Baptist Health
HEART INSTITUTE

PCP Danger Zone:

Commonly Prescribed Drugs and the Heart

David Jones, MD FACC

Disclosures

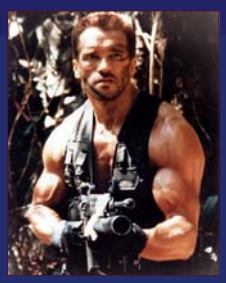
Financial - None

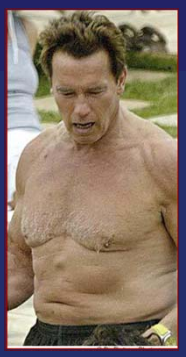
Medical - I am not a PCP. I don't know everything you know about these topics.

Outline

- Testosterone
- NSAIDs
- ADHD Drugs
- Grab Bag
  - Antibiotics
  - Herbals
  - OTC Cold/Flu/Decongestants
  - Weight Loss Medications
  - Migraine Medications

Testosterone and the Heart





Testosterone

- Testosterone has been shown to improve:
  - muscle strength
  - sexual function
  - bone density
  - (possibly) mood/cognition
- There is a postulation that men develop CAD 10 years earlier than women, and testosterone must be the cause

Low Testosterone and TRT

- 2.3 million Americans are using testosterone replacement therapy (TRT) for hypogonadism
- Half of all prescriptions are written by PCPs
- Dramatic increase in inappropriate use of testosterone therapy in healthy, middle-aged and older men likely due to direct-to-consumer advertising (DTCA) for nonspecific symptoms, such as decreased energy and sexual interest

Testosterone and Cardiac Effects

- POSITIVE
  - Low T tends to increase body fat and obesity thus increasing diabetes
  - Low T was shown to increase the risk of PAD in a Swedish study and palpitations in another study
  - Low T therapy does not increase the overall risk of heart disease in all-comers
  - T replacement might improve vascular reactivity
  - T replacement has shown an improvement in exercise ability in patients with CAD and CHF

Testosterone and Cardiac Effects

- NEGATIVE
  - Testosterone in high doses raises LDL and lowers HDL
  - Testosterone replacement might worsen sleep apnea, erythrocytosis, and venous thromboembolism
  - Androgen deprivation with prostate cancer can also: raise cholesterol levels, produce insulin resistance and increase the risk of diabetes (FDA warning 10/10)

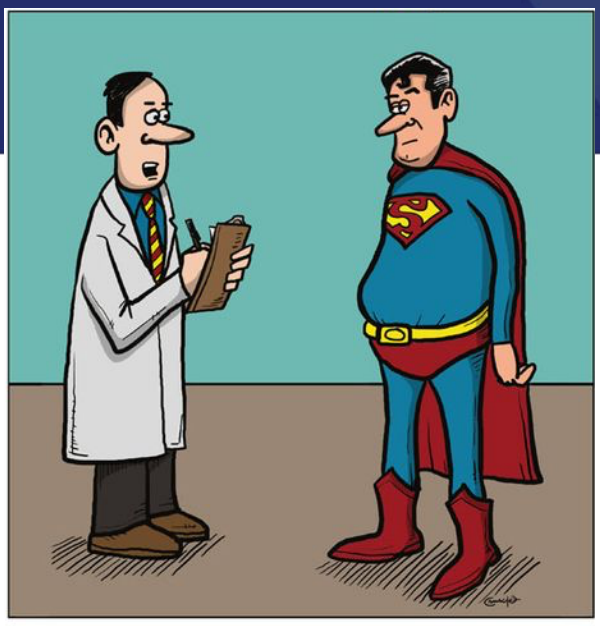
The Data is Lacking

- A meta-analysis of 51 trials of men with hypogonadism showed no increased CV risk
- A randomized trial on older men (mean age 74) was stopped early due to MI
- Two retrospective cohort studies showed an increased MI risk in the first 3 months of therapy
- Despite conflicting and inconclusive evidence, the FDA placed a warning about MI and CV risk on testosterone for hypogonadism

Anecdotal Evidence

Recommendations

- Testosterone replacement appears to be safe in appropriate patients with hypogonadism
- Testosterone has a risk of MI, stroke, and death especially in patients who are at risk for CV disease
- TRT can increase CV symptoms in patients so make sure they have the correct indication for TRT



"You need to stop flying and start jogging."

