Management of Erectile Dysfunction and Cardiovascular Disease
Princeton III Consensus Recommendations
Reptile Dysfunction

I think something’s wrong with my rattler. I shake it, but it just doesn’t rattle.

Sounds like a reptile dysfunction.
This is a talk about sex, and contains potentially offensive images…
Men Avoid Doctors

- Twice as many men than women have no regular source of medical care
- Men comprise 70% of those who haven’t seen a doctor in the past 5 years
- 25% of men would wait “as long as possible” to see a doctor
And, yet…

• What universally gets a man’s attention:

ED
Older Men Are Still Sexually Active

Sexual activity = Intercourse, masturbation and any activity that the participant considered “sexual”

Rosen R. Multinational Survey of the Aging Male (MSAM-7). Presented at the Annual Meeting of the AUA; May 26, 2002; Orlando, Fla.
Massachusetts Male Aging Study: Prevalence of Erectile Dysfunction (ED)

- In 2005, 30 million men are affected worldwide
- By 2025, over 300 million men will have ED

CV risk for Men With ED Aged Matched to Those Without ED

<table>
<thead>
<tr>
<th>Relative Risks for Men With Erectile Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>All-cause mortality</td>
</tr>
</tbody>
</table>

Adapted
CAUTION: Stand Back
Firm Facts on ED

• Incident ED has a similar or greater predictive value for cardiovascular events as traditional risk factors, such as family history of myocardial infarction (MI), smoking, and hyperlipidemia.

• 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 (class Ia).

• Furthermore, evidence suggests that ED is predictive of peripheral arterial disease (PAD) and stroke.
Firm Facts on ED

• In a population-based study of men 40 to 70 years of age, addition of ED status to the Framingham Risk Score (FRS) in a multivariate statistical model resulted in reclassification of 5 of 78 low-risk patients (<5% risk) to intermediate risk (5% to <10% risk).

• In addition, data from the Olmsted County Study suggest that ED is far more predictive of CAD in men 40 to 49 years of age than in older men, and the incidence of atherosclerotic cardiovascular events in men younger than 40 years with ED was more than 7 times the incidence in a general male population.
Firm Facts on ED

• Thus, ED may be particularly useful in assessing cardiovascular risk in younger men and in minorities, whose risk may be underestimated by global risk assessments such as the FRS.

• Finally, assessment of ED must include ED severity because more severe ED has been associated with greater risk of major cardiovascular events, CAD, extent of CAD, and risk of PAD (ACCF/AHA class Ia).
ED and Endothelial Injury

Precursors

- Diabetes
- Dyslipidemia
- Hypertension
- Tobacco

Oxidative Stress

Endothelial Cell Injury

- Vasoconstriction
- Atherosclerosis
- Erectile Dysfunction
- Thrombosis

Outcomes

References:
- Dzau et al. Am J Cardiol. 1997;80:331-391
Pooled odds ratios for the risk of cardiovascular events, coronary heart disease, and peripheral vascular disease in diabetic men (cross-sectional studies).

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klein 1996</td>
<td>6.16 (2.87, 13.24)</td>
<td>8.9</td>
</tr>
<tr>
<td>Fedele 2000</td>
<td>2.41 (1.12, 2.74)</td>
<td>24.6</td>
</tr>
<tr>
<td>Kalten-Leibovici 2005</td>
<td>5.67 (2.79, 11.11)</td>
<td>9.7</td>
</tr>
<tr>
<td>Berardis 2005</td>
<td>2.24 (1.67, 3.01)</td>
<td>20.0</td>
</tr>
<tr>
<td>Shiri 2006</td>
<td>4.45 (2.70, 7.34)</td>
<td>13.8</td>
</tr>
<tr>
<td>Gazzaruso 2006</td>
<td>4.51 (1.27, 16.02)</td>
<td>3.9</td>
</tr>
<tr>
<td>Yu 2009</td>
<td>3.67 (1.27, 10.61)</td>
<td>5.2</td>
</tr>
<tr>
<td>Gazzaruso 2011</td>
<td>3.43 (1.89, 6.24)</td>
<td>11.5</td>
</tr>
<tr>
<td>Malpartida 2011</td>
<td>5.19 (1.16, 23.26)</td>
<td>2.9</td>
</tr>
<tr>
<td>Overall</td>
<td>3.39 (2.58, 4.44)</td>
<td></td>
</tr>
</tbody>
</table>

