ED and Subclinical CVD:

And Insights on Medical Management

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Disclosure of Financial Relationships

Ryan P Terlecki, MD, FACS

Has disclosed relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

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Research Grants/Contracts

AMS/Boston Scientific
Allergan
Department of Defense

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Objectives (in 20 minutes)

- Highlight the data linking Erectile Dysfunction with cardiovascular health
- Discuss the steps in evaluation of the patient with ED prior to a trial of PDE5i, and opportunities for lifestyle modification
- Review the data on potential risks with PDE5is

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Audience Response Question 1

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Audience Response Question 2

Relevance

- ED (of some degree) is seen in the ***majority*** of men > 40 and nearly 20% of all men have moderate to severe ED

- Sexual dysfunction leads to reduced QOL, poorer physical health, loss of intimacy with partners, and loss of compliance and adherence to treatment

- ED may be sentinel symptom in those with undiagnosed PAD and/or CAD

Chrysant SG. Curr Opin Cardiol 2015; 30:383-90

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Canary in the Coal Mine

- Montorsi looked at 300 consecutive angina pts with angiographic CAD; 49% w/ED
- Of those w/CAD + ED, 67% had ED symptoms prior to angina with mean interval between of **38.8 months**

Montorsi et al. Eur Urol 2003 Sep; 44(3):360-4 PMID 12932937

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PCPT Data

- Men >/= 55y; about 9500 in placebo group
- Checked q3m for ED/CVD from 1994-2003
- Prevalent or incident ED after 5y significantly assoc'd w/subsequent CV events
- ***On par with smoking or family hx of MI***

Thompson et al. JAMA 2005 Dec 21; 294(23) 2996-3002; PMID 16414947

Olmsted County Study

- Eval'd assoc b/w ED and long-term risk of CAD
- Looked at age as modifier for association
- **For a man below the age of 50, having ED was assoc'd with ~50x inc'd incidence of CAD**

Inman et al. Mayo Clin Proc. 2009 Feb; 84(2):108-13. PMID 19181643

Younger Patients = Red Flag

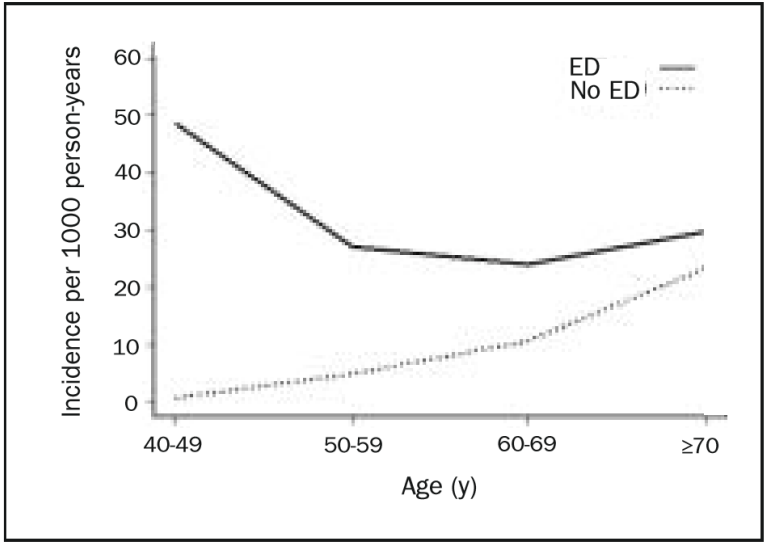

FIGURE. Incidence of coronary artery disease with respect to age and erectile dysfunction (ED) status.

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Mayo Data (Kopecky's group)

- Prospective study of 1057 men age 40-70
- Mean f/u >11y; 261 new cases of CVD
- ED sig assoc'd w/CVD (HR 1.42) even after controlling for age, assoc'd risk factors, and Framingham score
- However, ED did not improve prediction of CVD beyond traditional risk factors

Araujo et al. PMID 20117441; JACC 2010; 55:350-6

Initial Evaluation: History

- History (beyond the standard)
  - ED vs other
    - Libido issues (chicken or the egg?)
    - Ejaculation (premature, delayed, retrograde)
    - Orgasmic disorder
    - Peyronie's disease
    - Use SHIM questionnaire (**value of single question too**)
  - Lifestyle (drug/etoh/tob use, relationship status)
  - Reversible causes (meds, stress, depression, hormonal factors, partner-specific issues)

Simple Screen for Potential CVD

- “Any chest discomfort or SOB with exertion?”
- “Better with rest?”

