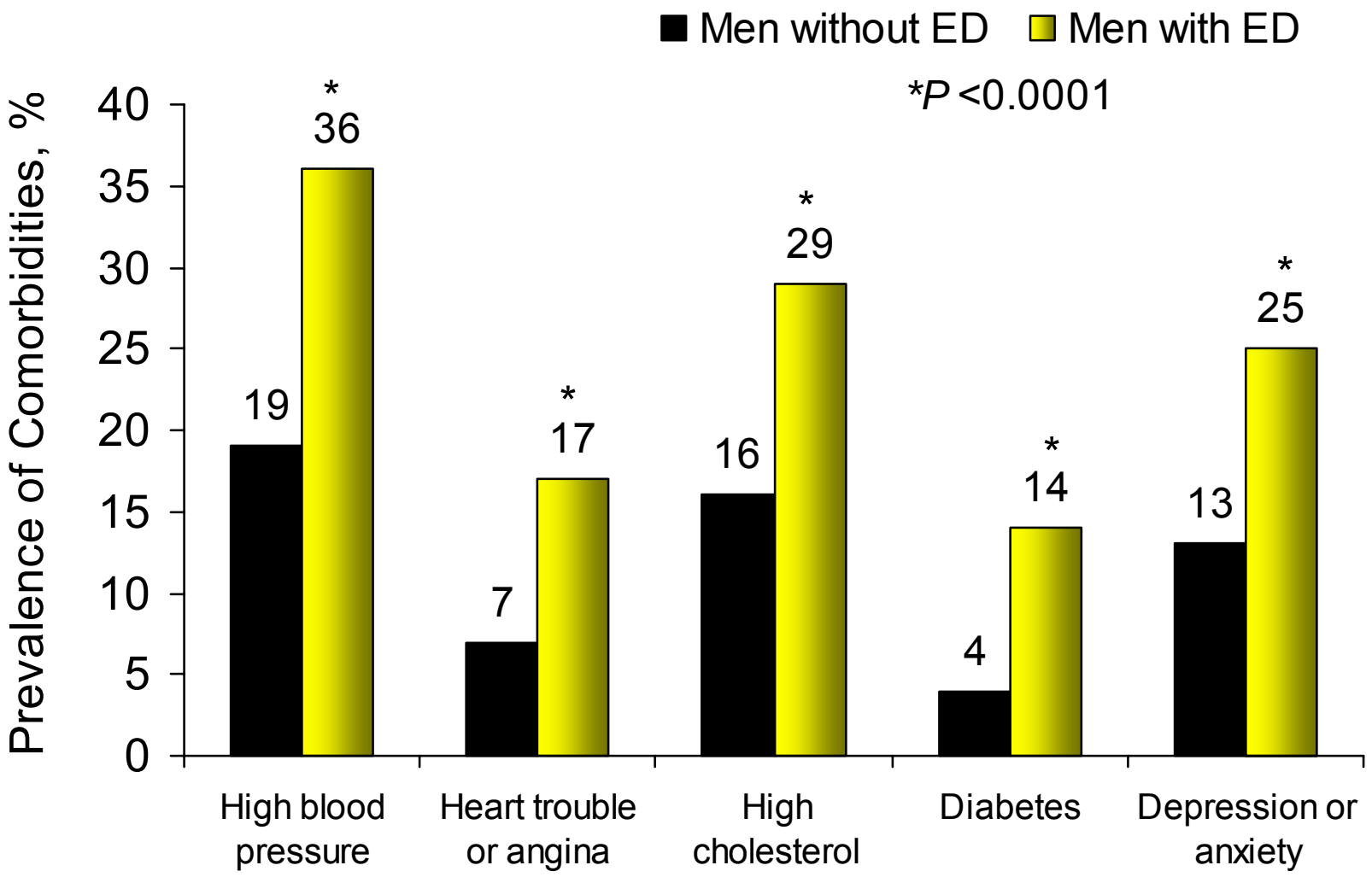
Adjusted prevalence rates* of 4 concurrent diseases in 272,325 patients with ED, 1995 - 2002



*Adjusted for region per 2000 census standard

Seftel et al. *J Urol*. 2004;171:2341-2345.

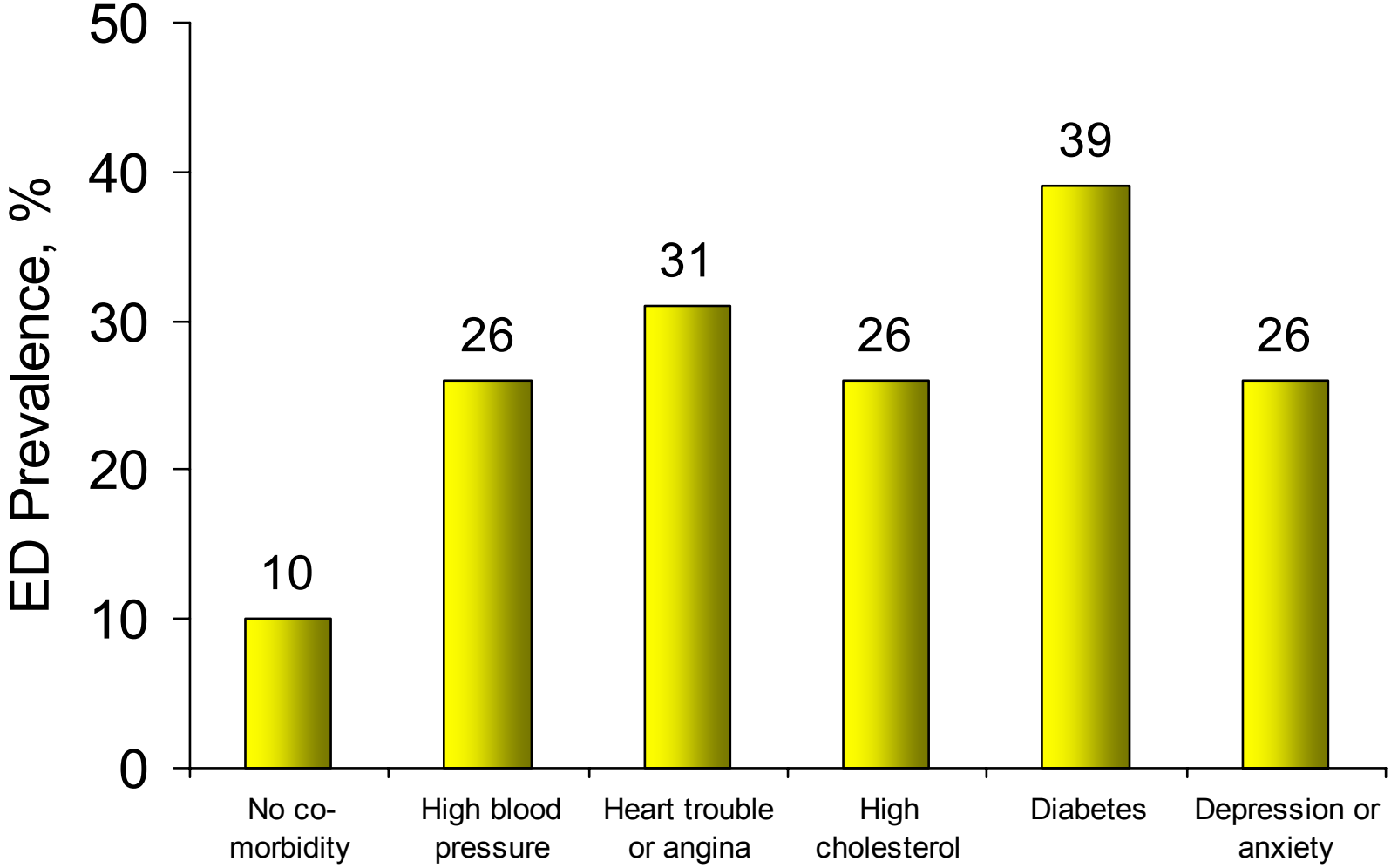
Comorbidities Are More Common in Men With ED



Based on a 2001 survey of nearly 28,000 men in 8 countries, including the US.

Rosen et al. *Curr Med Res Op.* 2004;20:607-617.

High Prevalence of ED in Men With Comorbidities

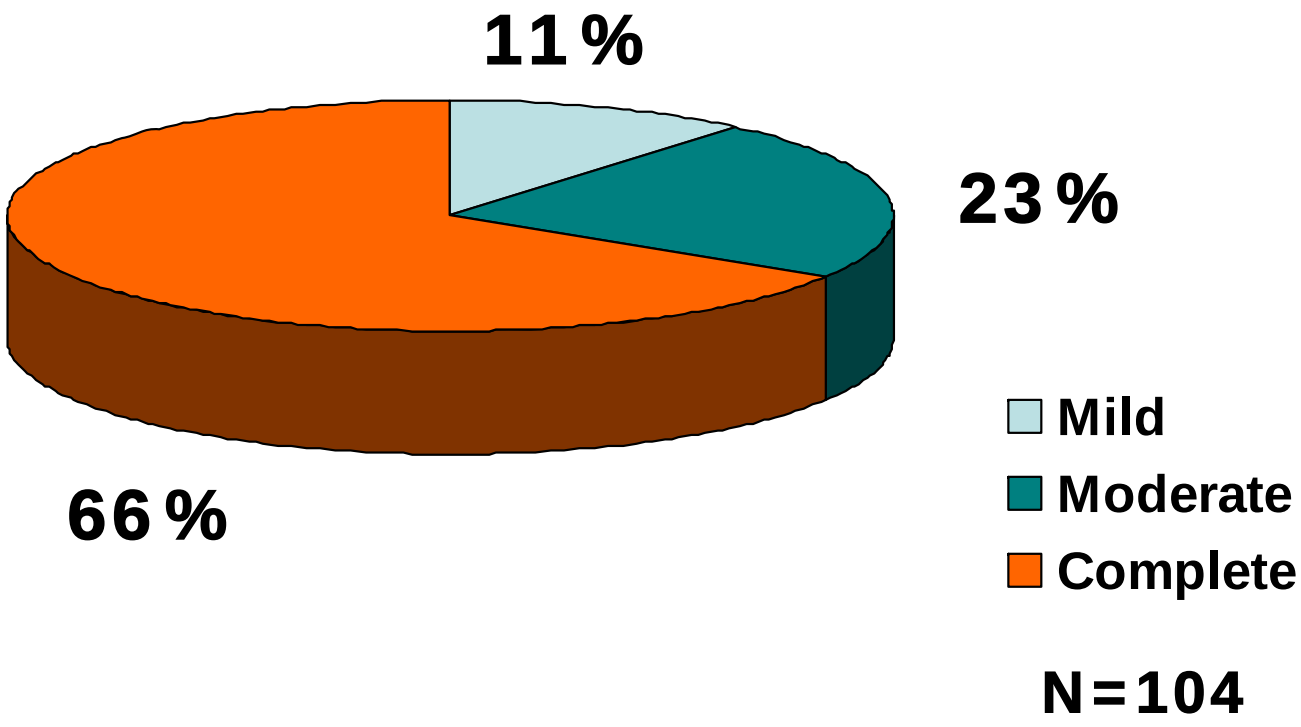


Based on a 2001 survey of nearly 28,000 men in 8 countries, including the US.

