



# **Erectile Dysfunction**

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***The New era***  
***Ameer Kabour, M.D., F.A.C.C.***

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# Definition of ED

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The persistent inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse

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NIH Consensus Development Panel on Impotence. *JAMA*. 1993;270:83-90.



# Major Points of This Discussion

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1. ED—a vascular condition
2. Management of ED in men with coronary artery disease (CAD)
3. Discussion of VIAGRA® (sildenafil citrate) for ED and the new PDE5 inhibitors
4. Medical management of ED
5. Integrating ED into a busy clinical practice

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.

# Epidemiology of ED

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- 30 million men in the United States
- 52% of men between the ages of 40 and 70
- Often caused by medical conditions

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Levine LA, Kloner RA. *Am J Cardiol*. 2000;86:1210-1213.

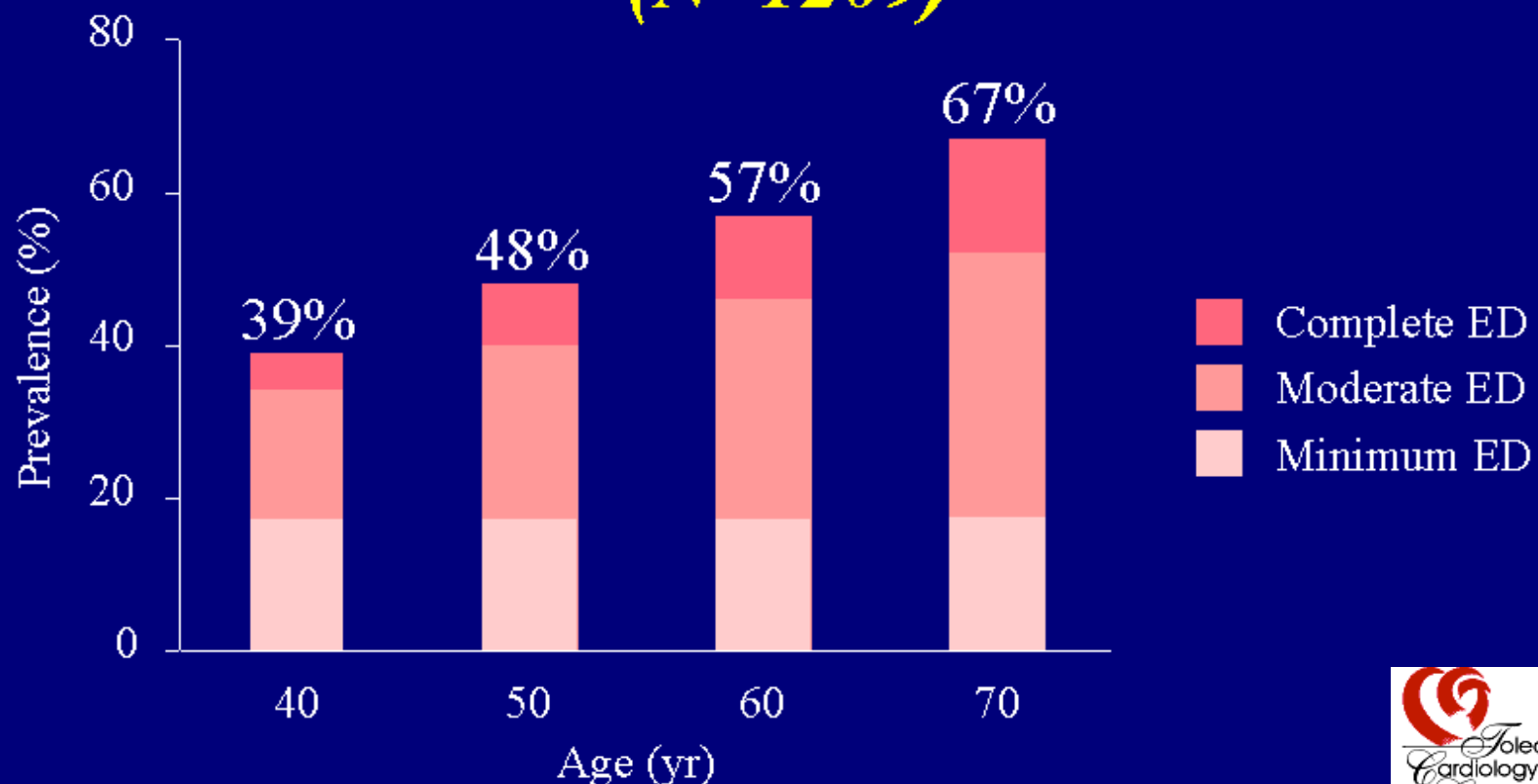
Feldman HA, et al. *J Urol*. 1994;151:54-61.

NIH Consensus Development Panel on Impotence. *JAMA*. 1993;270:83-90.



# Association Between Age and Prevalence of ED

## *Massachusetts Male Aging Study (N=1209)*



Data from Feldman HA, et al. *J Urol.* 1994;151:54-61.



# Shared Risk Factors: ED and Cardiovascular Disease (CVD)

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- Hypertension
- Diabetes
- Dyslipidemia
- Depression
- Smoking
- Obesity
- Sedentary lifestyle

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Jackson G, et al. *Int J Clin Pract.* 1999;53:445-451.

Levine LA, Kloner RA. *Am J Cardiol.* 2000;86:1210-1213.