Medication-Induced

- BP meds: thiazides, beta blockers other than nebivolol **(ACE inhibitors, ARBs, and CCBs have either a *neutral or beneficial* effect)**
- Possibility of Hawthorne effect in some patients (ED b/c they know med side efx)
- Antiandrogens (Lupron, chemo, ketoconazole, spironolactone, H2 blockers, cimetidine)
- Antiarrhythmics (Digoxin, Amiodarone)
- Statins (controversial b/c mixed data, but likely mildly ***beneficial***)
- Psych meds (TCAs, SSRIs, phenothiazines)
- Recreational drugs

Chrysant SG. Curr Opin Cardiol 2015; 30:383-90
Grimm et al. Hypertension 1997; 29:8-14

Initial Evaluation: Physical

- Physical Exam
  - Vitals (esp BP), Waist circumference
  - Traditional items (heart, lungs, pulses)
  - Testicular exam, signs of endocrine issues
  - Penile exam (e.g., plaques)
  - Signs suggesting vascular or neuro disease

Lab testing (optional)

- Fasting glucose and/or A1c (good idea)
- Lipid profile (need for risk score)
- CBC
- CRP
- Hormone profile in select cases (controversial)
  - Testosterone profile (BSSM, ISSM, and Princeton III advocate total T for those failing PDE5Is)
  - Estradiol
  - LH, TSH, FSH, Prolactin

Specialized testing

- Penile duplex with injection (invasive, less reliable with venous leak)
- Nocturnal penile tumescence (poor correlation with SHIM and obviated by good H/P)
- Psychological evaluation
- Neurophysiologic testing (doesn't assess autonomics, no universal criteria, time consuming)
- Arteriography (invasive, affected by method/timing)
- EndoPAT* (only FDA-approved noninvasive for EndoDys)

*Peyton et al. J Urol 2016. 195:1045-1050

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Erectile Dysfunction is Predictive of Endothelial Dysfunction in a Well Visit Population

Charles C. Peyton, Marc A. Colaco, Robert Caleb Kovell, Jung H. Kim and Ryan P. Terlecki*

From the Department of Urology (CCP, MAC, RPT), Wake Forest School of Medicine (JHK), Winston Salem, North Carolina, and Department of Urology, Hospital of the University of Pennsylvania (RCK), Philadelphia, Pennsylvania

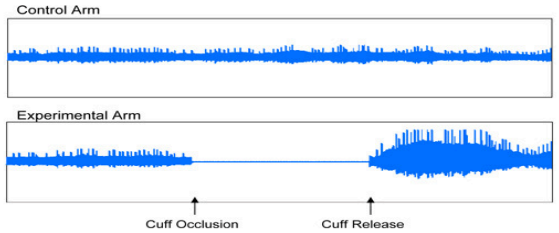

Figure 1: Normal Endothelial Vasodilator Function. Representative recording of an individual with normal endothelial vasodilator function, characterized by an increase in the signal amplitude after cuff release relative to baseline.

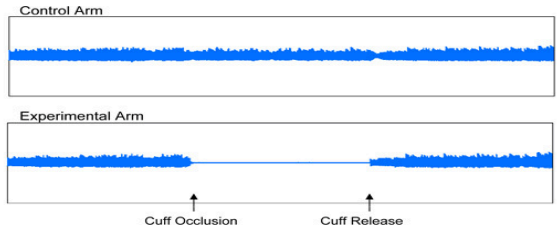

Figure 2: Endothelial Vasodilator Dysfunction. Representative recording of an individual with endothelial vasodilator dysfunction.

Penile Duplex

- Penis injected with intracavernosal agent +/- stimulation and duplex performed
- PSV > 30 cm/s is normal; < 25 suggests arterial insufficiency
- EDV > 5 cm/s suggests venous leak, but diagnosis can only be made in those with normal arterial function (i.e., nml PSV)
- ***This may provide information to the patient to understand their condition, but doesn't appear to influence management algorithm***

How it works

- Neural, Vascular, Hormonal, Psychological
- Need intact vascular endothelium
- Nerves→AcH→NO→cGMP→Flow
- Oxidative stress from ROS generated by diseases (HTN, DM, CVD) or meds (antihypertensives) leads to ***endothelial dysfunction and reduced NO***

Chrysant SG. Curr Opin Cardiol 2015; 30:383-90

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Link to CVD

- Endothelial dysfunction seems to be the common link
- This can be improved by wt loss and increased activity (shown by IL6 and CRP)
- Drugs like statins, ACEI, L-arginine, insulin, and Niaspan are shown to IMPROVE endothelial dysfunction (PDE5Is may as well)