Rosen et al. *Curr Med Res Op.* 2004;20:607-617.

Prevalence of ED in Hypertensive Patients

68% of hypertensive patients evaluated with IIEF had some level of ED



Burchardt et al. *J Urol*. 2000;164:1188-1191.

Increasing evidence suggest that ED is a vascular disease and may be a marker for occult cardiovascular disease and diabetes

Pritzker (1999): The Penile Stress Test: A Window to the Hearts of Man?

- 50 asx vasculogenic ED patients
- Risk profile anyalysis:

  multiple CV risk factors in 40/50

  smoking: 40 total cholesterol > 220: 35

  HTN: 24 DM: 10

  HDL<40: 18 positive FH: 32

  sedentary lifestyle: 38

- Graded exercise testing positive in 28/50

Pritzker II

- Coronary angiography in 20/50

  L main coronary obstrx or severe 3 vessel disease in 6/20

  moderate 2 vessel disease in 7/20

  significant single vessel disease in 7/20

- High prevalence of risk factors and significant CAD found in asx vasculogenic ED patients

Erectile Dysfunction and Subsequent Cardiovascular Disease

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Charles A. Coltman, MD

Context The risk factors for cardiovascular disease and erectile dysfunction are similar.

Objective To examine the association of erectile dysfunction and subsequent cardiovascular disease.

Design, Setting, and Participants Men aged 55 years or older who were randomized to the placebo group (n=9457) in the Prostate Cancer Prevention Trial at 221 US centers were evaluated every 3 months for cardiovascular disease and erectile dysfunction between 1994 and 2003. Proportional hazards regression models were

Thompson et al. *JAMA.* 2005;294:2996-3002.

Study Design

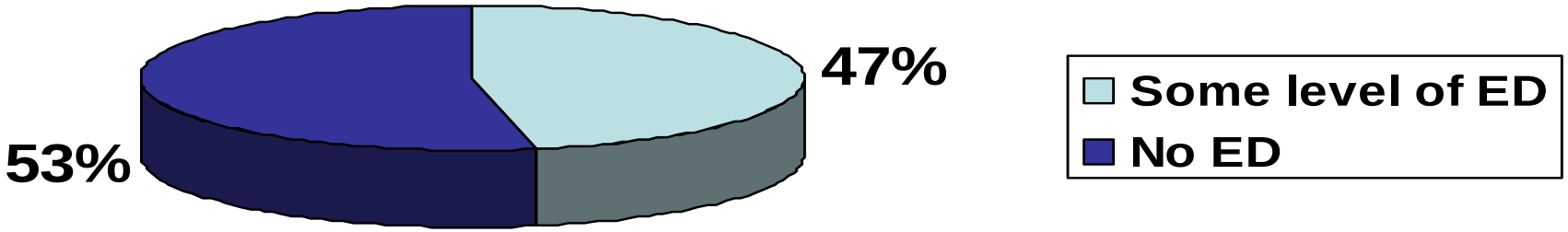
- Finesteride Prostate Cancer Prevention Trial, 1994-2003
- Subjects were ≥55 years, PSA <3.0 and normal DRE, no history of prostate cancer, life expectancy of ≥10 years
- Excluded subjects:
  - Men with CHF, MI, angina, TIA, arrhythmia or stroke
  - Men with any grade of ED
- Included were men with incident ED who had <u>not</u> experienced an incident cardiovascular event prior to developing ED

Thompson et al. *JAMA.* 2005;294:2996-3002.

Study Population

Prostate Cancer Prevention Trial (PCPT): Placebo Group

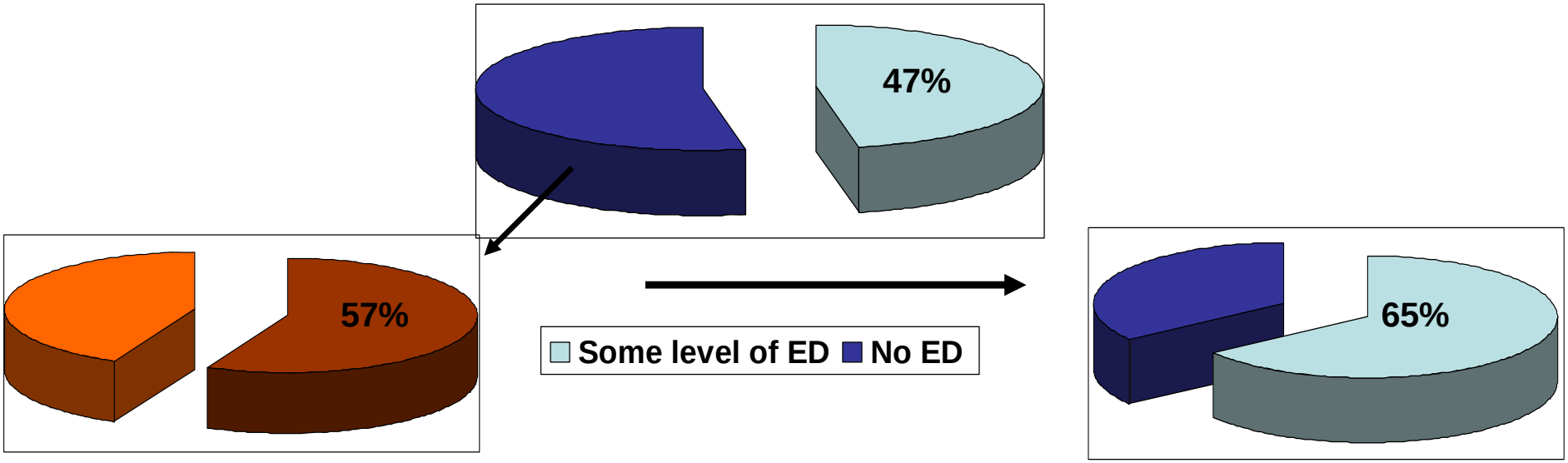
- 9457 men randomized to placebo, of which 8063 (85%) men had no CVD at study entry
- Of these 8063 subjects, 3816 (47%) had ED at entry. 4247 (53%) subjects were without ED and included in the study



Thompson et al. *JAMA*. 2005;294:2996-3002.

Study Results

- Of the subjects without ED, 2420 men (57%) reported incident ED after 5 yrs and 2760 (65%) reported ED after 7 years
- Incident ED was statistically significantly associated with subsequent development of CV events (MI, angina, CVA, TIA, CHF, nonfatal arrhythmia) relative to men without a report of erectile dysfunction after adjusting for potential confounders.



Thompson et al. *JAMA*. 2005;294:2996-3002.

A hazard ratio of 1.25 for development of subsequent cardiovascular events was seen

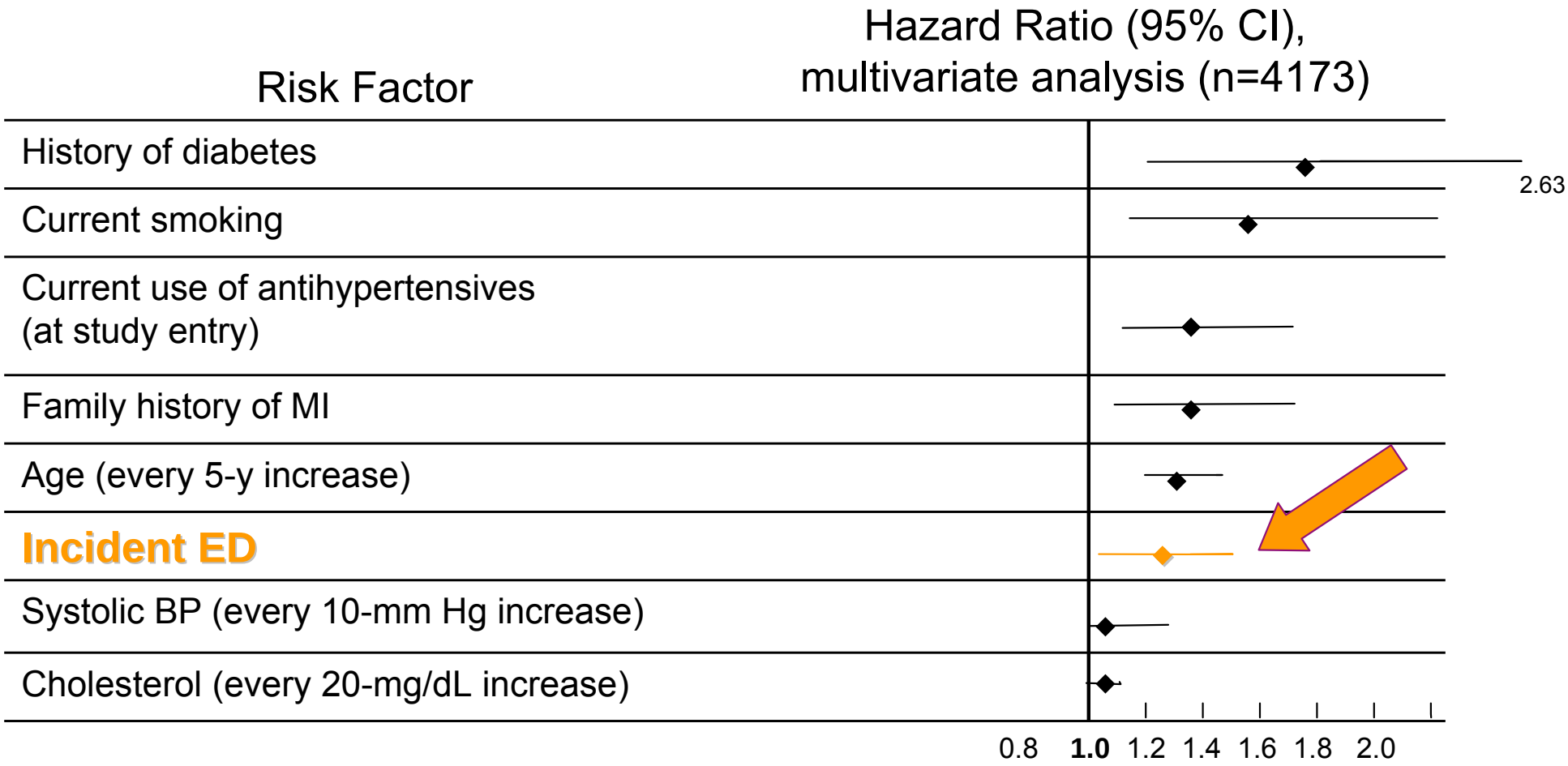
- 95% confidence interval
- Covariant adjusted model utilized

(Covariate adjusted model includes a number of confounders: age, BMI, systolic and diastolic BP, total cholesterol, HDL, DM, parent or sibling with MI, race (white vs other), current smoking, antihypertensive agents, physical activity, self-reported global health.)