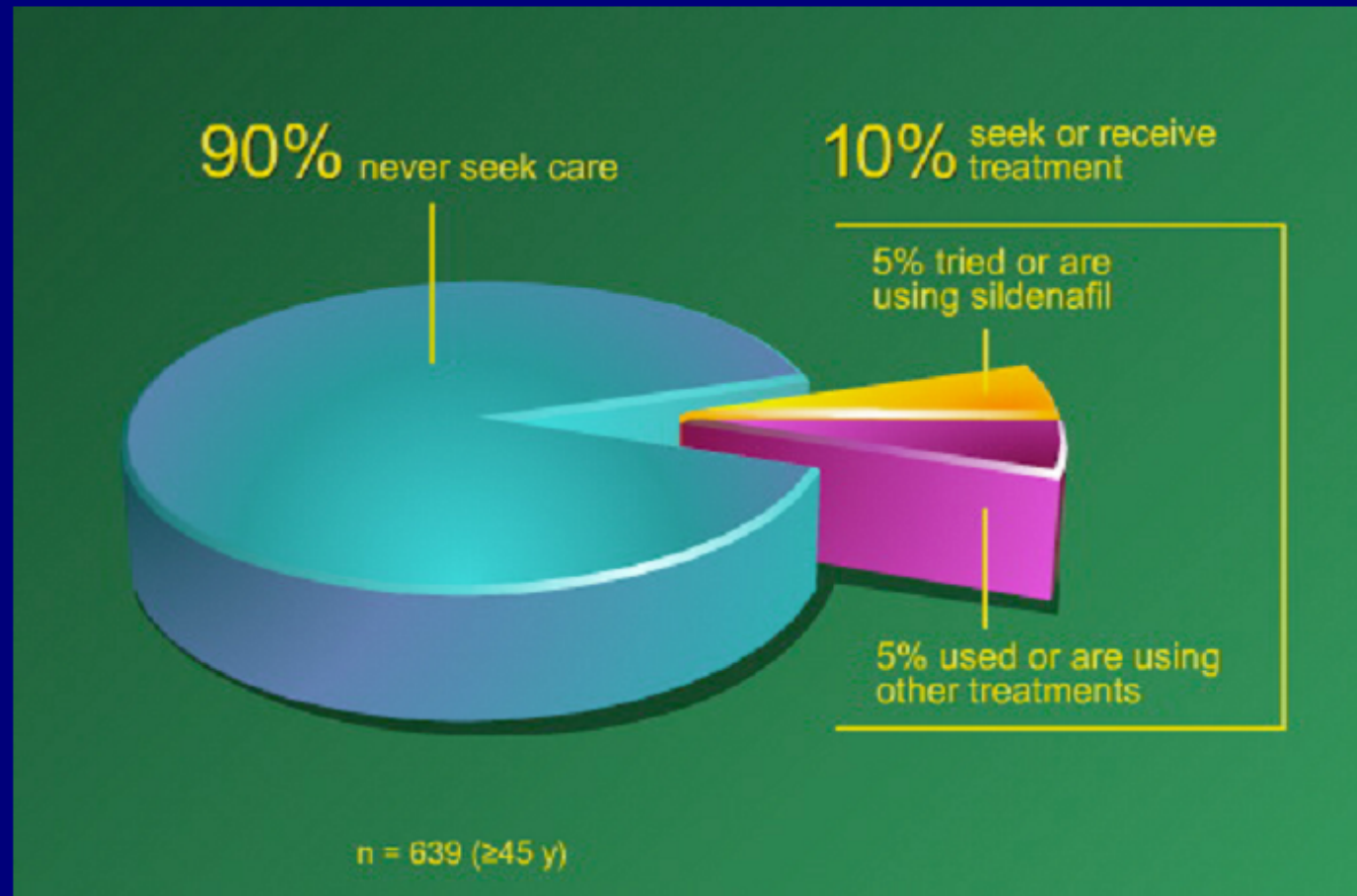
Feldman HA, et al. *Prev Med.* 2000;30:328-338.

Goldstein I. *Int J Impot Res.* 2000;12(suppl 4):S147-S151.

NIH Consensus Development Panel on Impotence. *JAMA.* 1993;270:83-90.



# Undertreatment of ED



Adapted with permission from McKinlay JB. *Int J Impot Res.* 2000;12(suppl 4):S6-S11.  
Based on data from AARP. *Modern Maturity Magazine.* Washington, DC; 1999.

# ED Is Important

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- ED—one symptom of early vascular disease
- Some men care more about current ED than about a future risk of myocardial infarction (MI)/stroke
- Interrelationship with depression
- ED can cause personal and relationship stress

Levine LA, Kloner RA. *Am J Cardiol.* 2000;86:1210-1213.  
Jackson G. *Int J Clin Pract.* 1999;53:363-368.  
Feldman HA, et al. *Prev Med.* 2000;30:328-338.  
Goldstein I. *Int J Impot Res.* 2000;12(suppl 4):S147-S151.  
Goldstein I. *Am J Cardiol.* 2000;86(suppl):41F-45F.





# ED: An Early Cry for Help

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- Penile vascular bed is unique, with smaller vessels feeding it
- ED is not a clinically silent condition—it can manifest before other cardiovascular (CV) conditions, but it can be silent to the health care provider
- Many men will remain silent about the symptom unless they are asked
- Your patients WANT you to bring it up



# ED: Cardiovascular Disease Below the Belt

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- 57% of men who have bypass surgery had prior ED
- 64% of men hospitalized for MI experienced prior ED
- Majority of ED is linked to vascular disease
- ED could be an indicator of systemic atherosclerosis or an early warning for MI or stroke

Jackson G, et al. *Int J Clin Pract.* 1999;53:363-368.

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

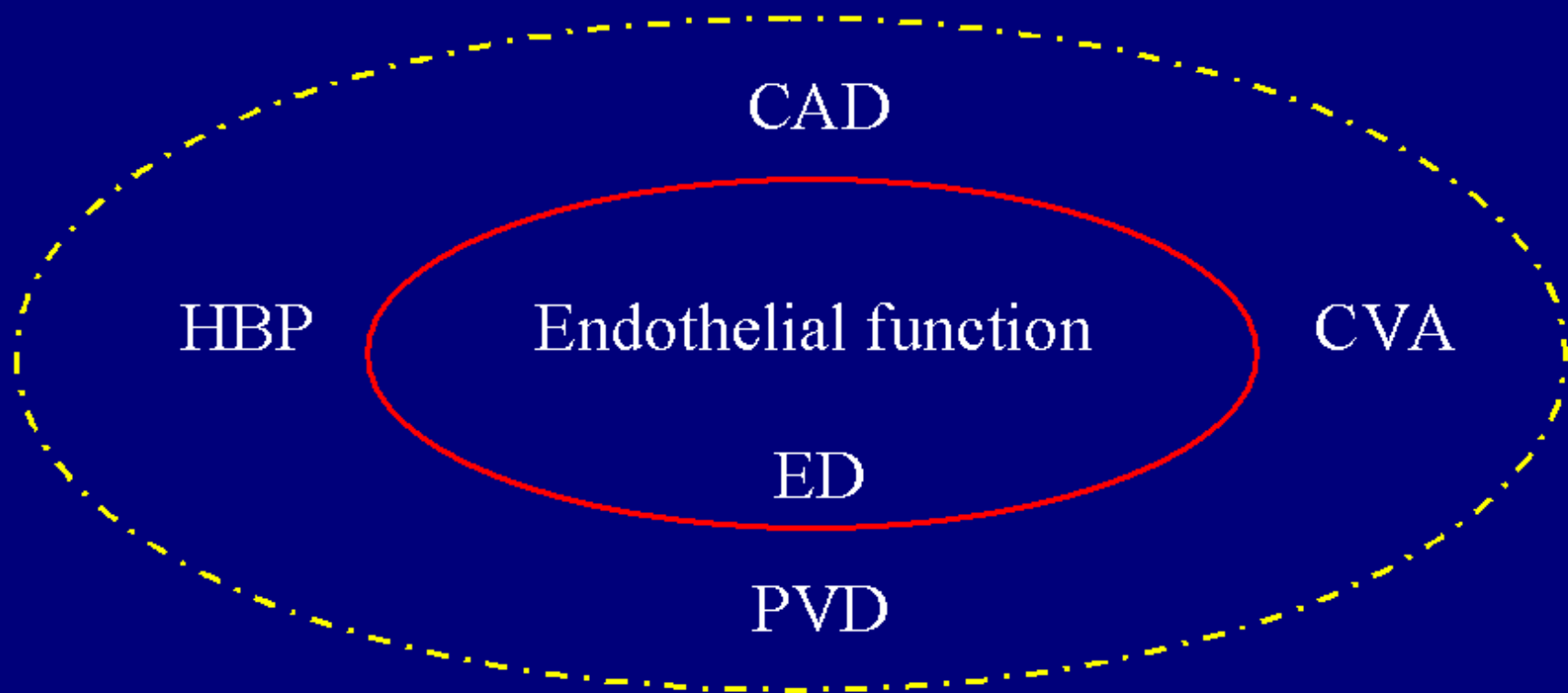
Levine LA, Kloner RA. *Am J Cardiol.* 2000;86:1210-1213.