Fonseca V and Jawa A. Am J Cardiol 2005; 96(suppl):13M-18M

ED and the Heart

- CAD could be a cause of ED, or a product of the same underlying issue
- Effective treatment of ED may lessen anxiety, prevent worsening of CAD, and improve QOL
- Coital angina (<5% of AP) can lead to avoidance of sexual activity and dec'd QOL

Kloner RA and Henderson L. Am J Cardiol 2013; 111:1671-76

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ED and the Heart

- **Princeton III: all w/ED should be assessed for cardiovascular risk (e.g., Framingham score)**
- Low risk warrants risk factor management and high risk should be sent to cardiologist
- Intermediate risk warrants evaluation of exercise ability and stress testing
- PDE5Is do **NOT** reduce exercise tolerance or increase CV events in men with CAD
- However, Avanafil is NOT recommended in those with event (e.g., MI) within past 6 months

Kloner RA and Henderson L. Am J Cardiol 2013; 111:1671-76
Miner et al. Am J of Med 2014; 127:174-182

Framingham Risk Score Calculator for Coronary Heart Disease

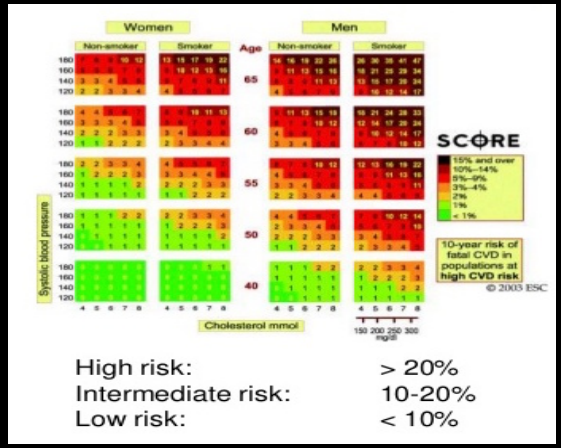
This **Framingham risk score calculator** estimates the 10-year coronary heart disease risk of any person based on certain criteria like gender, age, cholesterol and systolic pressure. You can discover more about this heart disease scoring system and about all the cardiovascular risk factors involved below the form.

Gender:*	Male
Age:*	58
Total cholesterol (mg/dL):*	225
HDL cholesterol (mg/dL):*	40
Under hypertension treatment?	Yes
Systolic blood pressure (mmHg):*	145
Smoker?	Yes

Calculate Reset

The 10-year cardiovascular risk for coronary heart disease (CHD) is over 30%.

Disclaimer: This tool should NOT be considered as a substitute for any professional medical service, NOR as a substitute for clinical judgement.



Multiple calculators online. Try **Clincalc.com**

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Bottom Line

- If you're gonna prescribe a tablet, you should check CVD risk
- If you treat ED up front successfully w/meds and patient returns annually for refills but doesn't address lifestyle, have you hurt him?
- Treating a bleeding chest wound with a red sweater (gets you to the party, but you won't be partying long).

Lifestyle Modifications

- Randomized single-blind trial of obese men with ED found that detailed advice resulted in greater drop in BMI, IL-6, and CRP (sig)
- Mean IIEF improved by about 3 pts (sig)
- On multivariate analysis, changes in BMI, physical activity, and CRP were independently assoc'd w/changes in IIEF

Esposito et al. JAMA 2004 Jun 23; 291(24):2978-84. PMID 15213209

Lifestyle Modifications

- A meta-analysis of 6 clinical trials noted significant improvements in ED (IIEF score) with lifestyle modifications
- Improvement on IIEF was 2.4-2.6
- Keep this in perspective

Gupta et al. PMID 21911624 Arch Int Med 2011; 171(20):1797-1803:

The holy grail

- Sildenafil (Viagra) was originally investigated to treat angina (marginal benefit)
- Peculiar “side effect” of improved erections
- Introduced clinically for ED in 1998, others followed
  - Vardenafil (Levitra)
  - Tadalafil (Cialis)
  - Avanafil (Stendra)
  - Lodenafil Microdenafil, Udenafil (outside US)

Other conditions treated

- First line for PAH (sildenafil, tadalafil)
- May be of benefit in management of:
  - CHF (improves hemodynamics and symptoms)
  - MI (reduces infarct size)
  - Altitude sickness
  - HTN
  - Raynaud's phenomenon
  - PAD (mouse model of limb ischemia)

Schwartz et al. JACC 2012; 59(1):9-15

Pharmacokinetics

- All should be taken on empty stomach, except Cialis
- Time to max concentration:
  - Viagra/Levitra: 60 min
  - Cialis: 120 min
  - Stendra: 30-45 min
- Half life/Efficacy period:
  - Viagra/Levitra: 4h/12h
  - **Cialis: 17.5h/36h; highest PDE5 selectivity**
  - Stendra: 3-5h; 6h

Which one is best?

