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Erectile Dysfunction Treatments and Cardiovascular Health

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Objectives

- To present cardiovascular risk associations with erectile dysfunction
- To describe clinical therapeutics for erectile dysfunction, with consideration of cardiovascular disease impact
- To review the role of PDE5 inhibitors for erectile dysfunction management and possible cardiovascular disease benefit

ED and CVD Share Common Risk Factors

- Age
- Obesity
- Inactivity
- Smoking
- Depression
- Dyslipidemia
- Hypertension
- Diabetes/Insulin Resistance

Jackson G, et al. *Int J Clin Pract.* 1999;53:445-451.
Nicolosi A, et al. *Urology.* 2003;61:201-206.
Solomon H, et al. *Int J Clin Pract.* 2003;57:96-99.

Prevalence and Risk Factors for Erectile Dysfunction in the United States

- Cross-sectional analysis of 2,126 men who participated in the 2001-2002 National Health and Nutrition Examination Survey (NHANES)
- Prevalence of ED in men aged ≥ 20 years was 18.4%, consistent with 18 million men affected by ED
- Risk factors: (including age-adjusted prevalence rates)
  - Age: 6.5% in men 20-39 yo, 77.5% in men >75yo
  - Diabetes: 38.6%
  - Hypertension: 27.7%
  - Cardiovascular disease: 24.7%
  - Hypercholesterolemia: 17.0%
  - Benign prostate enlargement: 19.6%
  - Physical inactivity: 23.3%

Selvin E, Burnett AL, Platz EA. Am J Med 120:151-7, 2007.

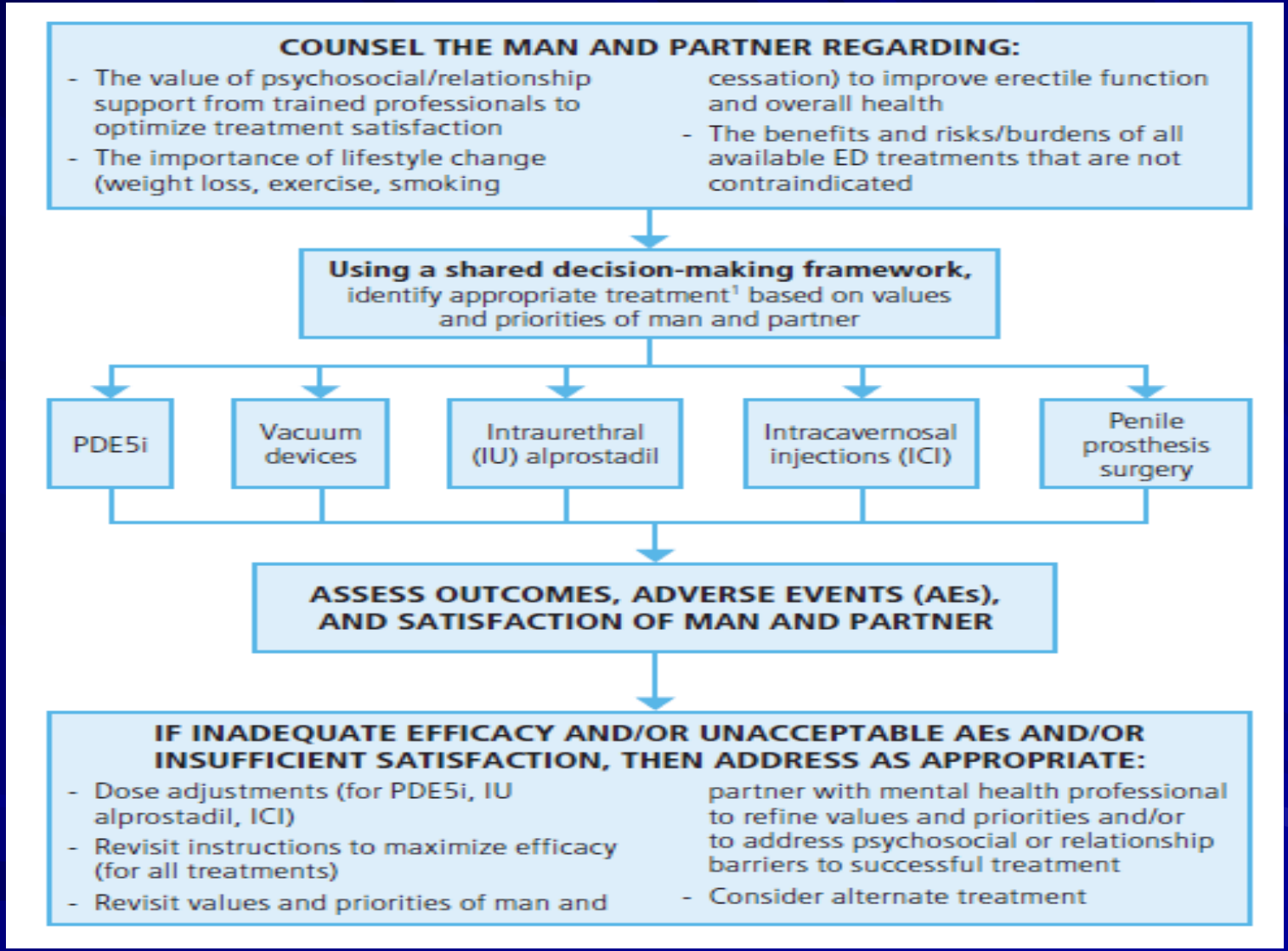
Management Principles

- Acknowledgment of the subjective complaint of erectile inability by the patient (or patient and partner)
- Structured process that incorporates several clinical practice concepts to bring patients the best therapeutic outcomes

Clinical Practice Concepts

- Early detection
- Goal-directed management
- Role of partner interview
- Cardiac risk assessment
- Step-care approach
- Shared decision-making and treatment planning
- Follow-up care

Management of ED

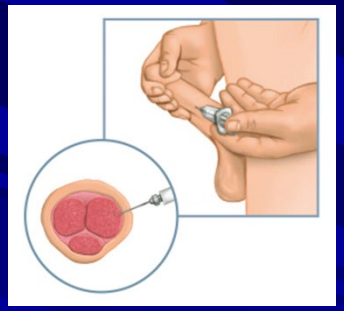


1 For men with testosterone deficiency, defined as the presence of symptoms and signs and a total testosterone <300 ng/dl, counseling should emphasize that restoration of testosterone levels to therapeutic levels is likely to increase efficacy of ED treatments other than prosthesis surgery.