Morley JE, et al. *Am J Med.* 1988;84:445-458.



# Putting ED Into Context

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HBP=high blood pressure; CAD=coronary artery disease;  
CVA=cerebral vascular accident; PVD=peripheral vascular disease.

Jackson G. *Int J Clin Pract.* 1999;53:363-368.

Levine LA, Kloner RA. *Am J Cardiol.* 2000;86:1210-1213.



# ED—A Focal Point for Men's Health Initiatives

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- ED may reflect endothelial dysfunction and signal early injury that later manifests as clinically apparent vascular disease
- ED and preventive cardiovascular medicine are linked and can be used to get men's attention
- Physicians have to ask questions at every visit—it makes good health sense

Jackson G. *Int J Clin Pract.* 1999;53:363-368.

Levine LA, Kloner RA. *Am J Cardiol.* 2000;86:1210-1213.

Morley JE, et al. *Am J Med.* 1988;84:445-458.



# Treating ED in Men With Cardiovascular Disease



# Assessment of ED and CV Risk

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- Ask patient about ED/VIAGRA<sup>®</sup> (sildenafil citrate)
- Determine level of risk associated with exertion of sexual activity
- Initiate further evaluation of cardiac status or trial of VIAGRA

DeBusk R, et al. *Am J Cardiol.* 2000;86:175-181.

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# **VIAGRA<sup>®</sup> (sildenafil citrate) in Men With Chronic Stable Angina:**

## **Study Design, Methods, and End Points**

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### Study Design

- Double-blind, placebo-controlled, parallel-group, multicenter study examining the effect of 100 mg VIAGRA given 1 hour before exercise

### Methods

- Evaluation of time to onset of limiting angina\* during incremental treadmill exercise
- 108 evaluable patients (56 VIAGRA, 52 placebo)

### End Points

- Primary: time to limiting angina
- Secondary: time to angina, time to 1-mm ST-segment depression, total exercise time, blood pressure, heart rate, rate-pressure product

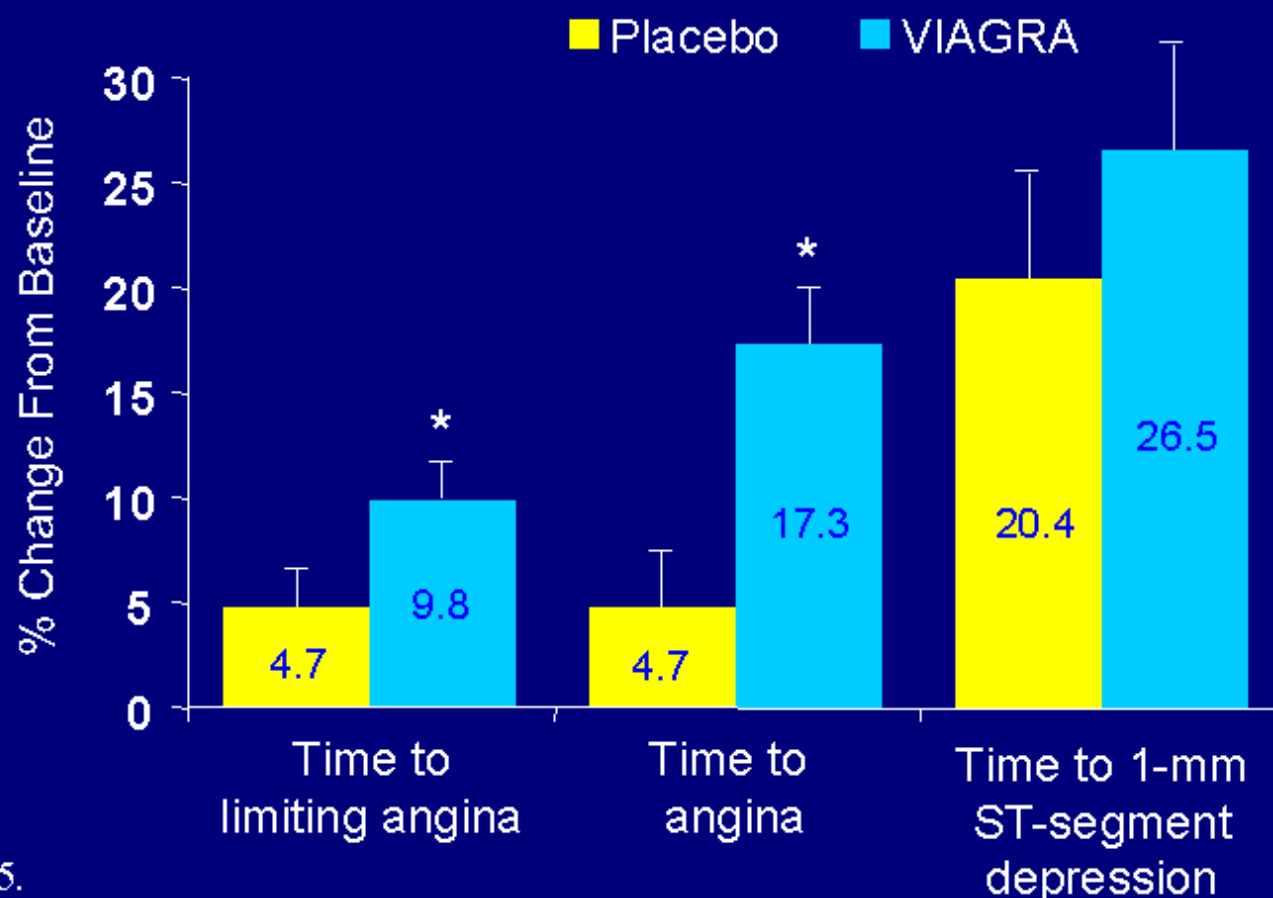
\*Defined as the level of angina symptoms that would normally make the patient want to discontinue the exercise.