- Meta-analysis of 118 trials involving PDE5Is sildenafil, vardenafil, tadalafil, avanafil, and two others approved only in Korea (udenafil and mirodenafil)
- Four principal findings:
  - PDE5Is superior to placebo
  - Tadalafil (Cialis) seems to be most effective
  - Adverse events mild and well tolerated
  - No significant difference in safety profile among different agents

Yuan et al. Eur Urol 2013; 63:902-12

Mechanism of action

- cGMP structural analogs
- Bind to catalytic site of PDE5 and inhibit hydrolytic activity
- cGMP levels rise and increase penile blood flow and amplify neurologic signal for erection

Safety and Side effects

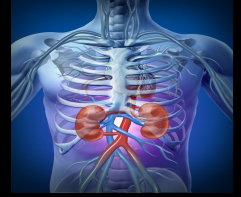
- Largely considered **SAFE**
  - Used in infants and adolescents with PAH
  - Safe and effective in **transplant** patients (kidney, cardiac, liver)

- Side effects fairly **COMMON** (headache, flushing, nasal congestion, dyspepsia, myalgia; color vision alteration with viagra)

- Based on effect on other PDE isoenzymes
  - PDE1 (explains interaction with NTG)
  - PDE6 (cyanopsia, blurred vision)
  - PDE11 (back pain, myalgia)

Sabri MR and Beheshtian E. Pediatr Cardiol 2014; 35:699-704

Safety: Renal patients



- ED seen in **71-80% HD pts** and reduces QOL; 50% of txp pts
- **Sildenafil absorbs faster after HD** and Cmax and t1/2 increased by **tacrolimus**

- Sildenafil: safe/well tolerated in HD and txp pts. ***If CrCl <30mL/min, start at 25 mg (no dose adjustments for vardenafil)***
- Tadalafil: for CrCl 31-50, start at 5 mg and **max dose of 10 mg** for 48hrs; If CrCl <30 or HD, do not exceed 5mg in 72 hrs (***daily dosing not recommended***)

Lasaponara F et al. J Sex Med 2013; 10:2798-2814

Chronic PDE5Is and the Heart

- Meta-analysis of 24 RCTs to evaluate efficacy and safety on cardiac morphology/function
- Authors concluded that PDE5Is have anti-remodeling properties and improve cardiac inotropism with good safety profile
- Ideal target population felt to be those with heart failure and left ventricular hypertrophy
- **Safe** when given **before CABG**

Giannetta et al. BMC Medicine 2014; 12:185
Ali et al. Cardiovasc Pharmacol 2013; 62(1):106-109

Chronic PDE5Is and Diabetes

- Meta-analysis of 6 RCTs to evaluate impact of chronic sildenafil on endothelial markers in type 2 DM

- Authors concluded that **chronic sildenafil seems to IMPROVE hemodynamic and serum pro-inflammatory markers (IL-6) in diabetic men**

Santi et al. European J Endocrinology 2015; 172:103-14

Nitrates

- Coadministration (24-48 hrs) ***still contraindicated and implicated in CAD-related deaths***
- NO donors further increase cGMP
- Short/long acting for angina; chronic use can lead to tachyphylaxis or tolerance
- One group demonstrated that **ranolazine** (2006 late Na current inhibitor) could be used as nitrate alternative

Udeoji DU and Schwarz ER. Clin Med Insights 2014; 7:131-134

Other Drug-Drug Interactions

- **Dose separation with alpha blockers** (not a problem if selective; issue with hypotension for non-selective)
- Adulterated supplements
- Dose adjustments with concomitant use of cytochrome P450 3A4 inhibitors (e.g., ritonavir, erythromycin)

Melanoma Risk? US Data

- An vitro study suggested sildenafil induced melanoma invasion (despite another study showing it slowed progression)
- US cohort study reported **HR 1.84** (1.02-3.22) for melanoma in men taking PDE5i
- Rationale of meds acting similarly to BRAF (proto-oncogene) activation and increasing invasiveness by lowering PDE5A expression
- US study: 14/142 cases used sildenafil (unclear CA stage or quantity of exposure)