Thompson et al. *JAMA*. 2005;294:2996-3002.

Results

Incident ED had an equal or greater effect on subsequent CV events of same magnitude as traditional risk factors

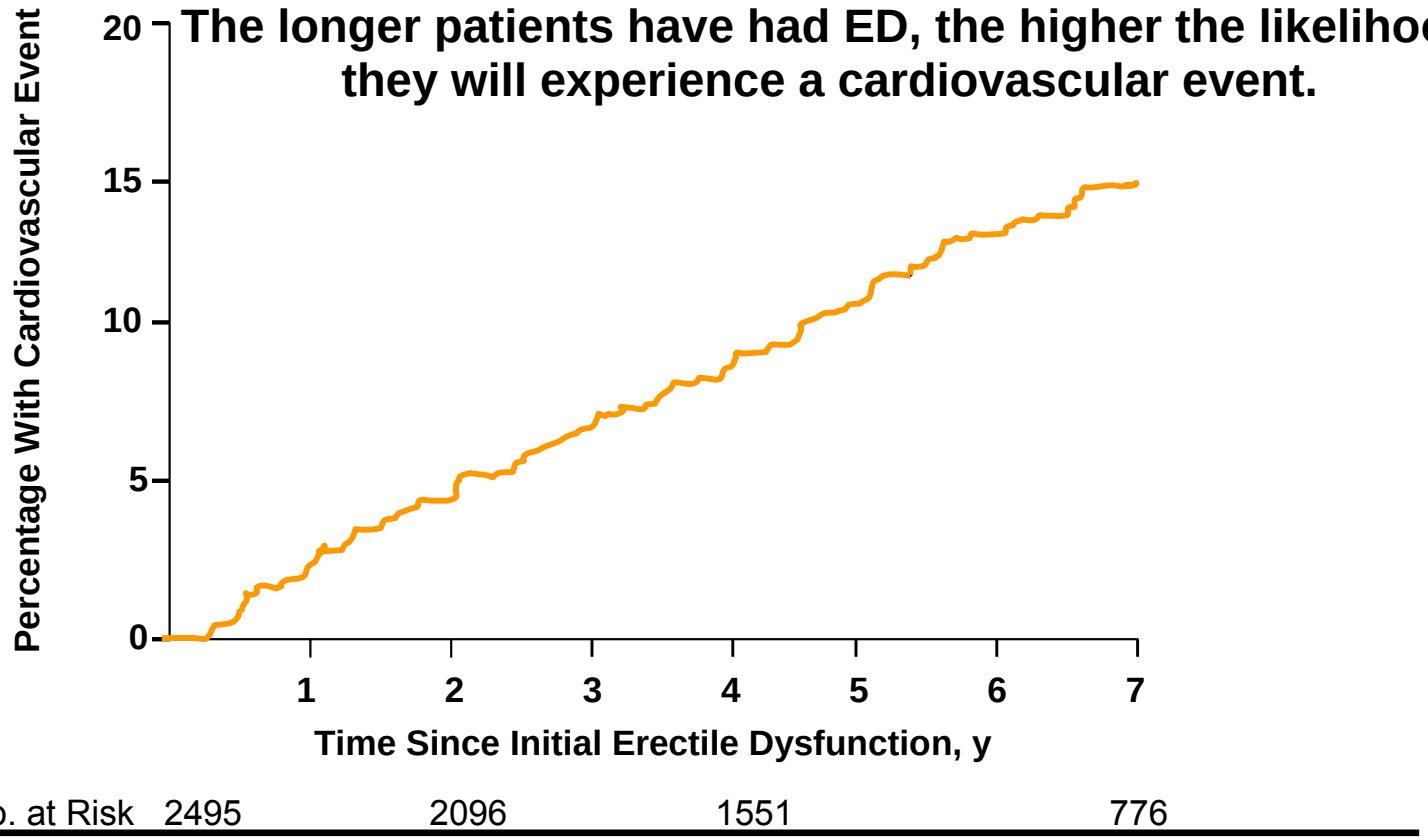


Thompson et al. *JAMA*. 2005;294:2996-3002.

ED Predicts CVD

Prostate Cancer Prevention Trial (PCPT): Placebo Group

Time to Any Cardiovascular Event From Initial Report of ED for those with Incident ED and No Previous Cardiovascular Event.



At risk, n = 2495; number of cardiovascular events, 255; 5-year estimate of cardiovascular events, 11%.

Thompson et al. *JAMA*. 2005;294:2996-3002.

Conclusions

In a prospective study, incident ED has an equal or greater effect on subsequent cardiovascular events of the same magnitude as a family history of MI, cigarette smoking, or measures of hyperlipidemia.

Thompson et al. *JAMA*. 2005;294:2996-3002.

Significance of Study

- Cardiovascular disease is the leading cause of death in the US
- Accounts for ~ 40% of deaths
- In men, 50% of deaths due to coronary heart disease occur in men without a history of cardiovascular disease
- ED is a predictive symptom or finding that allows for earlier intervention and possibly reducing morbidity and mortality due to cardiovascular disease

Thompson et al. *JAMA*. 2005;294:2996-3002.

What is the Link Between ED and Cardiovascular Disease?