Data on file, Pfizer Inc, New York, NY.

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# VIAGRA<sup>®</sup> (sildenafil citrate) in Men With Chronic Stable Angina: Results



\* $P < 0.05$ .

Data on file, Pfizer Inc, New York, NY.

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# VIAGRA® (sildenafil citrate) in Men With Chronic Stable Angina: Conclusions

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- This study provides evidence that VIAGRA does not increase cardiac workload in a population of men with coronary artery disease and ED
- The changes in heart rate observed in both treatment groups are similar to those recorded during sexual activity
- These data confirm the recommendations of the Princeton Consensus Panel: the use of VIAGRA is well-tolerated in patients with low to intermediate cardiac risk who are not using nitrates or nitric oxide donors

Data on file, Pfizer Inc, New York, NY.

DeBusk R, et al. *Am J Cardiol*. 2000;86:175-181.

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# Evaluation of the Risks of MI With Intercourse

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- Sexual activity causes increased oxygen demand by the heart
- 50-year-old man has baseline annual risk of MI of about 1.0%
- This annual risk increases to 1.01% with sexual activity
- Sexual intercourse with long-standing partner
  - Lower range 2 to 3 METs
  - Upper range 5 to 6 METs
- Golf (4 to 5 METs)
- Heavy chores (3 to 6 METs)

DeBusk R, et al. *Am J Cardiol*. 2000;86:175-181.  
Jackson G, et al. *Int J Clin Pract*. 1999;53:445-451.



# Low-Risk Patients

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- Asymptomatic, <3 major risk factors
- Controlled HBP
- Mild, stable angina
- Post-successful revascularization
- Uncomplicated past MI (>6–8 weeks)
- Mild valvular disease
- LVD/CHF (NYHA class I)

 Prescribe VIAGRA® (sildenafil citrate) for ED and schedule follow-up appointment

LVD=left ventricular dysfunction; CHF=congestive heart failure;  
NYHA=New York Heart Association.

DeBusk R, et al. *Am J Cardiol*. 2000;86:175-181.

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# Intermediate-Risk Patients

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- $\geq 3$  risk factors
- Moderate, stable angina
- Recent MI ( $>2$ ,  $<6$  weeks)
- LVD/CHF (NYHA class II)
- Noncardiac sequelae of atherosclerotic disease (eg, stroke or peripheral vascular disease)



Evaluate to determine cardiac risk

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DeBusk R, et al. *Am J Cardiol*. 2000;86:175-181.



# High-Risk Patients

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- Unstable or refractory angina
- Uncontrolled hypertension
- LVD/CHF (NYHA class III/IV)
- Moderate/severe valvular disease
- Recent MI (<2 weeks), recent stroke
- High-risk arrhythmias
- Hypertrophic obstructive and other cardiomyopathies

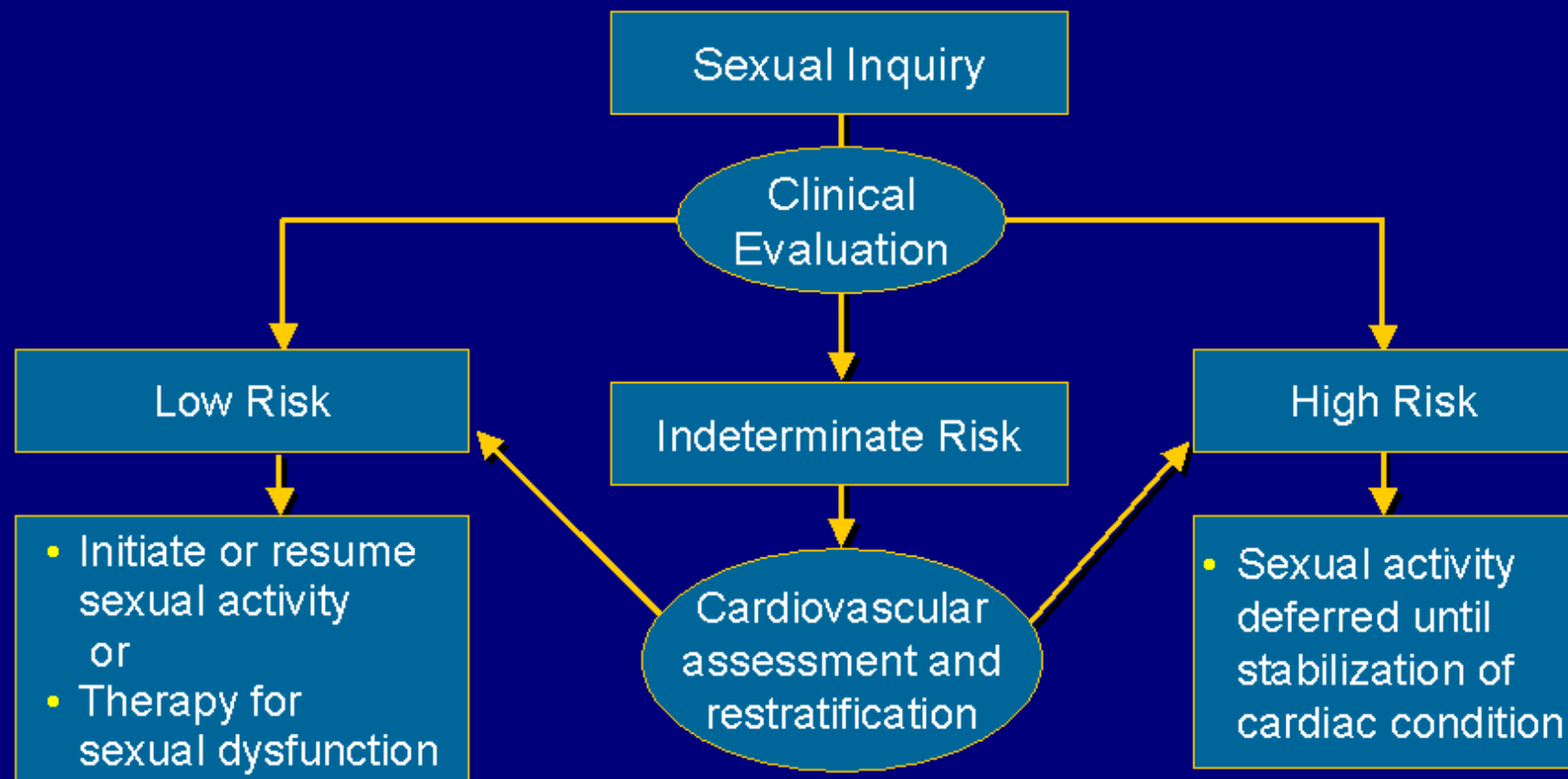
 Delay ED treatment and monitor closely

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DeBusk R, et al. *Am J Cardiol.* 2000;86:175-181.