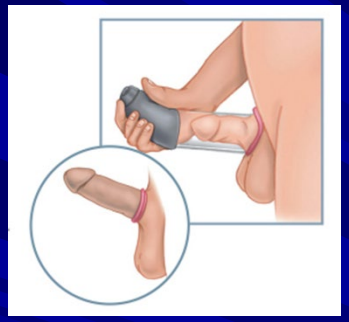
Burnett AL et al. J Urol 2018;200:633-41

Treatment options you may be familiar with

Oral Medications



Injections



Vacuum Erection Devices

Urethral Suppositories

Penile Implants

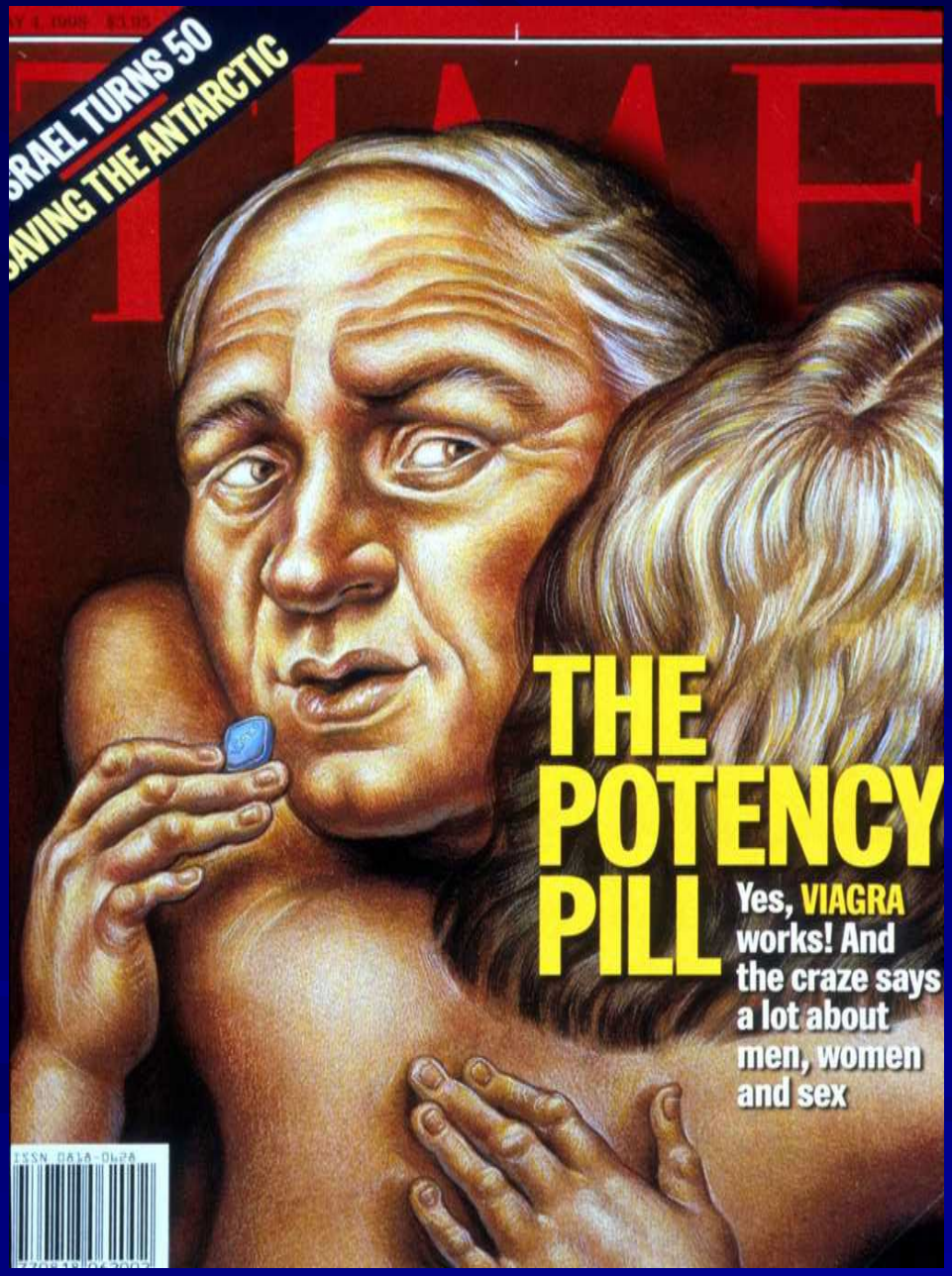
Lifestyle Modifications for Comorbid Conditions

7. Clinicians should counsel men with ED who have comorbidities known to negatively affect erectile function that lifestyle modifications, including changes in diet and increased physical activity, improve overall health and may improve erectile function. (Moderate Recommendation; Evidence Level: Grade C)
   - Metabolic conditions
   - Cardiovascular conditions

Clinical Therapeutics for ED: Treatment Outcomes

- Lifestyle modification
  - Beneficial
- Mental health counseling
  - Beneficial
- PDE5 inhibitors
  - 40% - 70% efficacy rates (for sexual intercourse)
- Vacuum devices
  - 90% efficacy rate, 30% - 70% satisfaction rate
- Intraurethral suppositories
  - < 40% efficacy rate
- Intracavernosal injections
  - 70% - 90% efficacy rates
- Penile prosthesis surgery
  - @ 100% efficacy rate, 80% - 90% satisfaction rate