Arozena et al. Cancer Cell 2011; 19(1):45-57
Meyer et al. Proc Natl Acad Sci USA 2011; 108:17111
Li et al. JAMA Intern Med 2014; 174:964-70
Loeb et al. JAMA 2015; 313:2449-55
Jiang et al. Br J Dermatol 2015; 172:885-915
Damber JE. Eur Urol 2015; 68:1098-1102

Melanoma Risk? Swedish Data

- F/U study of Sweden's melanoma registry with 30x more cases exposed to sildenafil with data on stage, #filled Rx, and data on vardenafil/tadalafil

- **Also showed increased association w/OR 1.21** (1.08-1.36)

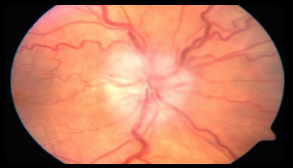
Li et al. JAMA Intern Med 2014; 174:964-70
Loeb et al. JAMA 2015; 313:2449-55
Jiang et al. Br J Dermatol 2015; 172:885-915
Damber JE. Eur Urol 2015; 68:1098-1102

Melanoma Risk: Data Critique

- There was no dose response, no different risk with longer acting drugs, and no association to late-stage disease
- Raises questions about actual causality
- Men using PDE5i were of higher ***socioeconomic status***
- Data shows men with higher SES have higher sun exposure, higher PDE5i use, higher risk of early stage disease, but lower risk of late stage disease and death
- Association ***may represent selection bias***

Li et al. JAMA Intern Med 2014; 174:964-70
Loeb et al. JAMA 2015; 313:2449-55
Jiang et al. Br J Dermatol 2015; 172:885-915
Damber JE. Eur Urol 2015; 68:1098-1102

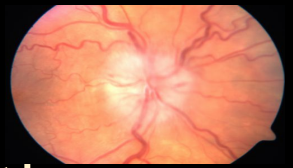
NAION



- Nonarteritic Anterior Ischemic Optic Neuropathy
- Approximately 40 case reports in peer-reviewed literature with possible relationship b/w PDE5Is and NAION; Hundreds of cases reported to FDA between 1999 and 2014
- Effect of sildenafil on retinal, optic disc and choroidal arterial circulation in healthy individuals is insignficant

Pomeranz HD. J Neuro-Ophthalmol 2015; 0:1-4

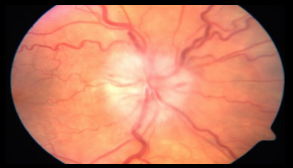
NAION



- One study noted a significant association with PDE5Is and NAION in those w/hx of MI
- After criticism, it was retracted
- Later study using health claims database concluded no association
- July 2005, **FDA mandated warning** on drug insert and that Pfizer/Bayer/Lilly perform studies

Pomeranz HD. J Neuro-Ophthalmol 2015; 0:1-4

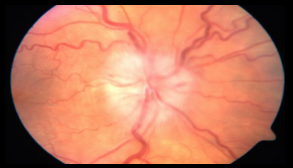
NAION



- Pfizer study found OR of 2.15 (1.06-4.34; P = 0.03) of developing definite NAION the day after PDE5I exposure
- Thus, 2x increase in risk of NAION in 2d after sildenafil/vardenafil and 5d after tadalafil
- Absolute risk still small (3 additional cases per 100,000 men 50 yrs or older per year)
- FDA mandated update to drug warning in March 2014

Pomeranz HD. J Neuro-Ophthalmol 2015; 0:1-4
Campbell et al. J Sex Med 2015; 12:139-151

NAION



- If NAION is diagnosed, ask about PDE5Is or any men's health supplements

- Risk to contralateral eye is 15%, so those men should be cautioned on further use

Cancer Controversies

- 2015 German study suggested PDE5Is may adversely impact **biochemical recurrence** after radical prostatectomy HR 1.38 (1.11-1.70, p=0.0035)
- Results were ***opposite the hypothesis*** given PDE5Is appear to have antineoplastic effect in vitro (melanoma, thyroid, colon, myeloma, leukemia)
- Follow-up Italian study with half as many patients did not find any increased risk
- ***Both retrospective and jury still out***

Michl et al. J Urol 2015; 193:479-83
Gallina et al. Eur Urol 2015; 68:750-753
Sponziello et al. Endocrine 2015; 50:434-441

Audience Response Question 1

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Conclusions

- Consistent with the Princeton III Consensus, all men should be asked about sexual function regardless of presenting complaint
- When ED is present, cardiovascular risk factors should be determined
- Oral therapies are safe and effective for most men
- No conclusive data has shown PDE5I use to be causal for malignancy, but **sunscreen** is a good thing