# Sexual Activity and Cardiac Risk: A Simplified Algorithm



DeBusk R, et al. *Am J Cardiol.* 2000;86:175-181.

# VIAGRA® (sildenafil citrate): Important Safety Information

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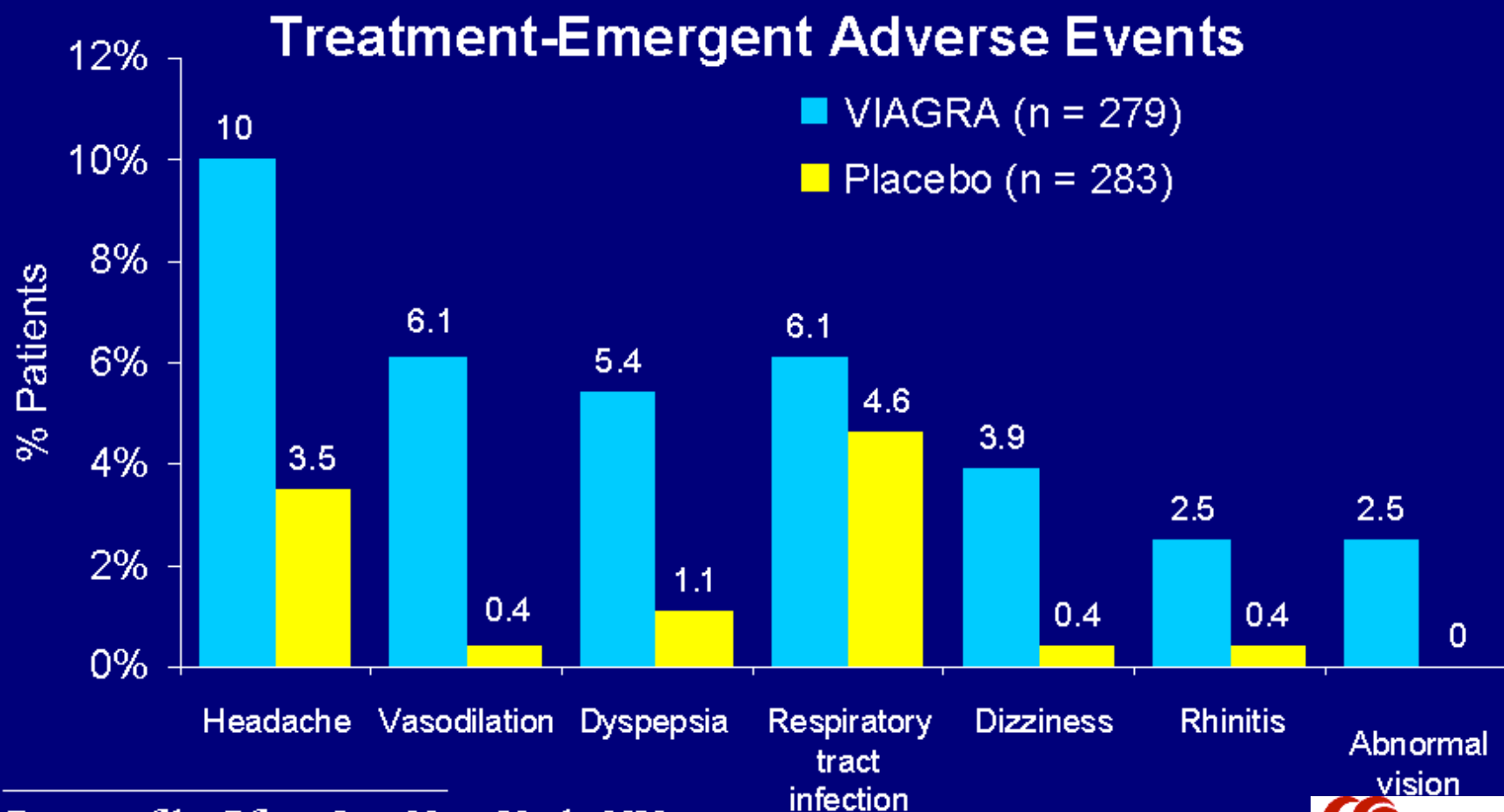
- Use of VIAGRA and organic nitrates in any form, at any time, is contraindicated
- Patients with recent serious cardiovascular events, hypotension, uncontrolled hypertension, or retinitis pigmentosa did not participate in preapproval clinical trials. In these patients, physicians should prescribe VIAGRA with caution

VIAGRA [package insert]. New York, NY: Pfizer Inc; 2000.

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# Safety of VIAGRA® (sildenafil citrate) in Men With ED Taking Multiple Antihypertensives



Data on file, Pfizer Inc, New York, NY.

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.





# VIAGRA<sup>®</sup> (sildenafil citrate): Important Safety Information

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- In a controlled interaction study of VIAGRA and amlodipine, the mean additional reduction in supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic
- When the  $\alpha$ -blocker doxazosin (4 mg) and VIAGRA (25 mg) were administered simultaneously to patients with BPH, mean additional reductions of supine blood pressure of 7 mm Hg systolic and 7 mm Hg diastolic were observed. When higher doses of VIAGRA and doxazosin (4 mg) were administered simultaneously, there were infrequent reports of patients who experienced symptomatic postural hypotension within 1 to 4 hours of dosing. Doses of 50 mg or 100 mg of VIAGRA should not be taken within 4 hours of  $\alpha$ -blocker administration. A 25-mg dose of VIAGRA may be taken at any time

VIAGRA [package insert]. New York, NY: Pfizer Inc; 2000.