Burnett AL et al. J Urol 2018;200:633-41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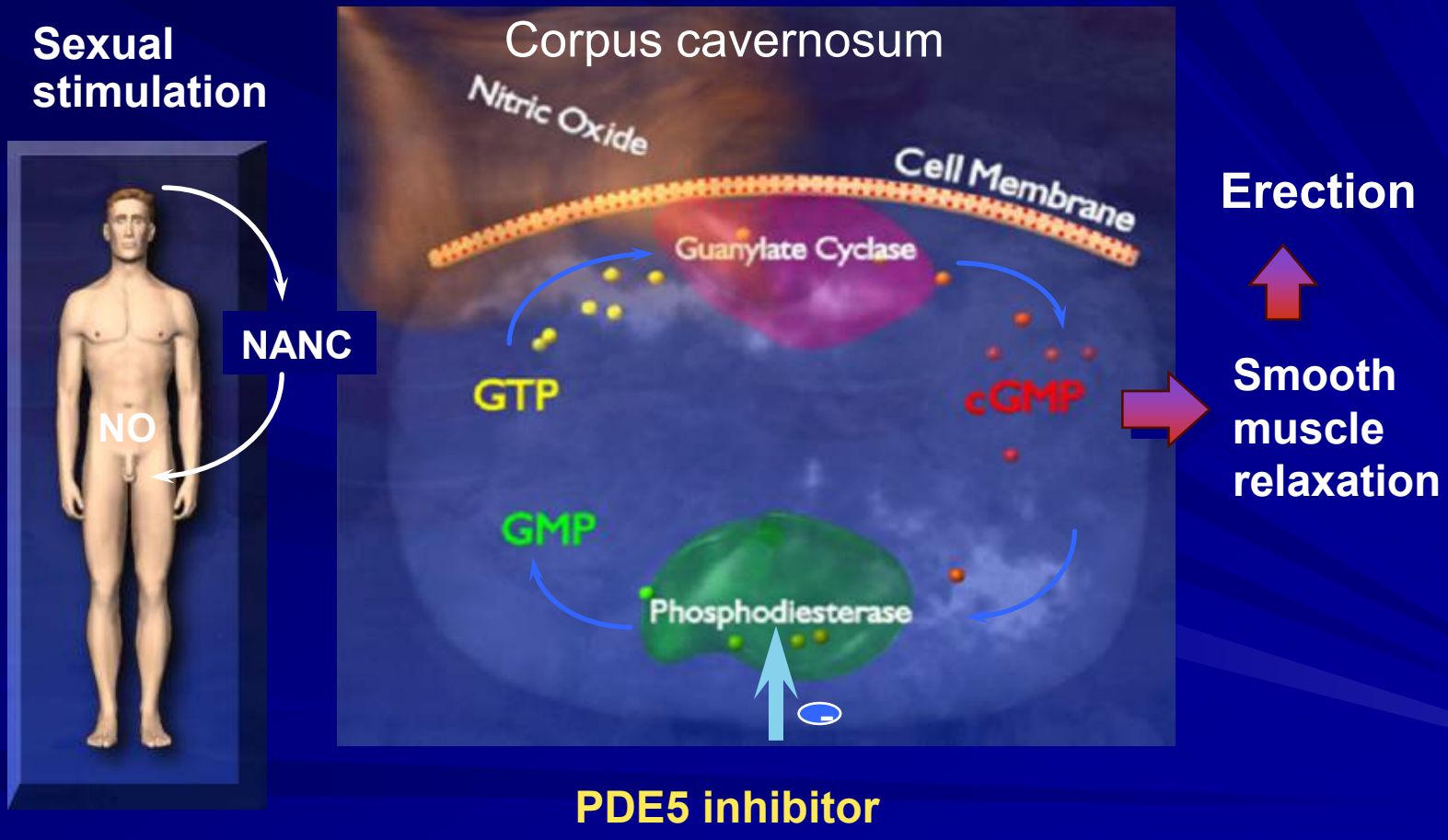
PDE5 Inhibitor Erectogenesis: NO and cGMP Actions in the Penis



cGMP=cyclic guanosine monophosphate. GTP=guanosine triphosphate. NANC=nonadrenergic, noncholinergic neurons. NO=nitric oxide. PDE5=phosphodiesterase type 5.

PDE5 Inhibitor Therapeutic Response Rates

- Successful sexual intercourse rates of approximately 70% in general
- Intercourse success rates of 40-50% in patients with ED who have diabetes mellitus or post-prostate cancer treatments (presumably because of cavernous nerve function requirement for treatment effect)

Carson C and Lue T. BJU Int 96:257-280, 2005.
Hatzimouratidis K et al. Eur Urol 55:334-347, 2009.

Strategies to Optimize Success of PDE5 Inhibitors

- Sexual stimulation required
- Educate!
  - 55% of initial sildenafil nonresponders achieved successful results through re-education
- Dose titration
- High-fat meal may result in delayed absorption
- Check testosterone and lipid profile
- Treat comorbid conditions
  - Preserve endothelial/smooth muscle function (reduce smoking, encourage exercise)

Levine LA. *Am J Med.* 2000,109(suppl 9A):3S-12S.
McCullough AR, et al. *Urology.* 2002;60(2 suppl 2):28-38.
Physicians' Desk Reference. 58th ed. Montvale, NJ: Thompson PDR;2004:2662-2665.
Process of Care Consensus Panel. *Int J Impot Res.* 1999;11:59-74.

Combination Therapies: Using PDE5 Inhibitors

- PDE5 inhibitors and psychosocial counseling[1]
- PDE5 inhibitors and testosterone replacement therapy[2]
- PDE5 inhibitors and transurethral alprostadil[3,4]
- PDE5 inhibitors and intracavernous pharmacotherapy[5]
- PDE5 inhibitors and vacuum erection device[6,7]

1. Althof SE et al. J Sex Med 2:793-800, 2005.
2. Shabsigh R et al. J Urol 172:658-663, 2004.
3. Mydlo JH et al. Eur Urol 38:30-34, 2000.
4. Nehra A et al. Int J Impot Res 14 Suppl 1:S38-S42, 2002.
5. McMahon CG et al. J Urol 162:1992-1997, 1999.
6. Chen J et al. J Urol 171:292-295, 2440.
7. Canguven O et al. J Sex Med 6:2561-2567, 2009.

PDE5 Inhibitors: Diverse Applications in Disease

- Genitourinary system
  - Erectile dysfunction, lower urinary tract symptoms
- Cardiovascular system
  - Hypertension, heart failure, atherosclerosis
- Neurologic system
  - Neurodegenerative disease, e.g., dementia, Alzheimer's
- Oncology
  - Cancer (breast, lung, prostate, leukemia, head & neck, colorectal)

Observation and Hypothesis : Are PDE5 Inhibitors Cardioprotective?

Since the action of PDE-5 inhibitors is achieved systemically, improving NO-mediated vasodilatation and endothelial functions with PDE-5 inhibitors is not specific for the vascular of the genitals but involves the vasculature of the entire body. This systemic benefit led Rosano et al (Eur Urol 2005; 47: 214) to postulate that pts with known endothelial dysfunction including diabetes may show benefit from this therapy.