(I-squared 58%, p<0.001)

| Coronary Heart Disease     |                     |          |
| Fedele 2000                | 2.41 (1.12, 2.74)  | 34.1     |
| Kalten-Leibovici 2005      | 5.46 (2.51, 11.87) | 12.1     |
| Shiri 2006                 | 4.45 (2.70, 7.34)  | 19.7     |
| Gazzaruso 2006             | 4.51 (1.27, 16.02) | 5.7      |
| Yu 2009                    | 2.50 (0.80, 7.46)  | 7.6      |
| Gazzaruso 2011             | 3.43 (1.89, 6.24)  | 16.5     |
| Malpartida 2011            | 5.19 (1.16, 23.26) | 4.3      |
| Overall                    | 3.43 (2.46, 4.77)  |          |

(I-squared 49%, p<0.001)

| Peripheral Vascular Disease|                     |          |
| Klein 1996                 | 6.69 (3.00, 14.93) | 23.2     |
| Berardis 2005              | 1.62 (0.93, 2.81)  | 29.0     |
| Shiri 2006                 | 3.25 (1.66, 6.38)  | 26.1     |
| Yu 2009                    | 1.33 (0.67, 2.60)  | 3.0      |
| Malpartida 2011            | 1.47 (0.50, 4.29)  | 17.8     |
| Overall                    | 2.03 (1.41, 4.91)  |          |

(I-squared 60%, p=0.002)
1. A man with organic ED should be considered at increased CVD risk until recommended checks suggest otherwise.

2. ED identifies increased CVD risk in the presence or absence of CVD symptoms or history.
What to Do for Men with ED and NO KNOWN CVD

- Patient history with attention to CV risk factors such as
  - Age
  - Abdominal obesity
  - Hypertension
  - Dyslipidemia
  - Diabetes
  - Symptoms suggestive of obstructive sleep apnea
  - Family history of premature atherothrombotic CVD
  - Smoking history
  - Activity levels
  - Diet
What to Do for Men with ED and NO KNOWN CVD

• Physical examination with attention to
  • BP
  • Waist circumference (WC)
  • Body mass index (BMI)
  • Cardiac auscultation
  • Carotid bruits
  • Palpation of femoral and pedal pulses
  • Assessment of ED severity and duration (International Index of Erectile Function score or Sexual Health Inventory of Men)
What to Do for Men with ED and NO KNOWN CVD

• Laboratory Evaluation
  • Resting electrocardiogram
  • Fasting plasma glucose level
  • Serum creatinine level (estimated glomerular filtration rate)
  • Total testosterone (TT) level (before 11 am)
  • Plasma lipid levels (total, low-density lipoprotein, and HDL cholesterol and triglyceride values)
Age-Related Changes in Testosterone

Rates of Low T in Selected Conditions

**Prevalance of Low Testosterone**

- Obesity: 52%
- Type 2 Diabetes: 50%
- Hypertension: 42%
- Hyperlipidemia: 40%

**Other Areas of Concern**

**HIV/AIDS**

30% of HIV-infected men and 50% of men with AIDS have low testosterone.²

**Chronic Pain**

74% of men consuming sustained-action oral opioids have low testosterone.³

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DO NOT TOUCH ANY OF THESE WIRES
Potential Effects of Hypogonadism

Long-term complications
- Decline in libido and erectile function
- Increased body fat mass
- Decreased muscle mass, bone mass, and strength
- Possibly: fatigue, mood / cognitive changes
- Increased incidence of osteoporosis