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# VIAGRA<sup>®</sup> (sildenafil citrate): Important Safety Information

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- Before treating ED, physicians should consider the impact of resuming sexual activity and the mild and transient vasodilatory effects of VIAGRA on blood pressure. Physicians should carefully consider whether patients with underlying cardiovascular disease or other more unusual conditions could be adversely affected by vasodilatory effects, especially in combination with sexual activity

VIAGRA [package insert]. New York, NY: Pfizer Inc; 2000.  
Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# Summary of Cardiovascular Safety Issues

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- Assess the risk of a cardiac event with sexual activity
- VIAGRA<sup>®</sup> (sildenafil citrate) is a well-tolerated medication to treat ED, used in many men with CVD
- Always follow-up regarding efficacy of treatment and symptoms associated with return to sexual activity

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Jackson G, et al. *Int J Clin Pract.* 1999;53:445-451.

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# Critical Facts

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1. New onset or a progressive decline in erectile function is a red flag for possible cardiovascular problems
2. ED can be a barometer of overall vascular fitness
3. Questions about ED should be included in the review of systems for men over 30 years of age
4. Patients deserve and need a thorough evaluation before treatment—it can be simple and non-time consuming
5. Use ED as a “hook” to gain compliance with aggressive management of existing CVD

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Levine LA, Kloner RA. *Am J Cardiol.* 2000;86:1210-1213.

Jackson G. *Int J Clin Pract.* 1999;53:363-368.

Morley JE, et al. *Am J Med.* 1988;84:445-458.



# Basic ED Evaluation

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- Identify the condition early in the visit to avoid “Oh, by the way” at the end of the visit
- Impact assessment
- History: risk-factor assessment and medical conditions are already a part of patient’s chart

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Miller TA. *Am Fam Physician*. 2000;61:95-104, 109-110.



# Risk Factors for ED

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- Hypertension
- Hyperlipidemia
- Hypogonadism
- Endocrine disorders
- Smoking
- Alcohol abuse
- Drug abuse
- Anemia
- Trauma or surgery to the pelvis or spine
- Coronary artery or peripheral vascular disease
- Peyronie's disease
- Vascular surgery
- Depression

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Benet AE, Melman A. *Urol Clin North Am.* 1995;22:699-709.



# Drugs Associated With ED

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- Alcohol
- Estrogens
- Antiandrogens
- H<sub>2</sub>-receptor blockers
- Anticholinergics
- Ketoconazole
- Antidepressants
- Marijuana
- Antihypertensives
- Narcotics
- $\beta$ -blockers
- Psychotropics
- Cigarettes
- Cocaine
- Spironolactone
- Lipid-lowering agents
- NSAIDs
- Cytotoxic drugs
- Diuretics

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Benet AE, Melman A. *Urol Clin North Am.* 1995;22:699-709.



# Basic ED Evaluation (cont'd)

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- Physical examination
  - Secondary sexual characteristics
  - Check for penile abnormalities
  - Check for groin and peripheral pulses
- Lab studies
  - Fasting lipids, glucose, and androgens

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Miller TA. *Am Fam Physician*. 2000;61:95-104, 109-110.





# When to Refer a Patient

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- Provider not interested or comfortable in treating ED
- Men on nitroglycerin
- Primary or secondary ED in young men
- Men with penile abnormalities (Peyronie's)

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The Process of Care Consensus Panel. *Int J Impot Res.* 1999;11:59-74.  
Sadovsky R, et al. *Am J Managed Care.* 1999;5:333-341.



# When to Refer a Patient (cont'd)

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- When there are clear relationship issues prior to taking VIAGRA® (sildenafil citrate) or that emerge after medication has been prescribed, refer for therapy
- Men with severe depression
- Men unresponsive to VIAGRA

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Miller TA. *Am Fam Physician*. 2000;61:95-104, 109-110.

Sadovsky R. *Am J Med*. 2000;109:22S-28S.

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# **VIAGRA<sup>®</sup> (sildenafil citrate) as the First-Line Choice for ED**

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# Impact of VIAGRA® (sildenafil citrate)

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- Initial evaluation and management of ED is taking place in the primary care or medical specialty offices
- Influx of younger men (35 to 60 years old) seeking treatment before problem gets worse

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# PDE5 Inhibitors

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- Pertinent pathophysiology
- Mechanism of action for medical therapies
- Discussion of PK parameters of VIAGRA<sup>®</sup> (sildenafil citrate), vardenafil, and tadalafil

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.

# Regulation of Smooth-Muscle Relaxation: Effect of PDE5 Inhibitors

Neurons or  
endothelium

Nitric  
oxide

Guanylyl Cyclase

GTP

cGMP

PKG

ATP

ADP

protein-P

lower  $\text{Ca}^{2+}$

RELAXATION OF  
VASCULAR  
SMOOTH MUSCLE

PDE5

5'-GMP

inhibition

PDE5  
inhibitors

# Pharmacokinetics of PDE5 Inhibitors

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- Potency
- Selectivity
- Onset of action
- Duration of action
- Half-life

# Structures of PDE5 Inhibitors

- PDE5 inhibitors are competitive inhibitors that resemble cGMP (the substrate) and bind to the active site of PDE5



cGMP



VIAGRA®  
(sildenafil citrate)



Vardenafil



Tadalafil

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

Eardley I, et al. *Int J Clin Pract.* 2002;56:300-304.

Ormrod D, et al. *Drugs Aging.* 2002;19:217-227.

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# Biochemical Potency

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- Potency data (IC<sub>50</sub>)
  - VIAGRA® (sildenafil citrate) 0.5–4.0 nM
  - Tadalafil 0.9–6.7 nM
  - Vardenafil 0.1–0.7 nM
- Clinical efficacy is independent of potency; hence, more potent drugs given at lower doses cannot be assumed to be either better or safer than less potent drugs

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Bischoff E, et al. *Int J Impot Res*. 2001;13(suppl 4):S41. Abstract 113.  
Corbin JD, Francis SH. *Int J Clin Pract*. 2002;56(6):453-459.  
Eardley I, Cartledge J. *Int J Clin Pract*. 2002;56:300-304.  
Ormrod D, et al. *Drugs Aging*. 2002;19:217-227.

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# Selectivity for PDE5 Inhibitors VIAGRA<sup>®</sup> (sildenafil citrate), Vardenafil, and Tadalafil: PDE 1–6

IC <sub>50</sub> Values (nM) vs. PDE5						
	PDE1	PDE2	PDE3	PDE4	PDE5	PDE6
VIAGRA	60	—	2600	1800	1	7.4
Vardenafil	257	>10,000	3600	5700	1	16
Tadalafil	>10,000	>10,000	>10,000	>10,000	1	780

Data on file, Pfizer Inc, New York, NY.

Saenz de Tejada I, et al. *Int J Impot Res*. 2001;13:282-290.

Porst H. *Int J Impot Res*. 2002;14(suppl 1):S57-S64.