Towards Better Penile Health: Hypothesis

Vasoactive Therapy

↓

Activation of NO/cGMP Signaling

↓

Erectile Tissue Relaxation

↓

Penile Vascular Function and Homeostasis

↓

Cardiovascular Health and Wellness

Proposed Mechanistic Effects of PDE5 Inhibition in the Cardiovascular System

- Protection against ischemia/reperfusion injury
  - Activation of calcium-activated BK channels
- Activation of coronary microvascular endothelial cells
- Reduction in oxidative stress
- Promotion of calcium signaling in cardiomyocytes
- Regulation of platelet proteins
- Regulation of fibroblast-to-myofibroblast differentiation
- Inhibition of transforming growth factor-beta signaling

Beneficial outcomes of long-term PDE5 inhibitor treatment may include a decrease in blood pressure, improved cardiac contractility, platelet inhibition, and anti-inflammatory effects.

Friebe A et al. Naunyn-Schmiedeberg's Arch Pharmacol 390: 1177-88, 2017.

Literature Review

Consistent with this hypothesis, some studies in at-risk for atherosclerosis population of men have reported reductions in adverse cardiac events associated with PDE-5 inhibitors including:

- Men with diabetes (Anderson SG et al Heart 2016; 102: 1750; Gazzaruso C et al JACC 2008; 51: 2040; Hackett G et al World J Diabetes, 2017; 8: 104)
- Known CAD and post MI (Andersson DP et al. Heart 2017; 103: 1264; Andersson DP et al JACC 2021; 77: 1535); including one study versus alprostadil.
- And a more general population of men in Denmark where the benefit was short lived (Vestergaard et al Eur J Prev Cardiol 2017; 24: 1498).

There has been a lack of this type of data in a large general population of men with ED in the United States followed for a long period of time, assessing all MACE and its components as well as overall mortality and assessment by level of exposure.

The Effect of PDE-5 inhibitors on Major Adverse Cardiovascular Events and Mortality in a Large Cohort of Men with Erectile Dysfunction from a Nationwide Insurance Database: A retrospective study

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Objectives

Measure the associations between PDE-5i and MACE & Mortality

1. Among commercially-insured men with ED (without evidence of MACE in the 12 months before ED diagnosis)
2. Among men with ED **AND** no coronary artery disease, but with cardiovascular risk factors.
3. Among men with ED **BY** level of exposure to PDE-5i
4. Among men with ED **AND** Type 2 Diabetes or coronary artery disease

Methods

- A retrospective observational cohort study was conducted in a large US commercial and Medicare insurance claims database in men 18 years old or older with ≥1 diagnosis of ED without prior MACE within 1 year from Jan 2006 to Oct 2020.
- The exposed group had ≥1 claim for PDE-5i; the unexposed group had no claims for PDE-5i and were matched 2:1 on baseline risk variables.
- The PDE-5 inhibitor exposed group filled one or more prescriptions for an approved PDE-5 inhibitor (sildenafil, tadalafil, vardenafil, or avanafil) after diagnosis of ED without any PDE-5 inhibitor or MACE in prior 12 months. Identified controls not on PDE-5 inhibitors.
- The primary outcome was MACE and secondary outcome was overall mortality, determined by matching for risk factors and medicines and multivariable Cox proportional hazard modeling. Death data were obtained via National Death Index linkage.

Results

- Table. Baseline demographics, clinical conditions, treatment use in patients with erectile dysfunction
- Exposed group = 23,816
- Unexposed group = 48.682
- Avg. age = 52 years

Acronyms: n= Number, SD= Standard Deviation, ED= Erectile Dysfunction, EPA/DHA= Eicosapentaenoic acid/ Docosahexaenoic acid, PDE-5i= Phosphodiesterase-5 inhibitors, MUSE= Medicated Urethral System for Erections

	Exposed group	Unexposed group	p-value
Number of patients	23,816	48,682	---
Age on index date, Mean(SD),years Matched	51.7 (10.4)	52.0 (10.4)	---
Time between ED diagnosis and index date, Mean(SD), months Matched	2.0 (4.8)	1.5 (3.8)	---
Smoking, n (%) Matched	2,022 (8.5%)	5,414 (11.1%)	<0.001
Clinical comorbidities, n (%)			
Ischemic heart disease/Coronary artery disease Matched	505 (2.1%)	894 (1.8%)	---
Type 2 diabetes mellitus Matched	2,187 (9.2%)	4,316 (8.9%)	---
Hypertension Matched	8,303 (34.9%)	17,215 (35.4%)	---
Hypercholesterolemia, dyslipidemia Matched	8,894 (37.3%)	17,682 (36.3%)	---
Atrial fibrillation	401 (1.7%)	754 (1.5%)	0.080
Peripheral arterial disease	237 (1.0%)	598 (1.2%)	<0.001
Benign prostatic hypertrophy	3,768 (15.8%)	7,571 (15.6%)	0.551
Hypogonadism	2,039 (8.6%)	4,957 (10.2%)	<0.001
Treatment use in baseline period, n (%)			
Warfarin, Direct oral anticoagulants	381 (1.6%)	796 (1.6%)	0.878
Antiplatelets including acetylsalicylic acid Matched	76 (0.3%)	118 (0.2%)	---
Nitrates – short- and long-acting	101 (0.4%)	255 (0.5%)	0.001
Statins Matched			
High-intensity	1,139 (4.8%)	2,436 (5.0%)	0.001
Moderate-low intensity	4,511 (18.9%)	8,903 (18.3%)	<0.001
Non-statin lipid lowering agents			
Ezetimibe/ Cholesterol absorption inhibitors	426 (1.8%)	596 (1.2%)	<0.001
Fibrates	727 (3.1%)	1,488 (3.1%)	0.909
Niacin	204 (0.9%)	318 (0.7%)	0.002
EPA/DHA	193 (0.8%)	308 (0.6%)	0.009
Anti-hypertensives Matched			
Angiotensin-converting enzyme inhibitors	4,169 (17.5%)	8,899 (18.3%)	0.251
Angiotensin receptor blockers	2,282 (9.6%)	4,509 (9.3%)	0.002
Beta-blockers	2,261 (9.5%)	4,898 (10.1%)	0.007
Calcium channel blockers	2,300 (9.7%)	5,137 (10.6%)	<0.001
Diuretics	1,837 (7.7%)	3,690 (7.6%)	0.009
Type 2 diabetes mellitus therapy			
Metformin	1,377 (5.8%)	2,764 (5.7%)	0.693
Dipeptidyl peptidase 4 inhibitors	302 (1.3%)	590 (1.2%)	0.436
Glucagon-like peptide-1 receptor agonists	174 (0.7%)	354 (0.7%)	0.810
Sodium-glucose cotransporter-2 inhibitors	117 (0.5%)	247 (0.5%)	0.521
Sulphonylureas	685 (2.9%)	1,377 (2.8%)	0.701
Insulin	464 (1.9%)	1,003 (2.1%)	0.007
Androgen/testosterone replacement therapy	1,222 (5.1%)	2,922 (6.0%)	<0.001
Non-PDE5i ED therapy (Rx and nonpharmacologic)			
Alprostadil (injectable and MUSE)	49 (0.2%)	44 (0.1%)	<0.001
Nonpharmacologic (implant/pump, vacuum, revascularization)	118 (0.5%)	163 (0.3%)	<0.001