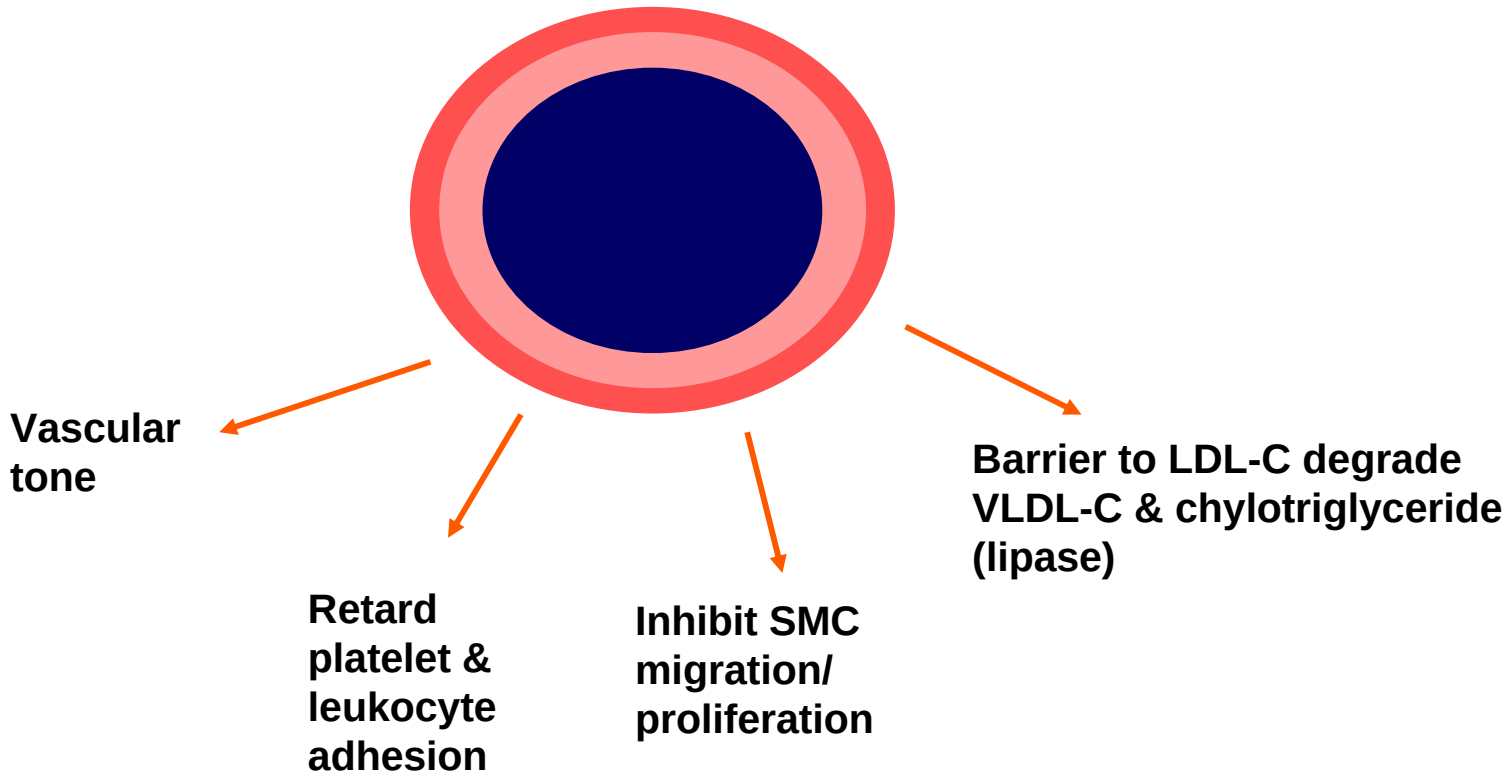
ED = ED

ED

- Erectile dysfunction
- Endothelial dysfunction
- Early death

Endothelium Maintains Vascular Health

Normal Endothelium

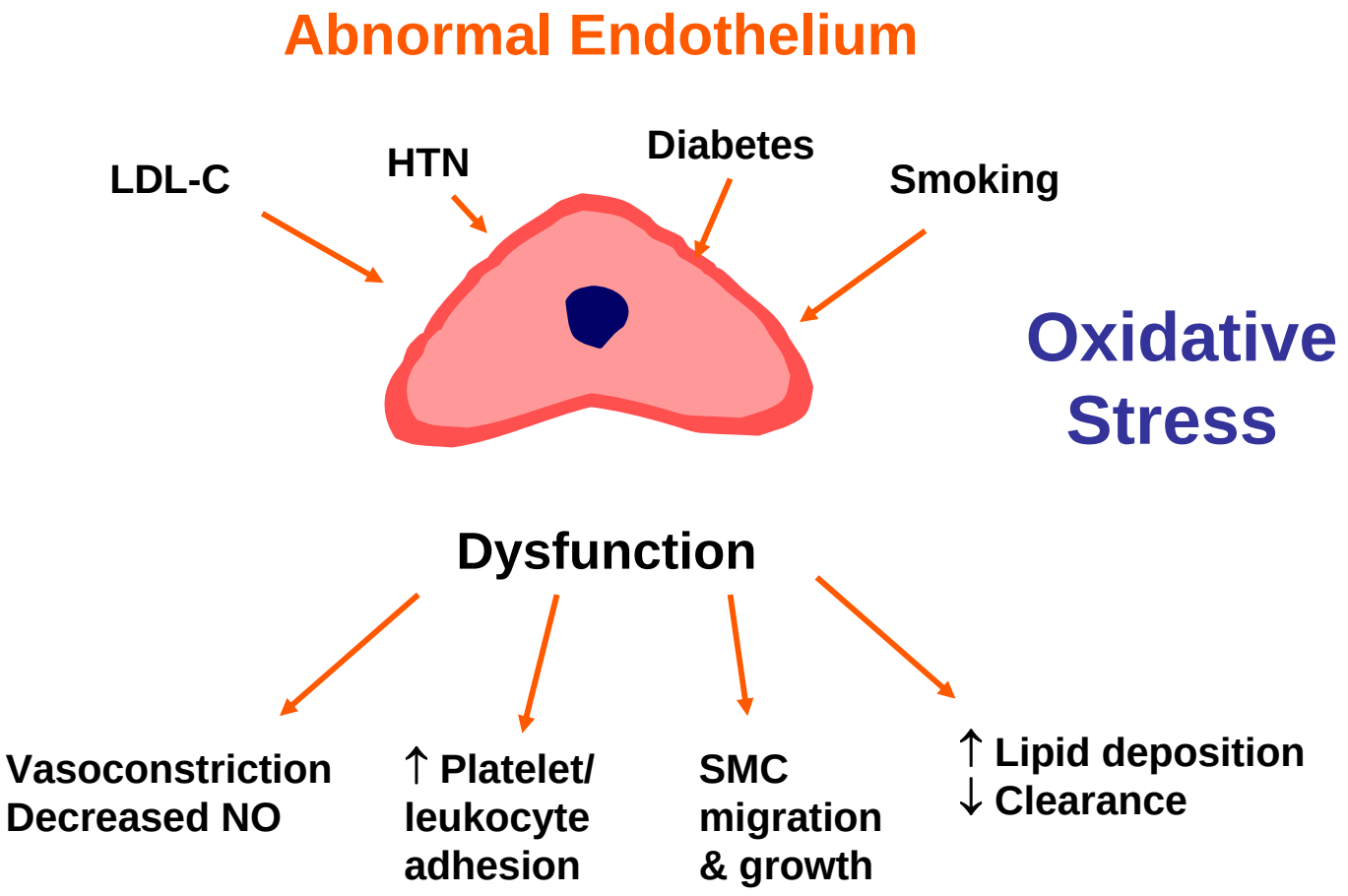


Adapted from Omoigui N, Dzau VJ. *J Vasc Med Biol.* 1991;3:382-391.

Roles of Healthy Endothelium

- Passive barrier for arterial and venous blood
- Releases a variety of factors that affect contractile and relaxatory behavior of underlying smooth muscle and thus modulates vascular tone and blood flow in response to humoral, neural, and mechanical stimuli
- Plays a role in the regulation of inflammation, platelet aggregation, vascular smooth muscle proliferation, and thrombosis

Endothelial Dysfunction Promotes Vascular Disease



Adapted from Omoigui N, Dzau VJ. *J Vasc Med Biol.* 1991;3:382-391.

Endothelial Dysfunction

- A decrease in endothelium-dependent smooth muscle cell relaxation caused by a loss or increased destruction of NO bioactivity
- With disruption of the functional integrity of endothelium the response to local hemodynamic changes and paracrine and autorcrine factors changes
- Refers to several pathological conditions, including altered anticoagulation and anti-inflammatory activities, impaired modulation of vascular growth, and dysregulation of vascular remodeling

Endothelial dysfunction, including impaired endothelium-dependent vasodilatation (NO-mediated) has been seen in patient subgroups and often is evident prior to the development of vascular occlusive disease.

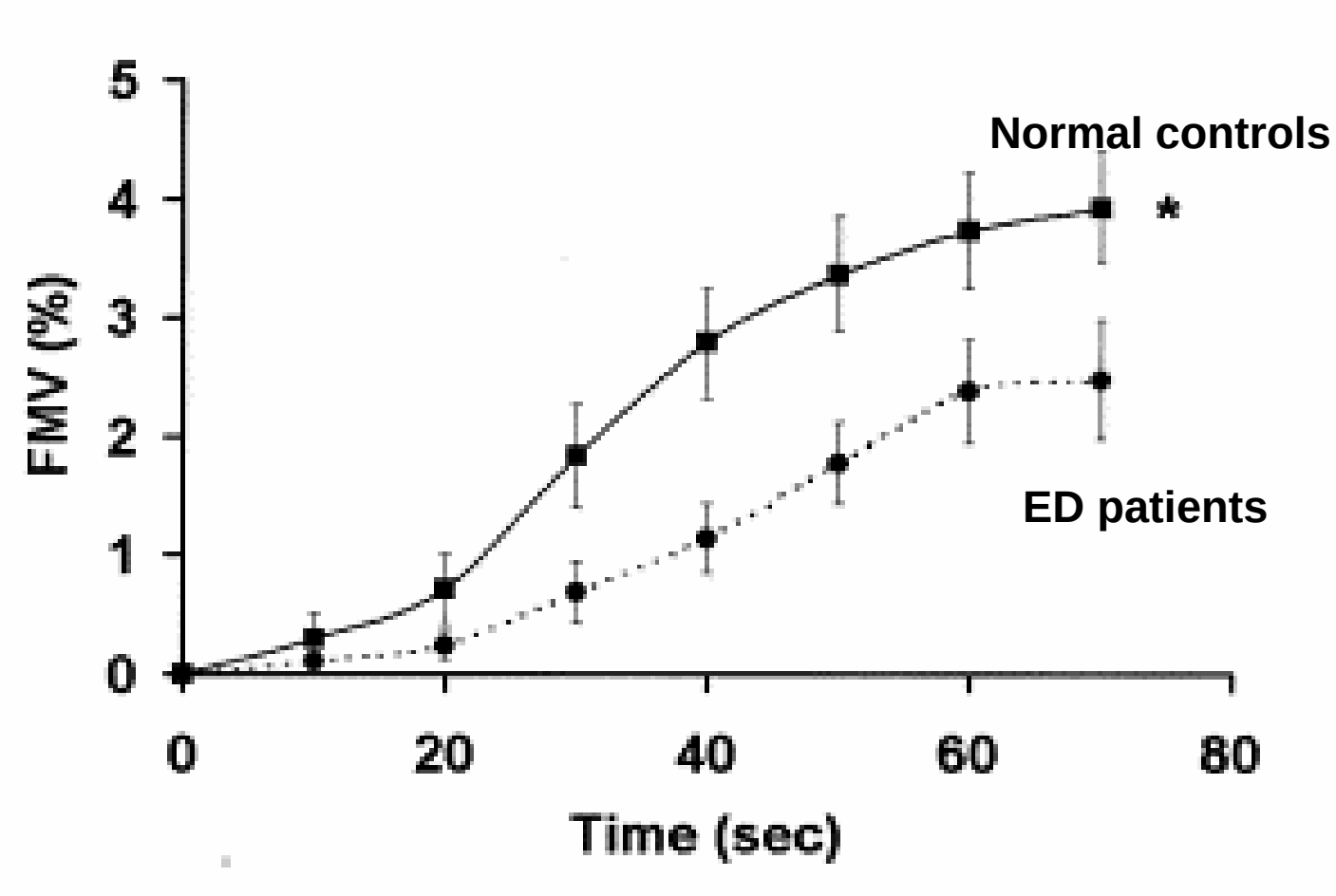
Impaired brachial artery endothelium-dependent and independent vasodilatation in men with erectile dysfunction and no other clinical cardiovascular disease.

Kaiser et al. *J Am Coll Cardiol.* 2004;43:179-184.

- 30 patients with ED and 27 age-matched normal control subjects
- No significant difference seen for
  - Fasting lipids, glucose, homocysteine
  - Coronary CTS, aortic PWV, or carotid IMT

CTS: computed tomographic scan; PWV: pulse wave velocity; IMT: intima-media thickness; FMVD: flow-mediated vasodilatation

Kaiser et al. *J Am Coll Cardiol.* 2004;43:179-184.



This study demonstrates a defect in the peripheral vascular NO-cGMP system in patients with ED but no other clinical cardiovascular disease. This defect is predominantly in the smooth muscle and can occur before the development of other overt functional or structural systemic vascular disease.

Kaiser et al. *J Am Coll Cardiol.* 2004;43:179-184.

Low Brachial Artery Flow

- Significant reduction in brachial artery FMVD studies (1.3 vs 2.4%, *P*=0.014) and vasodilation to nitroglycerin (13.0 vs 17.8%, *P*<0.05)
- This suggests that an abnormality in the peripheral vascular NO-cGMP vasodilator system may result in ED as the first clinical manifestation of cardiovascular disease

"*Patients with ED but no clinical CVD have a peripheral vascular defect in endothelium-dependent and -independent vasodilation that occurs before…other overt functional or structural systemic vascular disease.*"

CTS: Computed tomographic scan; PWV: pulse wave velocity; IMT: intima-media thickness; FMVD: flow-mediated vasodilation

Kaiser et al. *J Am Coll Cardiol.* 2004;43:179-184.

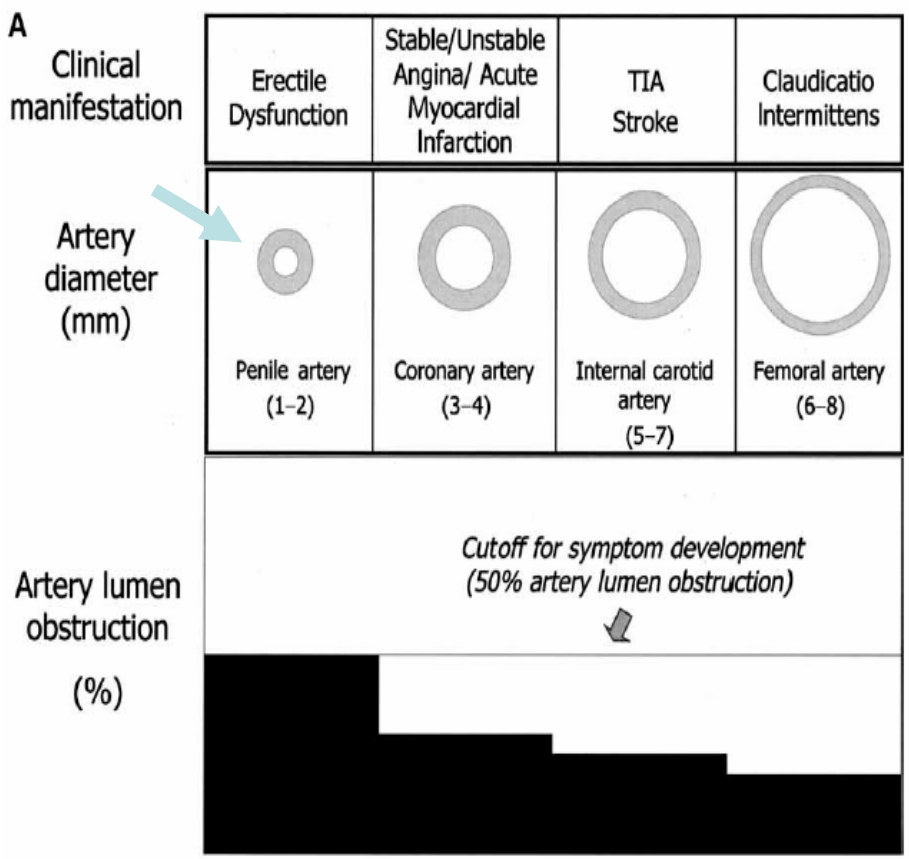
A Continuum Towards Structural Vascular Disease