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



## Selectivity for PDE5 Inhibitors VIAGRA<sup>®</sup> (sildenafil citrate), Vardenafil, and Tadalafil: PDE 7–11

### IC<sub>50</sub> Values (nM) vs. PDE5

	PDE5	PDE7B	PDE8	PDE9A	PDE10	PDE11
VIAGRA	1	—	—	—	317*	700
Vardenafil	1	5290*	>10,000†	3870†	1150*	1160
Tadalafil	1	>10,000	>10,000	>10,000	>10,000	37.0

\*Human recombinant enzymes.

†Murine origin.

Data on file, Pfizer Inc, New York, NY.

Saenz de Tejada I, et al. *Int J Impot Res*. 2001;13:282-290.

Porst H. *Int J Impot Res*. 2002;14(suppl 1):S57-S64.

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# Summary:

## PDE5 Inhibitors

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- Biochemical potencies and selectivities of VIAGRA<sup>®</sup> (sildenafil citrate), vardenafil, and tadalafil are broadly similar
  - Each drug will have its own set of unique pharmacologic characteristics based on its specific molecular design and activity

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# Summary:

## PDE5 Inhibitors (cont'd)

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- VIAGRA® (sildenafil citrate) represents the premier PDE5 inhibitor and, after more than 4 years of widespread real-world use, is acknowledged as well-tolerated for ED in patients with underlying cardiovascular conditions and is effective and particularly well-tolerated in a broad range of patients

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# VIAGRA<sup>®</sup> (sildenafil citrate): Important Safety Information

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- Use of VIAGRA and organic nitrates in any form, at any time, is contraindicated
- The most common side effects of VIAGRA were headache (16%), flushing (10%), and dyspepsia (7%). Adverse events, including visual effects (3%), were generally transient and mild to moderate

VIAGRA [package insert]. New York, NY: Pfizer Inc; 2000.

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# Using VIAGRA® (sildenafil citrate) Effectively: Your Patients Must Understand the Facts

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1. Sexual stimulation is necessary
2. Best results after a low-fat meal
3. VIAGRA works as fast as 30 minutes and remains effective up to 4 hours
4. In most patients, start at 50 mg; can titrate to 100 mg or down to 25 mg

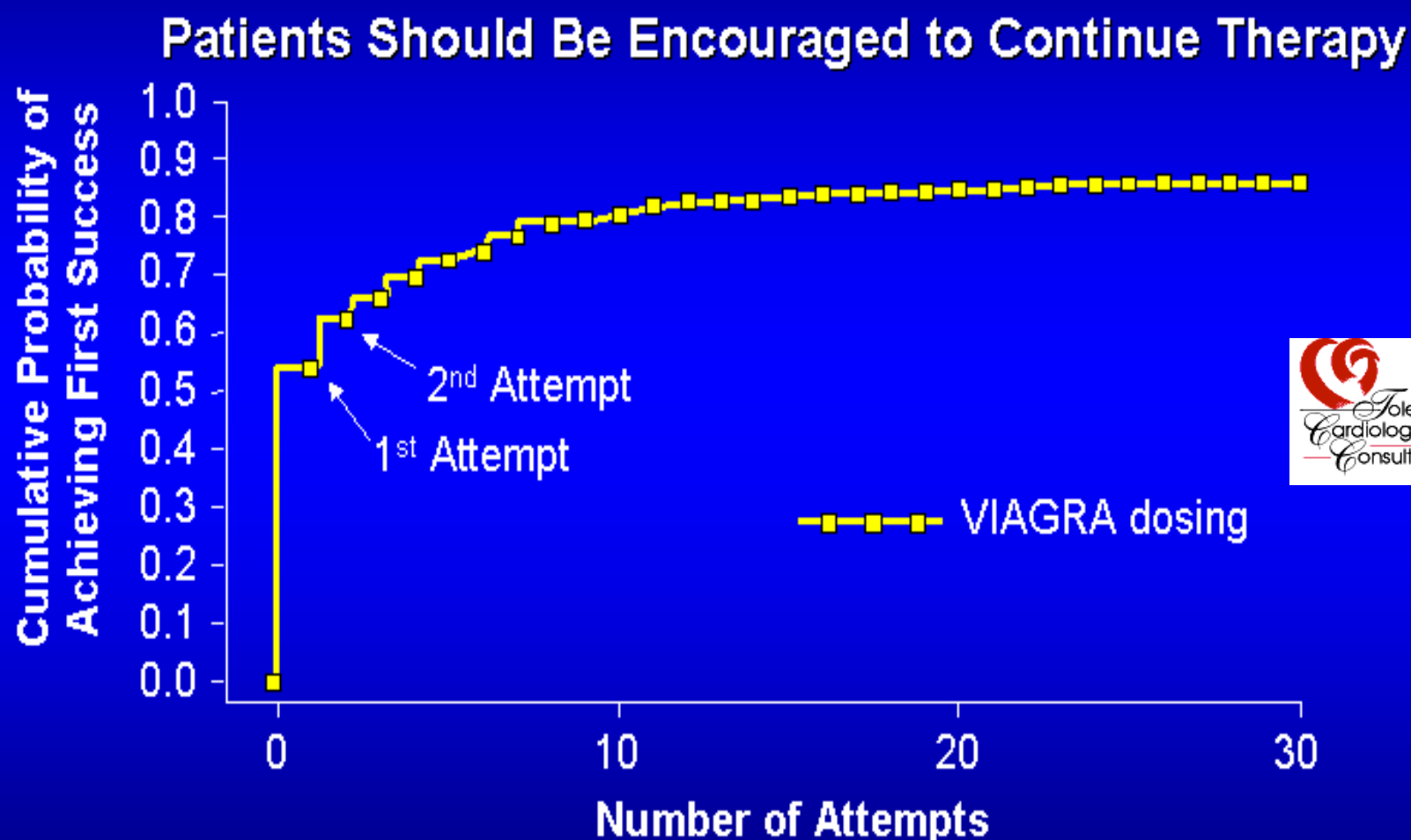
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Sadovsky R, et al. *Int J Clin Pract.* 2001;55:115-128.

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# Likelihood of Success With VIAGRA® (sildenafil citrate) Increases With Number of Attempts



Data on file, Pfizer Inc., New York, NY. Based on a retrospective analysis of the intent-to-treat population from 12 double-blind, placebo-controlled, flexible-dose, clinical trials.



# VIAGRA® (sildenafil citrate): Efficacy for ED

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- Hypertension
- Diabetes
- CAD
- Prostatectomy
- Depression
- Peripheral vascular disease
- Spinal cord injury
- Multiple sclerosis

Sadovsky R, et al. *Int J Clin Pract.* 2001;55:115-128.