Objective 1

Among commercially-insured men with ED (without evidence of MACE in the 12 months before ED diagnosis)

Compared to men unexposed to PDE-5i (n=48,682), after adjusting for baseline characteristics, those who were exposed to PDE-5i (n=23,816) had:

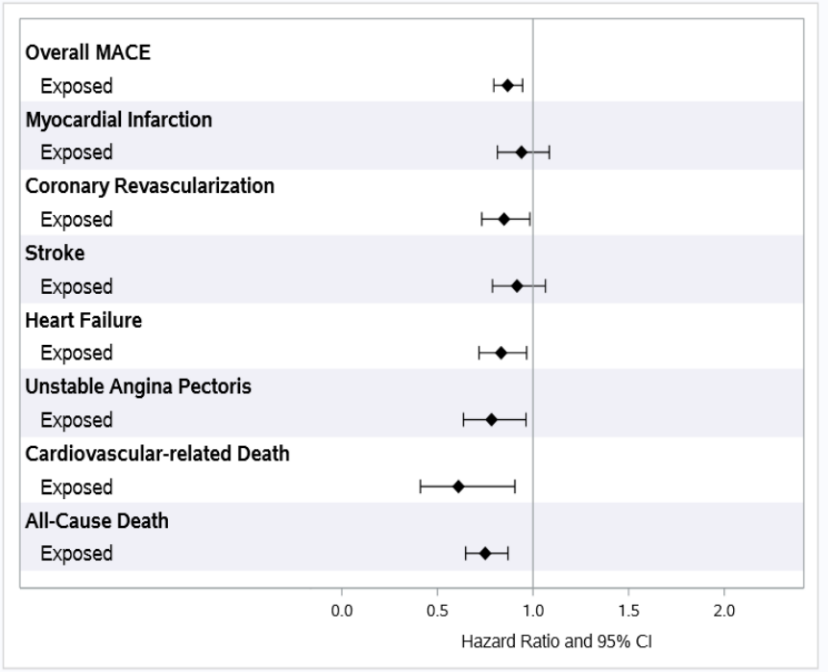
MACE:

- **13%** reduction in rate of overall MACE
  - (HR= 0.87; 0.79-0.95) **P=0.001**
- Individual MACE Components:
  - Myocardial infarction (HR= 0.94; 0.81-1.09) P=0.399
  - Coronary revascularization (HR= 0.85; 0.73-0.98) **P=0.029**
  - Stroke (HR=0.92; 0.79-1.06) P=0.254
  - Heart failure (HR= 0.83; 0.72-0.97) **P=0.016**
  - Unstable angina (HR= 0.78; 0.64-0.96) **P=0.021**
  - Cardiovascular-related mortality (HR = 0.61; 0.41-0.90) **P=0.014**

Mortality:

- **25%** reduction in rate of overall mortality
  - (HR= 0.75; 0.65-0.87) **P<0.001**

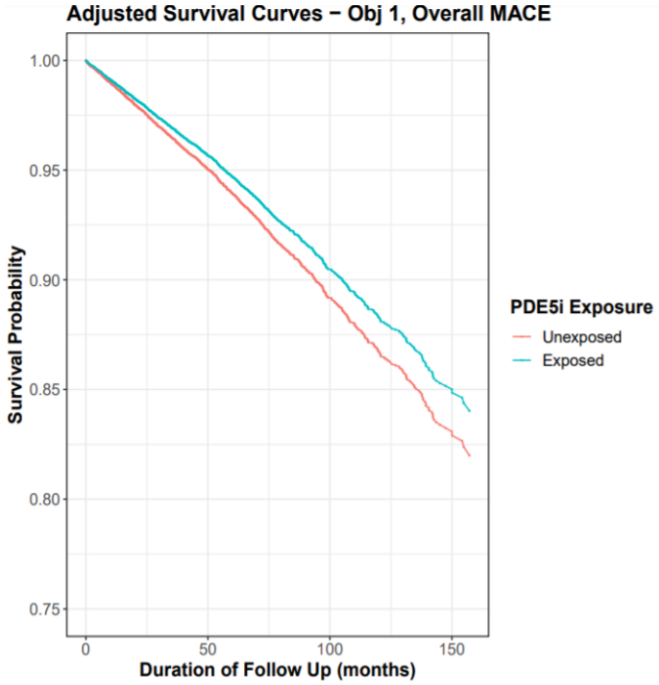
Objective 1: Matched and Adjusted Hazard Ratios



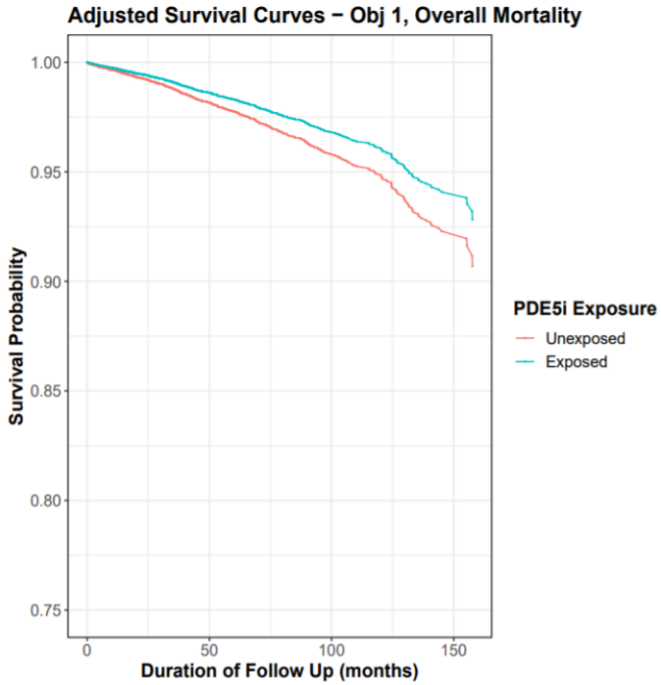
Median follow up was 24 months in the exposed group and 18 months in the non-exposed group.