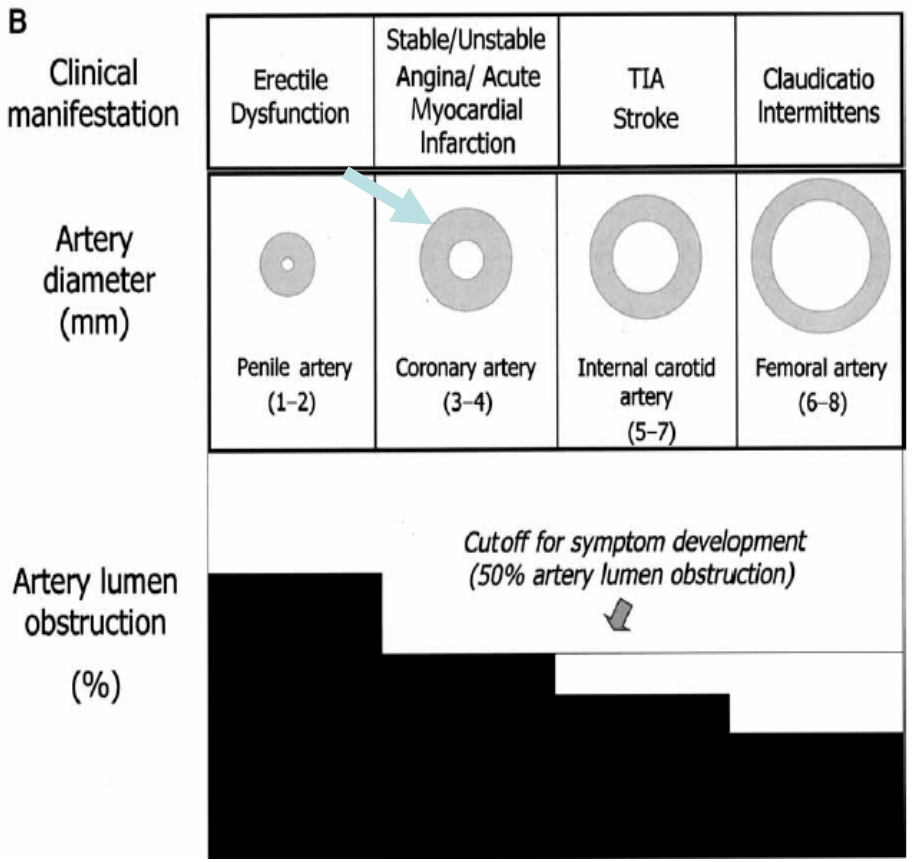
- Endothelial dysfunction is an early lesion in the development of vascular diseases. Systemic functional factors over time can lead to the development of chronic vascular disease (CAD, CVA, PVD).
- In atherosclerosis, a dysfunctional endothelium (via diminished NO bioavailability) results in the adhesion and infiltration of monocytes. Monocytes become resident macrophages and then foam cells—the epicenters of atherosclerotic plaque

“Artery-Size Hypothesis”

- Atherosclerosis, a systemic disorder, theoretically should affect all major vascular beds at the same time and to the same extent
- Multi-vessel involvement rarely becomes clinically evident at the same time because not all arteries are of the same size

“Artery-Size Hypothesis”





Early stage of atherosclerotic process; >50% narrowing of penile lumen artery leading to ED symptoms

Late stage of atherosclerotic process; significant obstruction of coronary circulation leading to angina pectoris

Montorsi et al. *Am J Cardiol*. 2005;96(suppl):19M-23M.

If the “artery-size hypothesis” is true …

ED is an early marker of largely sub-clinical vascular disease in evolving atherosclerosis. Conversely, later on, ED is only one of many vascular beds affected.

If the “artery-size hypothesis” holds true …

- Severity of ED correlates with the severity of cardiovascular disease
  - Greenstein (1997): A statistically significant correlation was demonstrated between erectile function and the number of coronary vessels involved
  - Solomon (2003): There is a link between total coronary artery plaque burden as assessed angiographically to objective measures of ED (IIEF score)

Greenstein et al. *Int J Impot Res*.1997;9:123-126. Solomon et al. *Heart*. 2003;89:251-254.

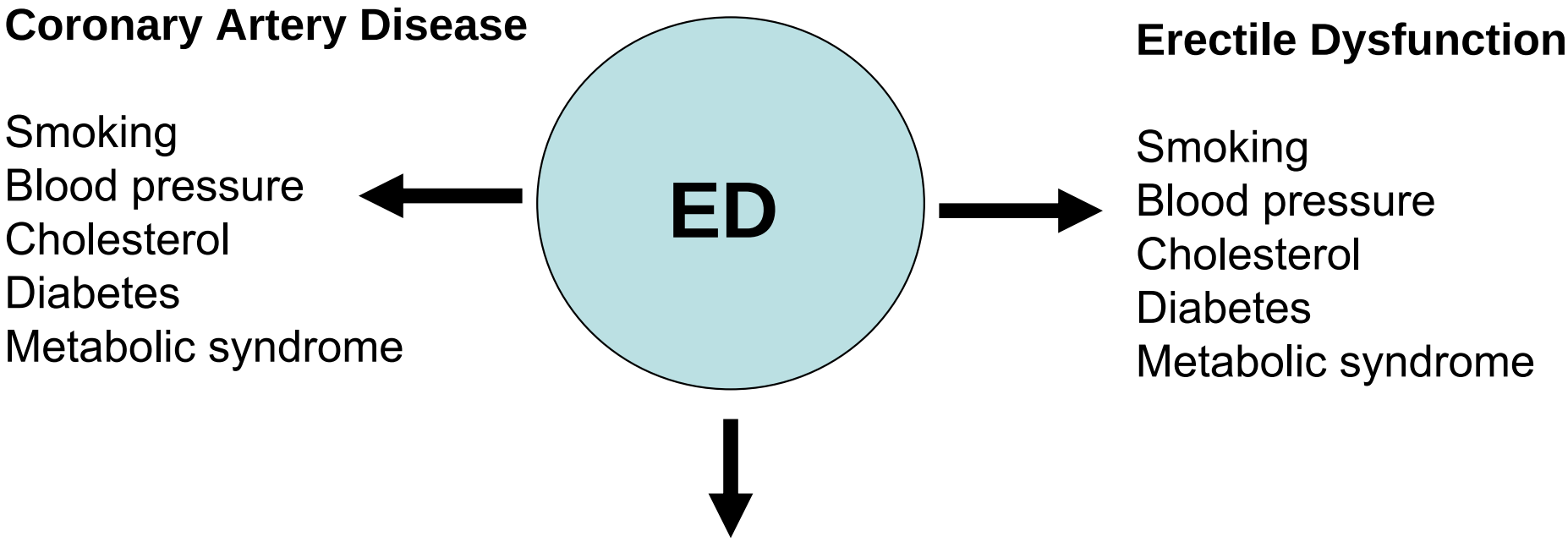
If the “artery-size hypothesis” is true …

- ED symptoms present earlier than symptoms of CAD
  - Mean time interval between onset of ED and onset of CAD is 39 months (range,1-165 months)

- This time interval gives physicians an early window of opportunity to identify those patients who are at high risk for systemic vascular complications

Montorsi et al. *Am J Cardiol*. 2005;96(suppl):19M-23M.

CAD and ED Share the Same Risk Factors



Endothelial Dysfunction — the common denominator

Adapted from Solomon et al. *Heart*. 2003;89:251-253.

A New Paradigm for the Etiology of Erectile Dysfunction

Old paradigm:

ED is a secondary complication of

- Diabetes
- Cardiovascular disease
- Hypertension
- Dyslipidemia

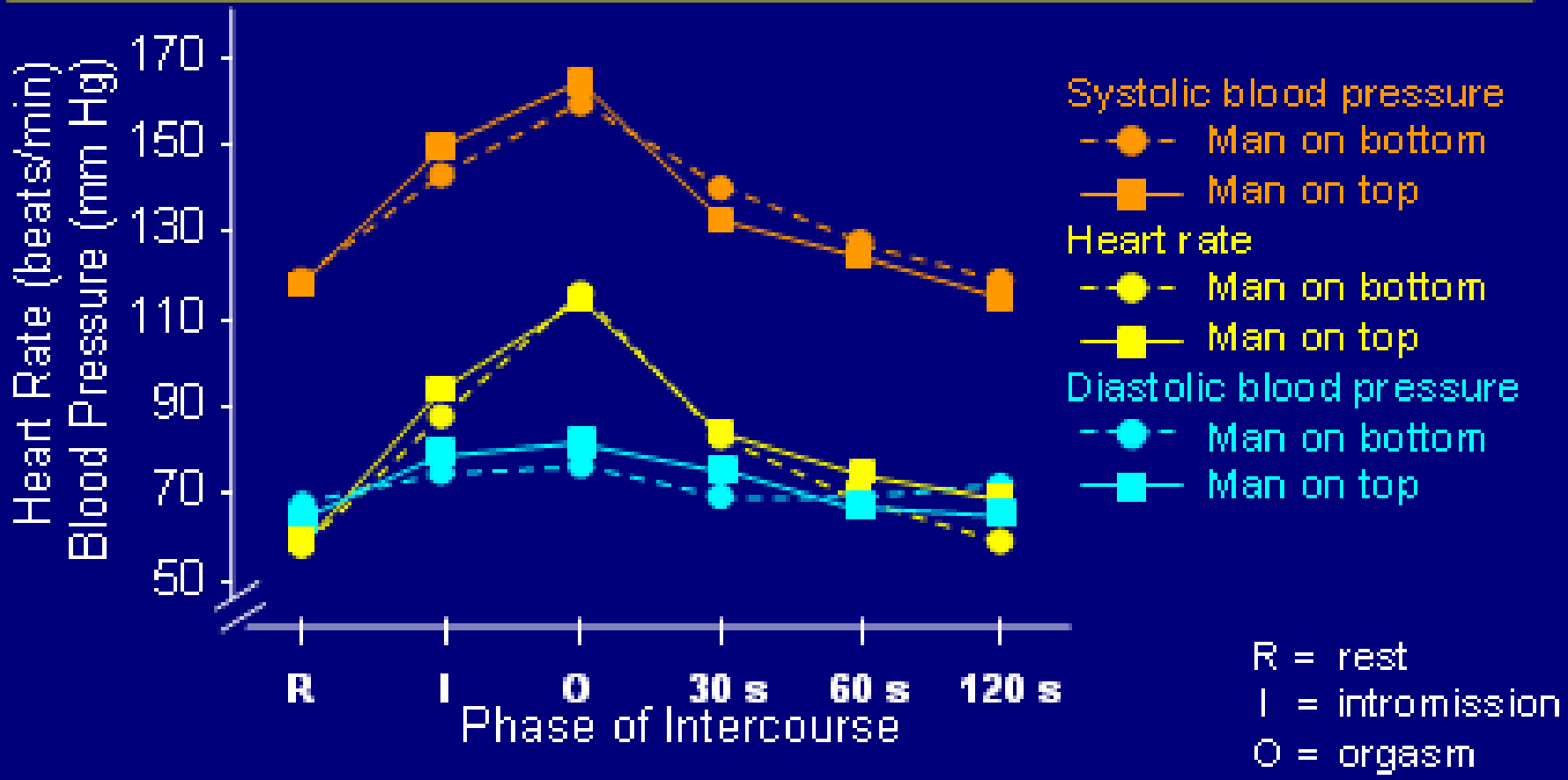
New paradigm:

ED is one of the earliest manifestations of atherosclerosis and a precursor to systemic vascular disease

Thompson et al. *JAMA*. 2005;294:2996-3002.

Is Sex Safe?

Blood Pressure and Heart Rate During Sex



Reprinted, by permission, from Skinner JS, 1995, "Sexual relations" in *Heart Disease and Rehabilitation*, 3rd ed., edited by Pollock ML, Schmidt DH (Champaign, Ill: Human Kinetics), 372.

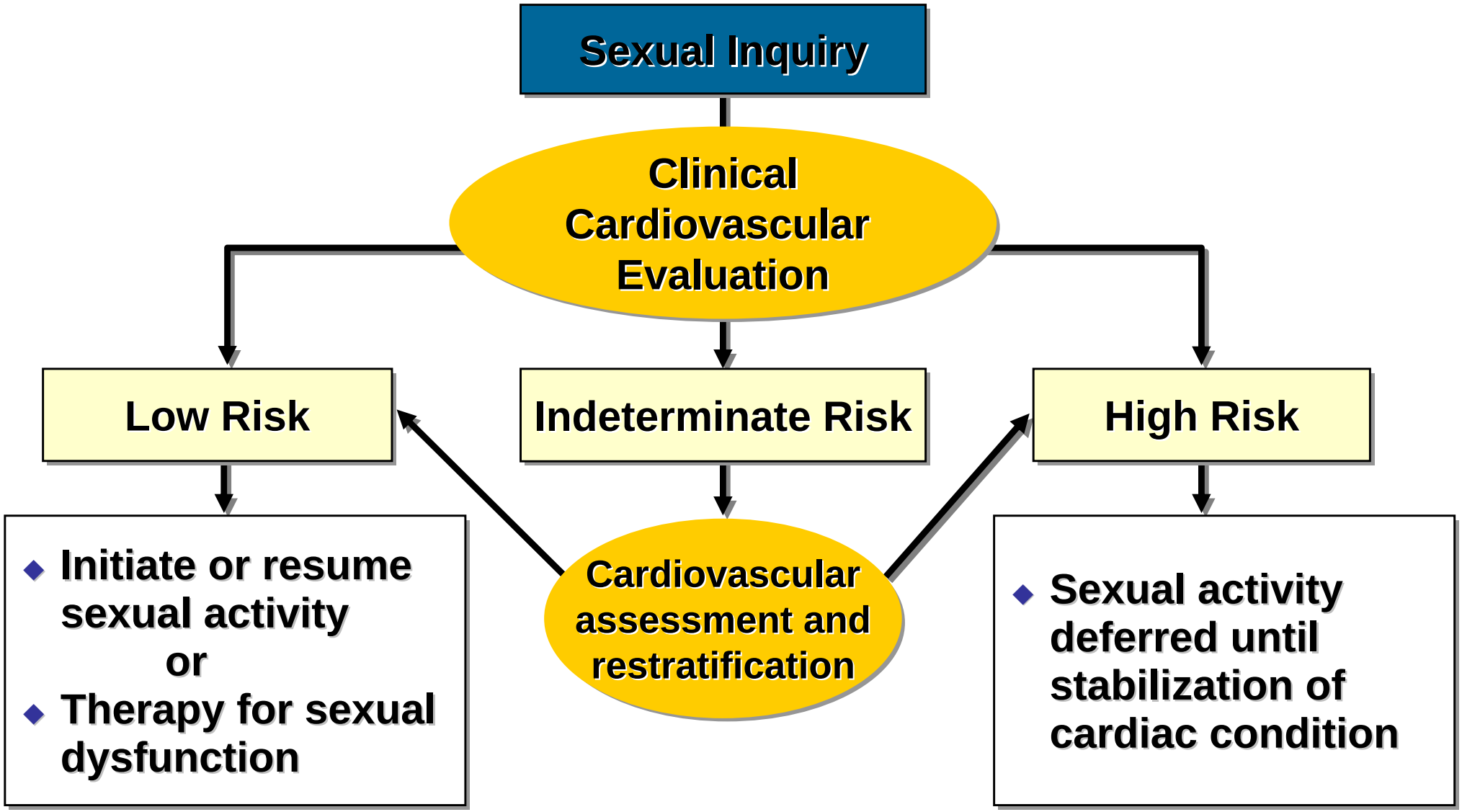
Sexual Activity Has the Same Exertion Effort as Normal Walking

Estimated METs	Description	Physical Activities
2	Sitting	Reading, watching TV
3	Very light exertion	Moderate sexual activity with long-term partner, office work, strolling in park
4-5	Moderate exertion	Vigorous sexual activity, normal walking, golfing on foot, gardening
5-6	Vigorous to heavy exertion	Running, racquetball, fast biking, heavy snow-shoveling

METs = metabolic equivalents of oxygen consumption.
Sexual activity qualifies as moderate exertion.

Adapted from DeBusk et al. *Am J Cardiol.* 2000;86:175-181.

Sexual Activity and Cardiac Risk: Princeton Guidelines Simplified Algorithm



Adapted from DeBusk et al. *Am J Cardiol*. 2000;86:175-181.

Stratification of Patients

Low Risk: sexual activity may be initiated without need for additional cardiac evaluation. Asymptomatic patients with less than 3 cardiac risk factors

- Controlled hypertension
- Mild stable angina
- Post successful CABG
- Uncomplicated old MI
- Mild valvular disease
- Class I NYHA CHF

Stratification of Patients

Intermediate/indeterminate Risk:

Cardiac condition is uncertain or risk profile requires further evaluation before sexual activity is resumed

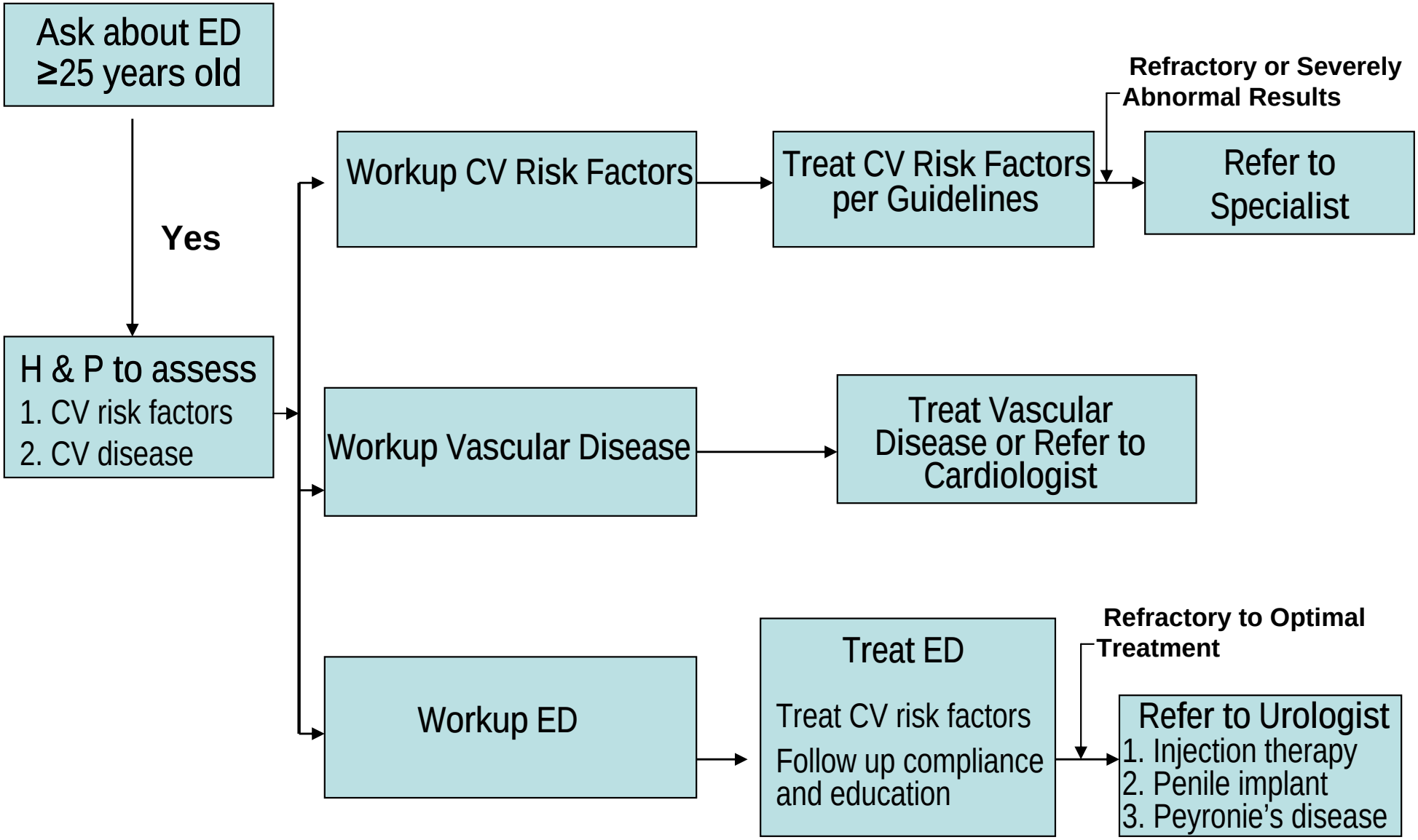
- >3 CHD risk factors
- Moderate stable angina
- Recent MI (2-6 wks)
- CHF (NYHA II)
- Non-cardiac sequelae of atherosclerotic disease (stroke, PVD)

Stratification of Patients

High Risk: Cardiac condition is severe or unstable and sexual activity poses significant risk. Sexual activity to be deferred pending further evaluation

- Unstable angina
- Uncontrolled hypertension
- CHF (NYHA III/IV)
- High risk arrhythmias
- Cardiomyopathies
- Moderate to severe heart disease

Model Algorithm for ED



Billups et al. *J Sex Med*. 2005;2:40-52.