Low T and the Heart

• Men with heart disease die sooner if their testosterone levels are low, a U.K. study shows.
• It's becoming clear that low testosterone is a risk marker for heart disease in men.
• Now it appears low testosterone predicts worse outcomes in men who already have heart disease.
Risks of Testosterone Replacement Therapy (TRT)

- Hepatic adverse effects with oral therapy
- Polycythemia
- Edema
- Gynecomastia
- Precipitation or worsening of sleep apnea
- Infertility
- Acceleration of BPH or Prostate Cancer

Absolute Contraindications of TRT

- Male breast cancer
- Known or suspected prostate cancer
- Hematocrit > 55%
- Known or suspected sensitivity to ingredients used in testosterone therapy systems

FDA Warning

Testosterone Can Kill
• Prescription testosterone products are approved for use only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain (hypothalamus) that cause hypogonadism.
FDA Warning

- FDA warns against the use of testosterone to relieve symptoms in men who have low testosterone for no apparent reason other than aging
FDA Warning

• FDA states that some studies have indicated increased risk of heart attack, stroke or death with testosterone treatment
Testosterone Delivery Systems

- Oral and transmucosal tablets
- Injectables
- Transdermal patches
- Transdermal gel

AndroGel® and Testim™

- Most physiologic application method
- Testosterone gel 1%

Recommended starting dose:
5 g / day to deliver 5 mg testosterone
Can be titrated up to 10 g per day
Wait 5-6 hrs after dosing to swim/shower
Avoid partner contact with area

Consensus Recommendations

- The consensus panel considers all men with ED who are older than 30 years and at increased CVD risk receive a thorough noninvasive and, when indicated, invasive evaluation of CVD status.
Evaluation of Known CVD Patients with ED

Sexual inquiry of all men

ED confirmed

Exercise ability

Low risk

Indeterminate risk

Stress test

Pass

Low risk

High risk

Fail

Cardiologist

High risk
<table>
<thead>
<tr>
<th>Estimated METs</th>
<th>Description</th>
<th>Physical Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Sitting</td>
<td>Reading, watching TV</td>
</tr>
<tr>
<td>3</td>
<td>Very light exertion</td>
<td>Moderate sexual activity with long-term partner</td>
</tr>
<tr>
<td>4-5</td>
<td>Moderate exertion</td>
<td>Vigorous sexual activity, normal walking, golfing on foot, gardening</td>
</tr>
<tr>
<td>5-6</td>
<td>Vigorous to heavy exertion</td>
<td>Running, racquetball, fast biking, heavy snow-shoveling</td>
</tr>
</tbody>
</table>

**METs** = metabolic equivalents of oxygen consumption

Evaluation of Known CVD Patients with ED

Sexual inquiry of all men

ED confirmed

Exercise ability

Indeterminate risk

Stress test

Pass
Low risk
Advice, treat ED

Fail
High risk
Cardiologist

Elective risk assessment

Low risk

High risk
Patient Preferences for ED Treatment Options

Oral therapies are the preferred treatment option by patients with ED

Mechanism of Action of PDE5 Inhibitors

Lue, T. *NEJM* 2000. 342:1802
## PDE5 Inhibitors: Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Tadalafil (Cialis) 20mg</th>
<th>Vardenafil (Levitra) 20mg</th>
<th>Sildenafil (Viagra) 100mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{1/2}$, h</td>
<td>17.5</td>
<td>4.6</td>
<td>3.7</td>
</tr>
<tr>
<td>$T_{max}$, h*</td>
<td>2.0 (0.5-12)</td>
<td>0.8 (0.3-2.0)</td>
<td>1 (0.5-2)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
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<tr>
<td></td>
<td></td>
<td>CYP3A5</td>
<td>CYP2C9</td>
</tr>
</tbody>
</table>

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*Median (range).*
My Take on PDE-5 Inhibitors

- All three are excellent drugs for ED
- All work best with practice
- All work least well in post-prostatectomy patients
- Can’t use ANY with nitrates
- Some patients prefer “spontaneity” of tadalafil
Always Aim High

Questions?