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# How to Ask About ED

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- “Do you have any concerns about your sexual functioning?”
- “I’m sure you’ve heard or read about VIAGRA<sup>®</sup> (sildenafil citrate)—have you ever thought about trying it?”
- “Many of my patients with [hypertension, CAD, diabetes, high lipids] experience difficulties with their sexual functioning—have you noticed any changes?”

Please see accompanying full prescribing information for VIAGRA 25-mg, 50-mg, 100-mg tablets available at this presentation.



# Take a Proactive Approach

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- Prime the patient: use the Sexual Health Inventory for Men (SHIM)
- Utilize the nursing staff for identification and education
- When appropriate, schedule the patient for a follow-up appointment to address ED; ask the patient to bring his partner

# Cardiovascular Safety Profile

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- Do not use VIAGRA® (sildenafil citrate) in men taking any form of organic nitrates
- No significant increased risk of MI or ischemic heart disease mortality seen in men using VIAGRA
- Most men with ED have vascular disease
- Consider appropriate stress testing to assess exertional capacity

Sadovsky R, et al. *Int J Clin Pract.* 2001;55:115-128.

Levine LA, Kloner RA. *Am J Cardiol.* 2000;86:1210-1213.

DeBusk R, et al. *Am J Cardiol.* 2000;86:175-181.

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# News Drugs On Demand

- **VIAGRA-SKI**

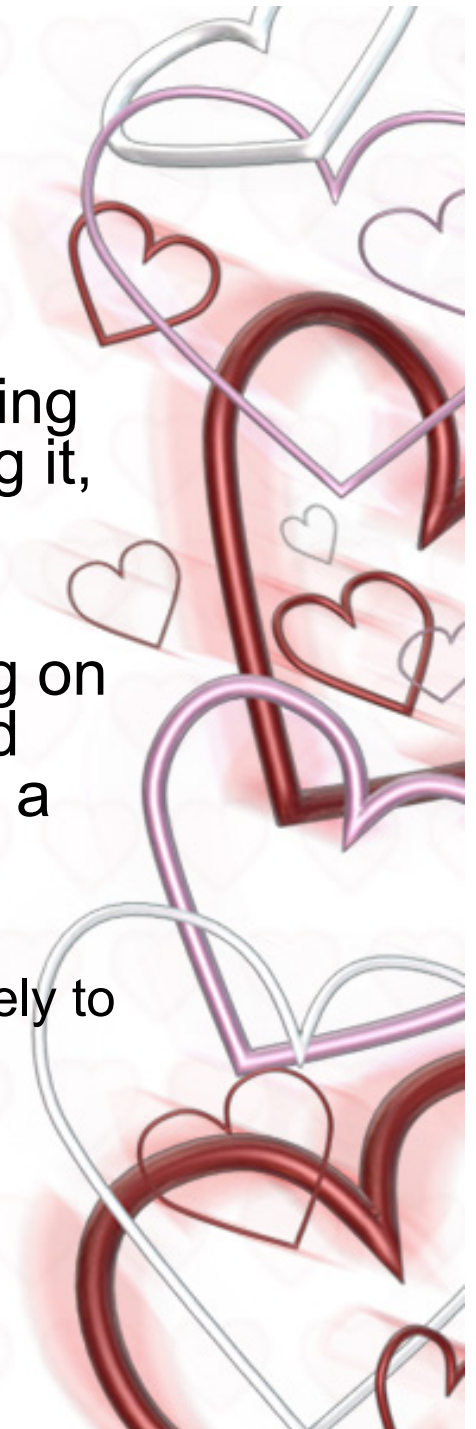
Wonderful for those who have a hard time getting up on water-skis. Forty-five minutes after taking it, you'll get up and stay up, out of the water.

- **DIRECTRA**

A dose of this drug given to men before leaving on car trips caused 72 percent of them to stop and ask directions when they got lost, compared to a control group of 0.2 percent.

- **PROJECTRA**

Men given this experimental new drug were far more likely to actually finish a household repair project before starting anew one.



# News Drugs On Demand

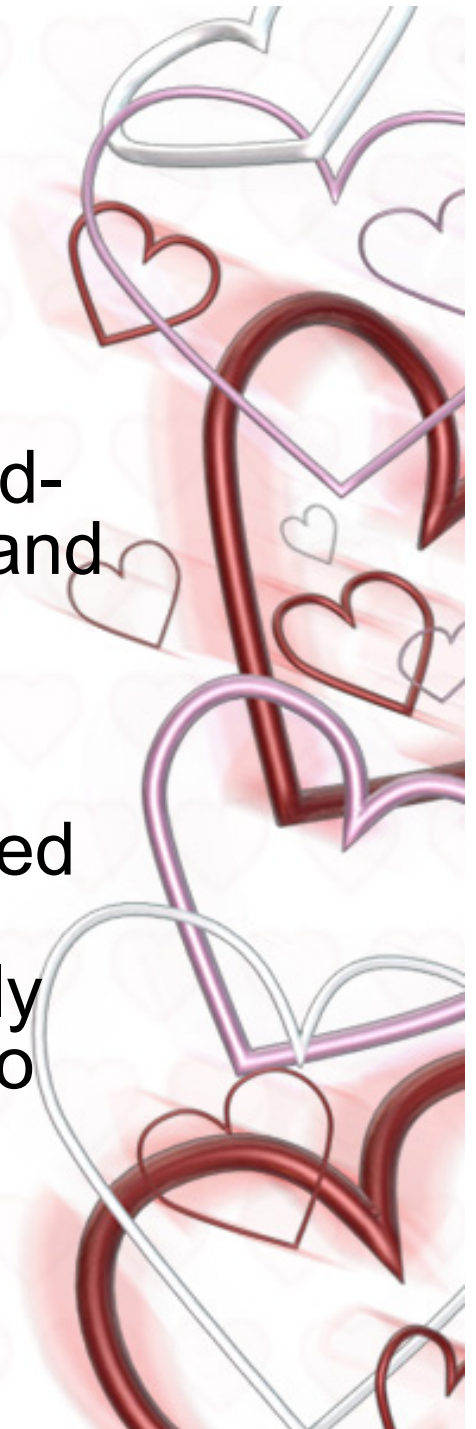
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- **CHILDAGRA**

Men taking this drug reported a sudden, overwhelming urge to perform more child-care tasks especially cleaning up spills and "little accidents".

- **COMPLIMENTRA**

In clinical trials, 82 percent of middle-aged men administered this drug noticed that their wives had a new hairstyle. Currently being tested to see if its effects extend to noticing new clothing.





# ***Most Popular News Papers***

## **The New Viagra Times**