Diagnosing ED

- Basic evaluation of sexual dysfunction
  - Sexual, medical, and psychosocial history
- Focused physical examination
- Recommended diagnostic tests including
  - Glucose, lipids, serum chemistries, testosterone, prolactin, prostate-specific antigen (PSA), and complete blood count

Empiric trials of therapy are discouraged without this basic evaluation.

The Process of Care Consensus Panel. *Int J Impot Res*. 1999;11:59-70.
Meuleman E, et al. In: Jardin A, et al, eds. *Erectile Dysfunction*. Plymouth, United Kingdom: Plymbridge Distributors; 2000:115-138.

Classification of ED: Psychogenic or Organic?

Psychogenic	Organic
Sudden onset	Gradual onset
Complete immediate loss	Incremental progression
AM erections present	Lack of AM erections
Varies with partner and circumstance	Lack of erections under most sexually stimulating circumstances

Ralph D, et al. *BMJ.* 2000;321:499-503. With permission from the BMJ Publishing Group.

Erectile Dysfunction: Management

Goal Directed Therapy: First Steps

- Aggressively manage risk factors
  - Smoking, alcohol, drug abuse
- Aggressively manage comorbid disease states
  - Hypertension, diabetes, depression, hyperlipidemia, coronary artery disease, peripheral vascular disease
- Consider changing to medications that have less of an impact on sexual function
- Address psychosocial needs

AACE Male Sexual Dysfunction Task Force. *Endocr Pract.* 2003;9:77-95.

Can Lifestyle Changes Modify Risk?

- 281 smokers who complained of ED and requested nicotine replacement therapy
- Grade of ED assessed before and at 1 year follow-up
- ≥25% of 118 ex-smokers reported improvement in erectile function
  - None of 163 continued smokers reported improvement
  - 2.5% ex-smokers and 6.8% current smokers had a deterioration in ED
- Among ex-smokers, patients with advanced ED and older patients had less improvement

Conclusion: Stopping smoking can improve ED in a considerable proportion of smokers

Pourmand et al. *BJU Int.* 2004;94:1310-1313.

Phosphodiesterase 5 inhibibition and the treatment of Erectile Dysfunction

Distribution of PDE Isoenzymes

- PDE1 Testes, heart, olfactory cilia, central nervous system (CNS)[1]
- PDE2 CNS, adrenal cortex[1]
- PDE3 Adipose tissue, cardiac muscle, vascular smooth muscle, liver, platelets[1]
- PDE4 Neural and endocrine tissues[1]
- PDE5 Vascular smooth muscle, corpus cavernosum, lung, kidney, platelets[1,2]
- PDE6 Retina (rods and cones)[1,2]
- PDE7 Skeletal and cardiac muscle, lymphoid tissue[1]

1. Francis SH, et al. In: *Progress in Nucleic Acid Research and Molecular Biology*. New York, NY: Academic Press; 2001:65:1-52.
2. Sadovsky R, et al. *Int J Clin Pract*. 2001;55:115-128.

Distribution of PDE Isoenzymes (cont'd)

- PDE8 Testes, ovary, colon, small intestine
- PDE9 Spleen, intestine, kidney, heart, brain
- PDE10 Not reported[1]
- PDE11* Penile smooth muscle, corpus cavernosum,[2] testes, prostate, pituitary, heart[3]

*Physiologic role and clinical relevance are not yet known.

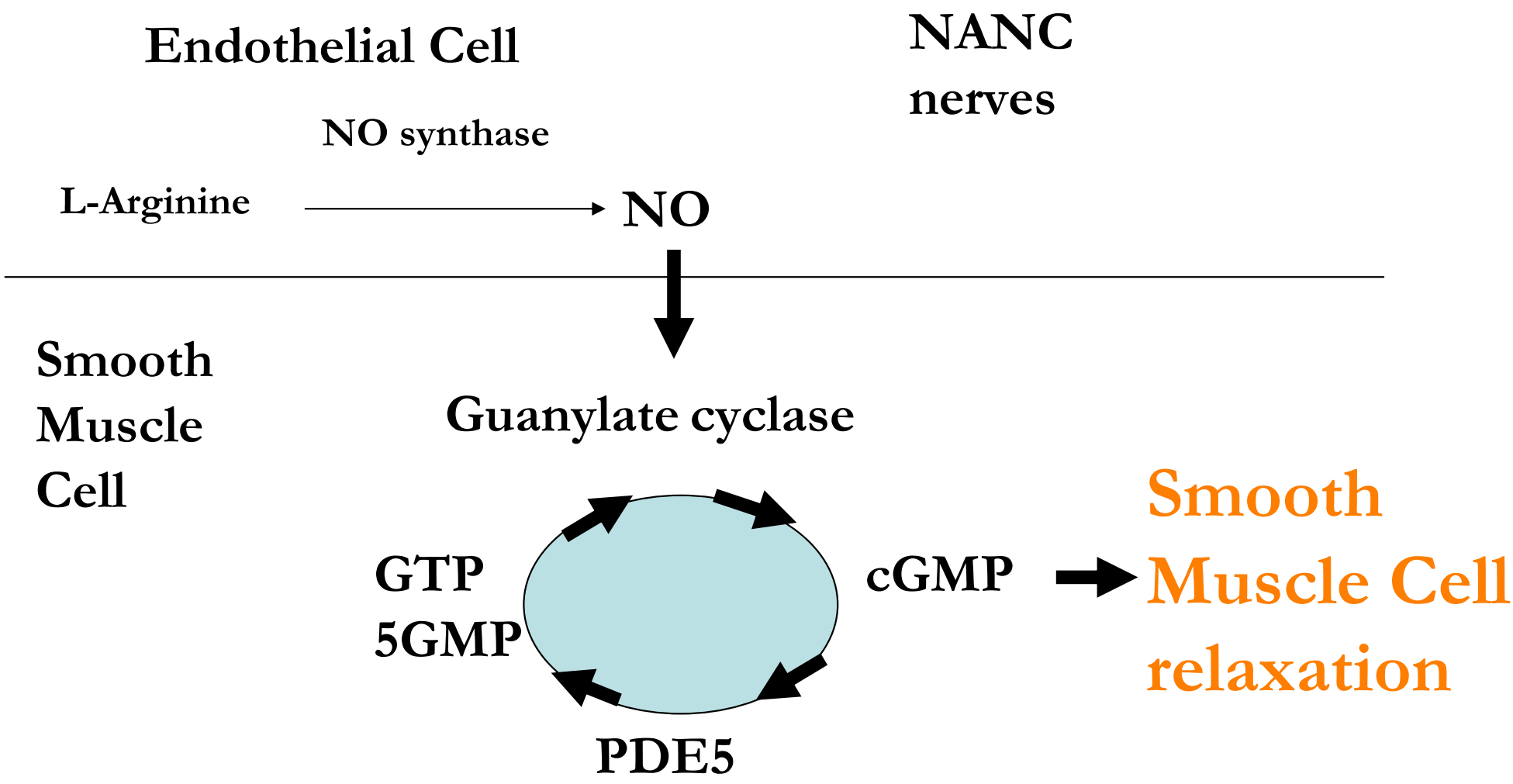
1. Francis SH, et al. In: *Progress in Nucleic Acid Research and Molecular Biology*. New York, NY: Academic Press; 2001:65:1-52.
2. Baxendale RW, et al. *J Urol*. 2001;165(suppl):223-224. Abstract 922.
3. Corbin JP, et al. *Int J Clin Pract*. 2002;56:453-459.

Pharmacokinetic Definitions

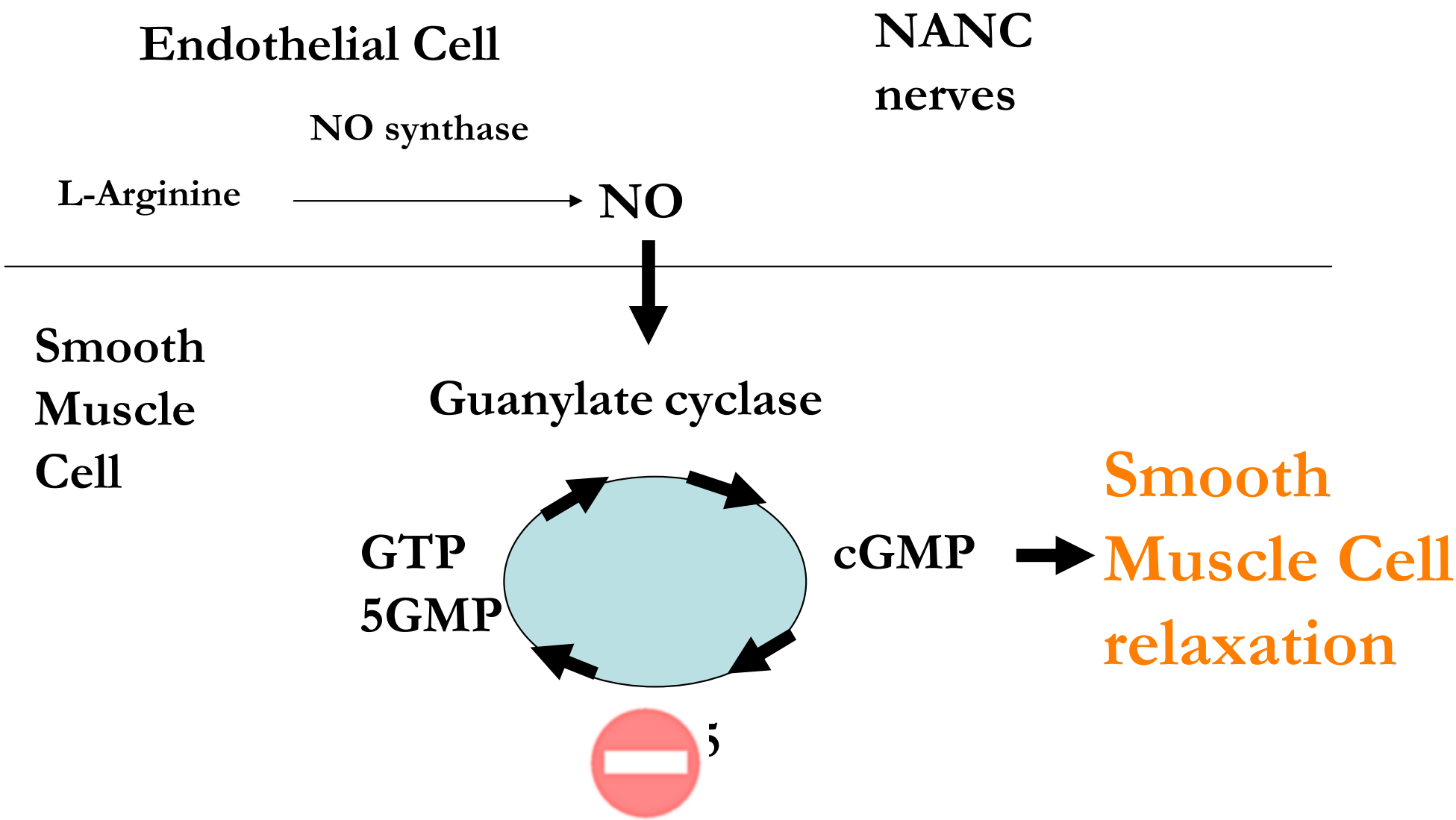
- **Potency** is the concentration that produces a given in vitro response
- **Onset of action** is the amount of time for the drug to take effect
- **Duration of action** is how long the drug works
- **Selectivity** is the key factor in determining an agent for a specific receptor's side effect profile

Corbin JD, Francis SH. *Int J Clin Pract*. 2002;56:453-459.