Objective 1

Among commercially-insured men with ED (without evidence of MACE in the 12 months before ED diagnosis)



Number at Risk	0	50	100	150
Unexposed	48,682	9,608	2,201	249
Exposed	23,816	6,526	1,940	202



Number at Risk	0	50	100	150
Unexposed	48,682	9,169	1,971	209
Exposed	23,816	6,285	1,773	174

Objective 2

Among men with erectile dysfunction **AND** no coronary artery disease, but with cardiovascular risk factors

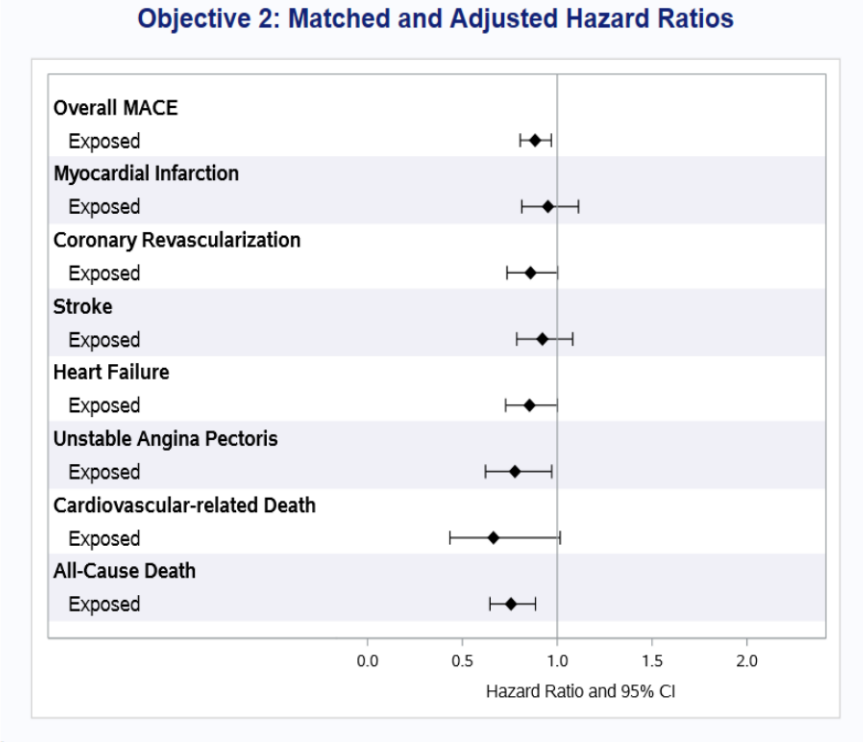
Compared to men unexposed to PDE-5i (n= 39,391), after adjusting for baseline characteristics, those who were exposed to PDE-5i (n= 19,205) had:

MACE:

- **12%** reduction in rate of overall MACE
  - (HR= 0.88; 0.80-0.97) **P=0.009**
- Individual MACE Components:
  - Myocardial infarction (HR= 0.95; 0.81-1.11) P=0.529
  - Coronary revascularization (HR= 0.86; 0.74-1.00) **P=0.055**
  - Stroke (HR=0.92; 0.79-1.08) P=0.318
  - Heart failure (HR= 0.85; 0.73-1.00) **P=0.052**
  - Unstable angina (HR= 0.78; 0.62-0.97) **P=0.026**
  - Cardiovascular-related mortality (HR = 0.66; 0.43-1.02) P=0.059

Mortality:

- **24%** reduction in rate of overall mortality
  - (HR= 0.76; 0.65-0.89) **P<0.001**



Objective 3

Among men with erectile dysfunction **by level of exposure**

After adjusting for baseline characteristics, compared to men with the lowest level of PDE-5i exposure (reference; n = 6,632), those with the highest level of exposure to PDE-5i (n= 5,638) had:

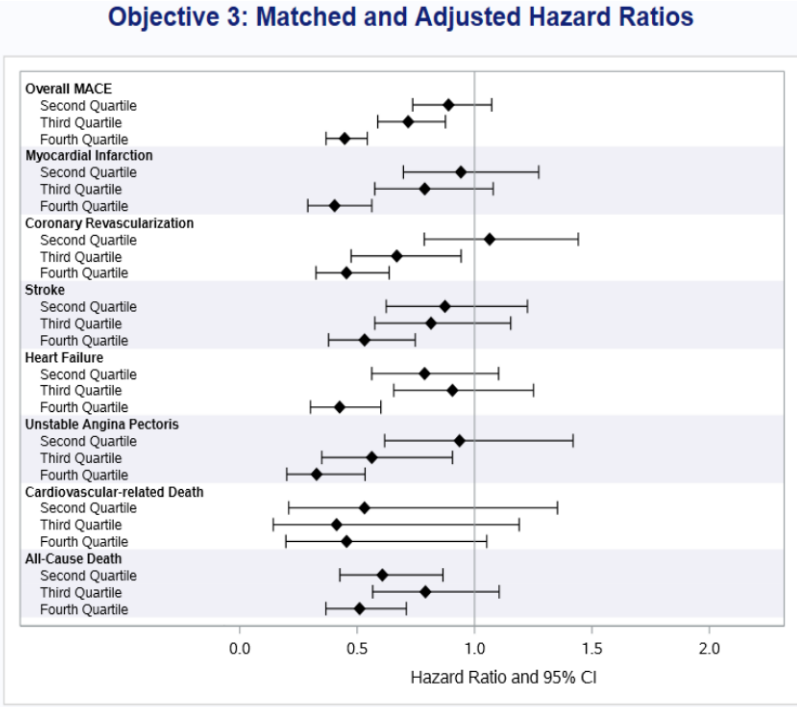
MACE:

- **55%** reduction in rate of overall MACE
  - (HR= 0.45; 0.37-0.54) **P<0.001***
- Individual MACE Components:
  - Myocardial infarction (HR= 0.40; 0.29-0.56) **P<0.001***
  - Coronary revascularization (HR= 0.45; 0.32-0.64) **P<0.001***
  - Stroke (HR=0.53; 0.38-0.75) **P<0.001***
  - Heart failure (HR= 0.43; 0.30-0.60) **P<0.001***
  - Unstable angina (HR= 0.33; 0.20-0.53) **P<0.001***
  - Cardiovascular-related mortality (HR = 0.46; 0.20-1.05) P=0.066*

* Fourth Quartile vs First Quartile

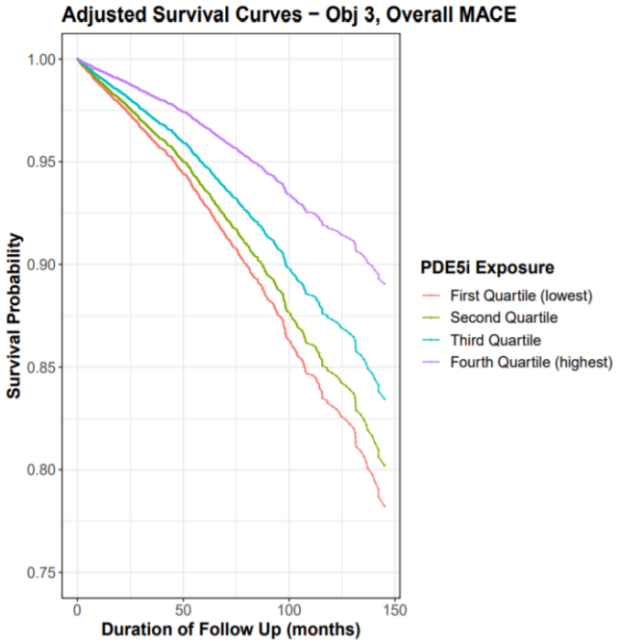
Mortality:

- **49%** reduction in rate of overall mortality
  - (HR= 0.51; 0.37-0.71) **P<0.001***

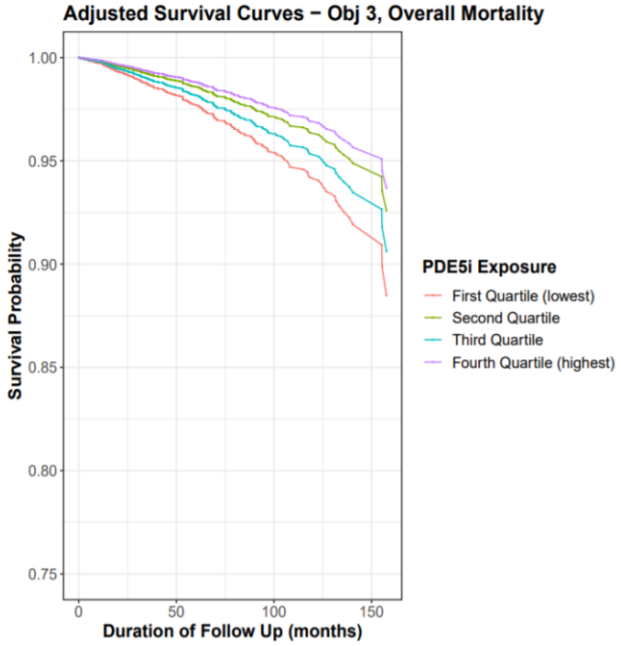


Objective 3

Among men with erectile dysfunction **by level of exposure**



Number at Risk	0	50	100	150
First Quartile	6,632	1,231	300	20
Second Quartile	6,453	1,294	339	28
Third Quartile	5,093	1,269	364	33
Fourth Quartile	5,638	2,491	770	93



Number at Risk	0	50	100	150
First Quartile	6,632	1,307	341	26
Second Quartile	6,453	1,360	376	37
Third Quartile	5,093	1,322	411	38
Fourth Quartile	5,638	2,537	812	101

Objective 4

Among men with erectile dysfunction **AND Type 2 Diabetes**

Limited precision due to smaller sample size and low number of events

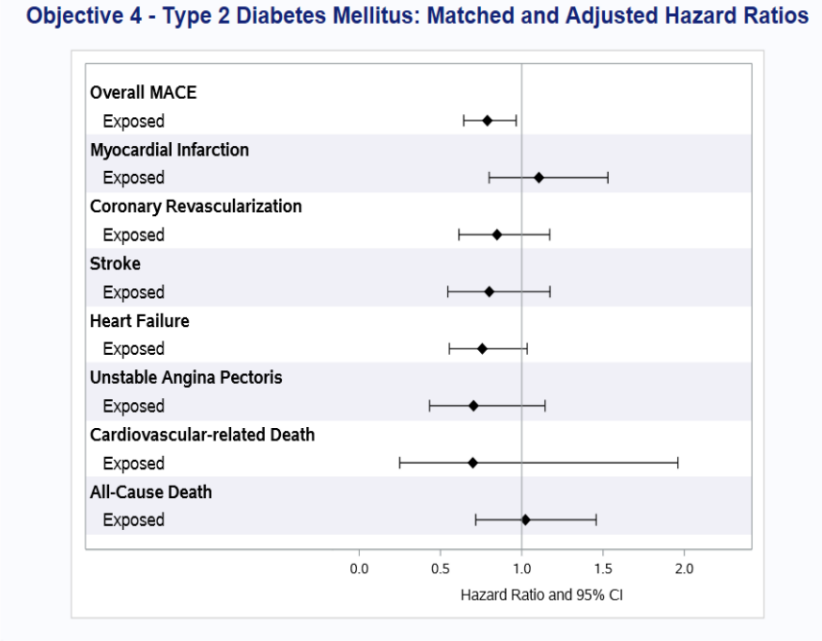
Compared to men unexposed to PDE-5i (n=4,316), after adjusting for baseline characteristics, those exposed to PDE-5i (n=2,187) had:

MACE:

- **21%** reduction in rate of overall MACE
  - (HR= 0. 79; 0.64-0.97) **P=0.022**
- No statistically significant reductions in rates of individual MACE components

Mortality:

- No statistically significant reduction in rate of overall mortality



Objective 4

Among men with erectile dysfunction **AND Coronary Artery Disease**

Limited precision due to smaller sample size and low number of events

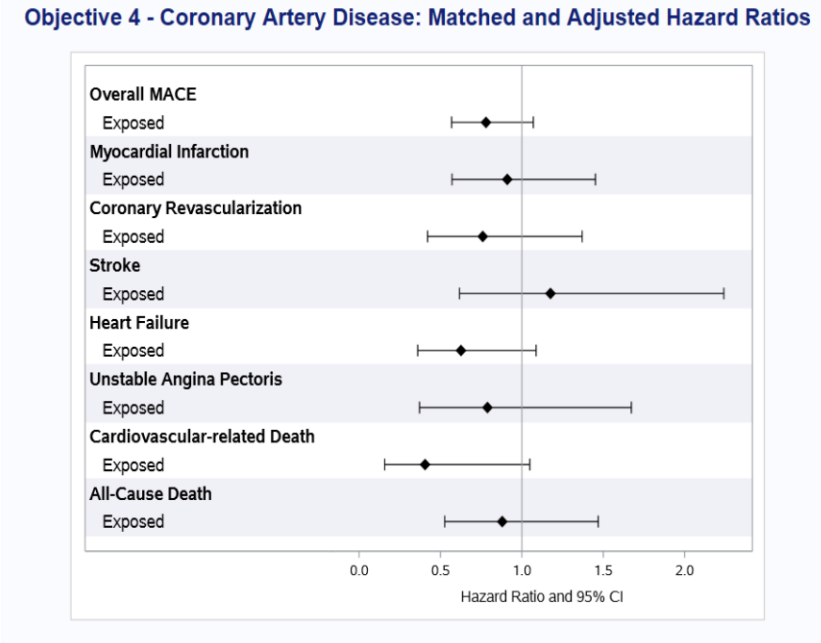
Compared to men unexposed to PDE-5i (n= 894), after adjusting for baseline characteristics, those exposed to PDE-5i (n= 505) had:

MACE:

- No statistically significant reduction in rates of overall or individual MACE components

Mortality:

- No statistically significant reduction in rate of overall mortality



Conclusions

Obj 1

Among commercially-insured men with ED (without evidence of MACE in the 12 months before ED diagnosis), PDE-5i was associated with:

- Significant & clinically meaningful reductions in MACE, total mortality and cardiovascular mortality
- Reductions in coronary revascularization, heart failure, unstable angina, and cardiovascular mortality

Obj 2

Among men with erectile dysfunction **AND no coronary artery disease, but with cardiovascular risk factors, PDE-5i was associated with:**

- Similar reductions in MACE, total mortality, and cardiovascular mortality

Obj 3

Among men with erectile dysfunction (Objective 1) **BY level of exposure to PDE-5i**

- Highest exposures to PDE-5i associated with the largest reductions in MACE compared to the lowest

Obj 4

Among men with erectile dysfunction **AND Type 2 Diabetes, PDE-5i was associated with:**

- Reduced MACE rate but not individual components of MACE in those exposed to PDE-5i

Among men with erectile dysfunction **AND coronary artery disease, PDE-5i was associated with:**

- Nonsignificant trend toward less cardiovascular mortality but not a statistically significant reduction in MACE with PDE-5i exposure

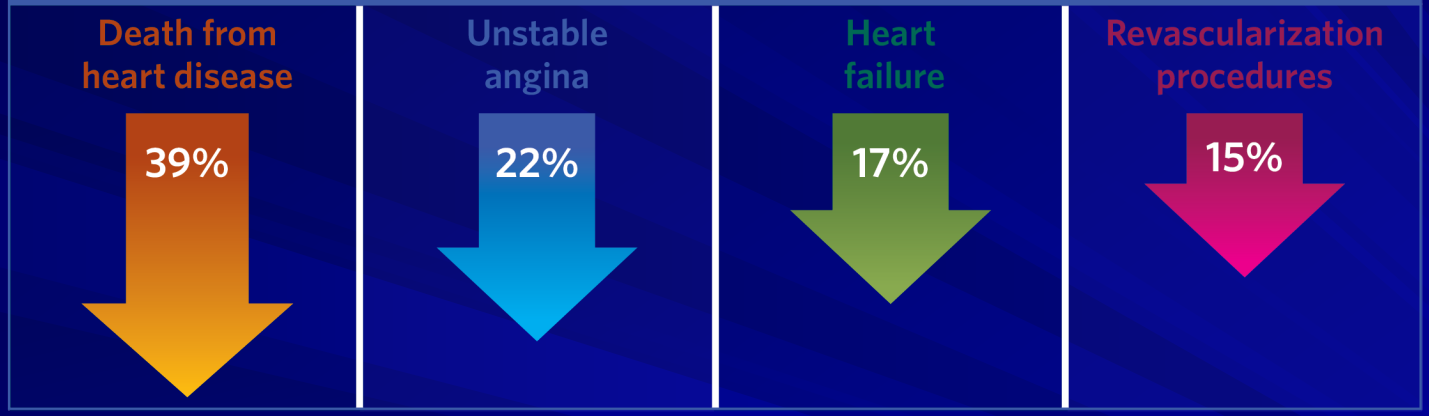
Discussion:

- Exposure to PDE-5i is associated with **significant and clinically meaningful reductions** in MACE, total mortality and cardiovascular mortality
- One of the **largest** cohort studies on topic to date
- Fills a significant **evidence gap** in men with ED at low risk for cardiovascular disease
- Findings may support Food & Drug Administration (FDA) review of **prescription to over-the-counter switch** for therapeutic class
- Results may offer basis to **consider a prospective study** of PDE-5i as a potential preventative therapy for cardiovascular disease

Limitations:

- Because of retrospective design, residual confounding is possible
- Inability to establish causation but dose response is promising
- PDE-5i exposure measured via tablets dispensed; adherence was not assessed
- PDE-5i and aspirin obtained outside of insurance benefit are not detected

Among men who took PDE-5i medications, the rate of major adverse cardiovascular events declined by 13% overall. The decline was even higher for:



Conclusions

- Erectile dysfunction and cardiovascular disease are intricately linked, epidemiologically and scientifically.
- Clinical therapeutics for erectile dysfunction may be influenced by cardiovascular disease conditions.
- Clinical therapeutics for erectile dysfunction may influence cardiovascular disease conditions. PDE5 inhibitors may provide cardiovascular disease benefit.