Nitric Oxide-cGMP Mechanism of Action in Corpus Cavernosal Smooth Muscle Relaxation and Penile Erection

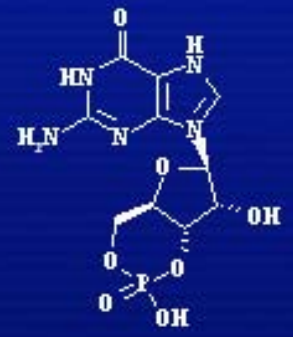


Nitric Oxide-cGMP Mechanism of Action in Corpus Cavernosal Smooth Muscle Relaxation and Penile Erection

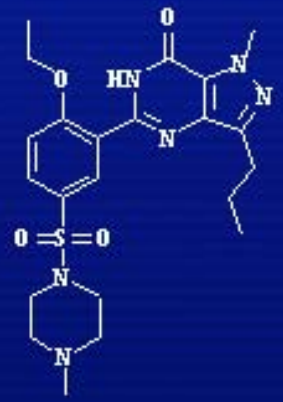


How Do the PDE5 Inhibitors Compare?

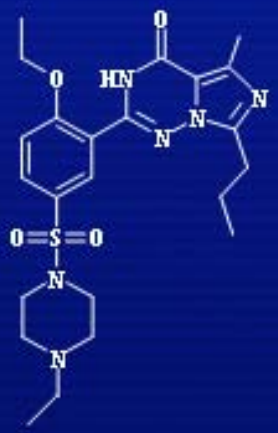
- Sildenafil, vardenafil, and tadalafil are all competitive inhibitors that resemble cGMP (the substrate) and bind to the active site of PDE5



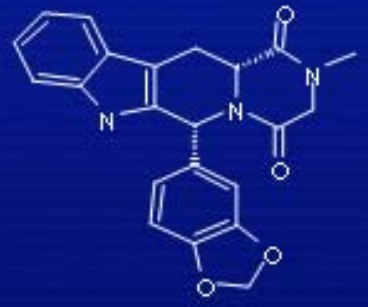
cGMP



Sildenafil



Vardenafil



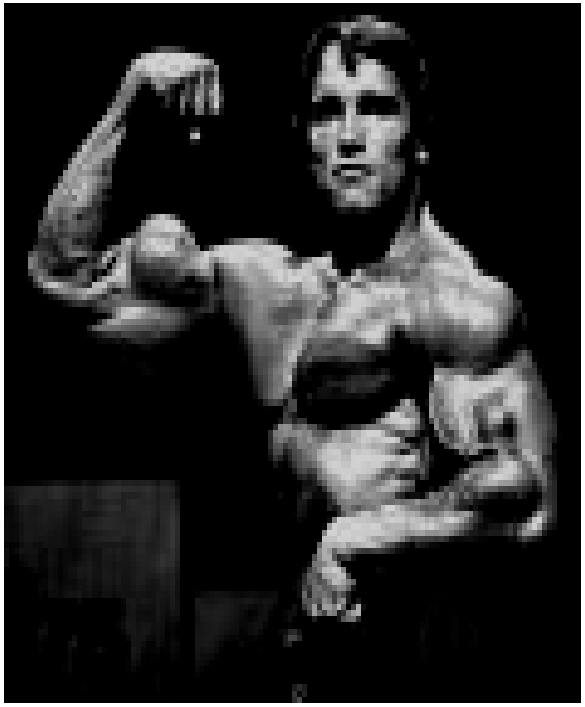
Tadalafil

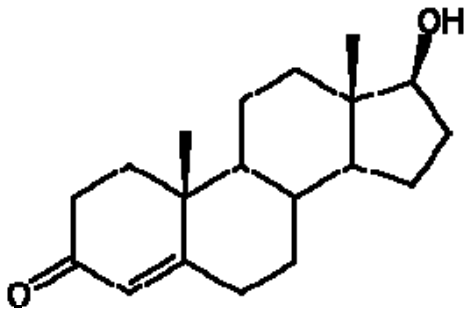
Are the 3 currently available PDE-5 inhibitors the same or are they different?

Can biochemical differences translate into clinical differences?

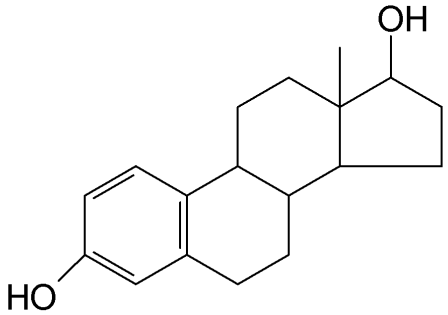
Can small differences make a big difference?

Small Differences ……





Testosterone



Estradiol

PDE-5 Inhibitors
Clinical Differentiation

Sildenafil, vardenafil, and tadalafil:

- All demonstrate efficacy as measured by several different assessment tools
- All demonstrate significantly improved efficacy vs. placebo in general population and different subpopulations
- All show moderate dose-response effect

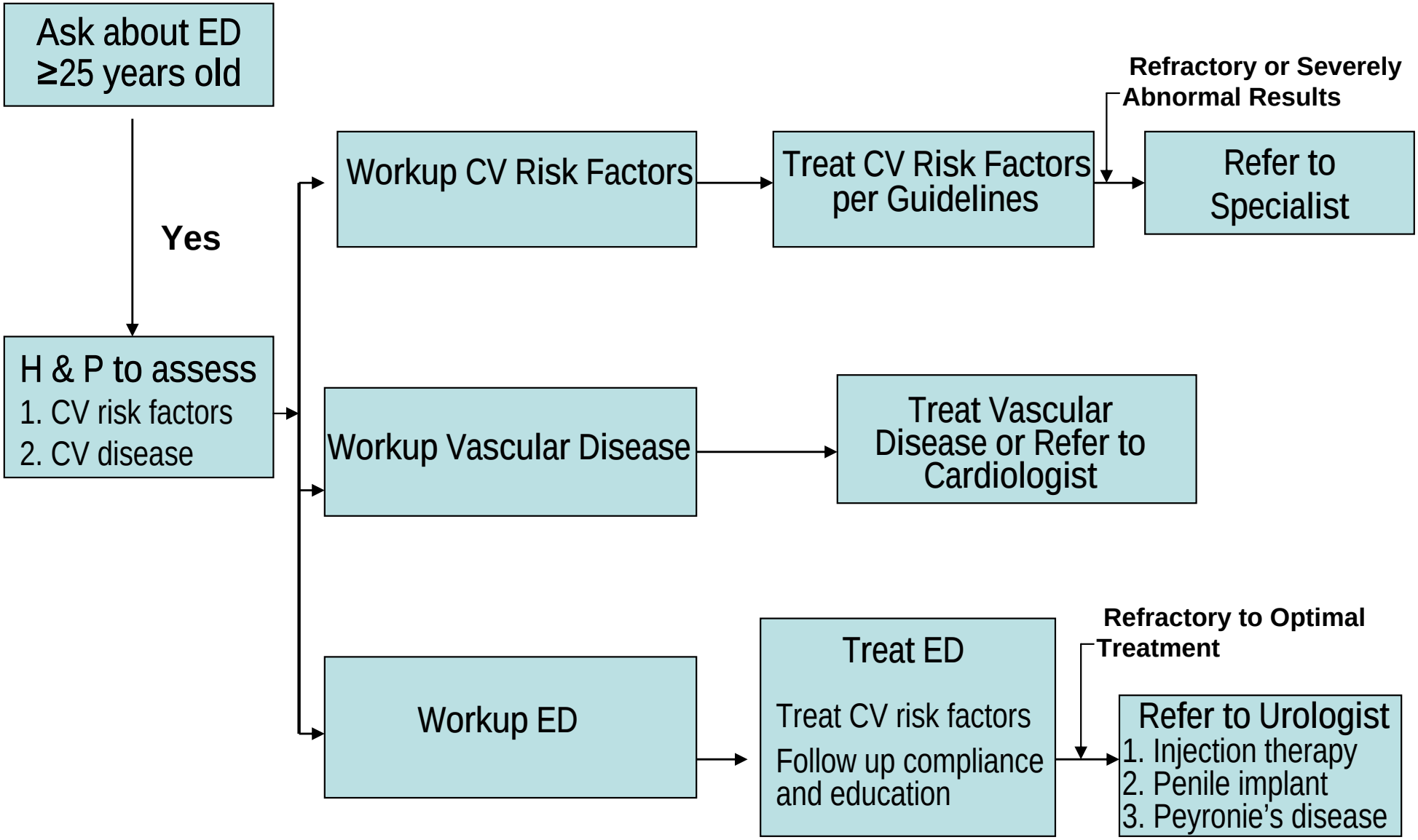
What differences might make a clinical difference?

- Binding characteristics
- Potency
- PDE selectivity
- cGMP accumulation
- Tolerability/Side effects
- Pharmacokinetics
- Drug interactions
- Clinical efficacy
- First time success
- Reliability
- Onset of action
- Duration of action
- Food/Alcohol interaction
- Safety

Other considerations

- Men’s sexual attitudes
- Partner’s sexual attitudes
- Age

Minority Health Institute (MHI) Practice Model Algorithm for Primary Care



Billups et al. *J Sex Med*. 2005;2:40-52.