NSAIDs and the Heart

NSAIDs and the Heart

- Increased Blood Pressure
- Increased Myocardial Infarction Risk
- Increased Congestive Heart Failure Risk
- Increased Arrhythmia Risk, specifically AFib
- Increased Bleeding Risk

Nonselective vs COX-2 NSAIDs

- Most of the trials are retrospective and non-randomized. The cardiovascular risk of MI and death is similar between these groups (PRECISION trial)
- Naproxen might be the safest nonselective, Celecoxib might be the safest COX-2
- The increased risk of NSAIDs seems to be the ATTENUATION of effect on acetylation of the active site of cyclooxygenase (COX)-1 in platelets thereby decreasing the effect of Aspirin
- The choice of nonselective vs COX-2 has to do with risk of GI bleeding and use of other anticoagulant

Myocardial Infarction Risk

- Low risk patients have a VERY SMALL risk of MI in a 2-week use
- 24k patients in the PRECISION trial (no prior CAD but >1 RF) showed a 2-5% event rate which is lower than expected
- 1 in 10,000 post-MI patients will have an event on Celecoxib during a 2 week use
- Risk increases with higher doses, frequency of use, and preexisting CV disease
- Celecoxib and Ibuprofen seem to be safer than other NSAIDs in non-randomized trials

Congestive Heart Failure Risk

- Coxibs and NSAIDs increase the risk of new onset CHF by two-fold
  - Still small = 1 in 1000 patient-years
- Coxibs and NSAIDs partially or completely block the effect of ACEi/ARB on patients with CHF leading to an increased risk of hospitalization and death
- New onset edema occurs in 1-10% of patients taking Coxibs and NSAIDs
- HTN is increased in patients taking Coxibs and NSAIDs leading to CHF

Arrhythmia Risk

- Case-control trials have shown an increase in AFib and AFlutter rates with all COX-2 and nonselective NSAIDs
- In a meta-analysis involving 116k patients from 127 randomized trials of coxibs, rofecoxib (now off the market) was associated with increased risk of arrhythmia, but other coxibs were not

Bleeding Risk

- Combining ASA, NSAIDs, and antiplatelet or anticoagulant agents increases the risk of bleeding

Recommendations

- Selective and non-selective NSAIDs increase the risk of MI, CHF, and arrhythmias
- Try to use an alternative first in patients with CVD and those at risk for CVD
- NSAIDs increase cardiac risk in a dose-dependent fashion so if an NSAID must be used, use the lowest effective dose at the lowest frequency

ADHD and the Heart

ADHD Drugs

- 4.4% of US adults and 8-10% of children/adolescents will have ADHD
- Adults receive 1/3 of all ADHD meds
- AAP and AHA recommend a full general evaluation prior to starting meds to include:
  - HR and BP measurement
  - Electrocardiogram (not necessary if no sxs)
  - Physical exam to exclude Marfan's syndrome
- Conflicting data about a possible increased risk of sudden cardiac death (SCD) with ADHD drugs in adults

BP and HR Effects with ADHD Drugs

- One study showed adults (n=26) treated with amphetamine for ADHD had statistically significant increase in mean change from baseline SBP and HR compared with placebo.
  - ***Mean Change +5.3 mmHg SBP, +7.3 HR***
- Another study showed a small but statistically significant increase in BP and HR in adults (n=141) treated with methylphenidate for ADHD in a 6-week randomized placebo-controlled trial.
- The package insert for Atomoxetine includes a precaution about BP and HR increases compared with placebo in clinical trials.
  - ***Mean increase in SBP (3 mmHg) and DBP (1 mmHg)***

Stimulant ADHD Drugs

- Methylphenidate
- Methamphetamine
- Dexmethylphenidate
- Dextroamphetamine
- Mixed Amphetamine Salts
- Lisdexamphetamine

Non-Stimulant ADHD Drugs

- Atomoxetine
  - a selective norepinephrine reuptake inhibitor
  - has been associated with:
    - QT prolongation
    - BP and HR increase
- Modanifil or Armodafanifil

Controversial Studies

- Schelleman showed a 1.8-fold increase in risk of sudden death or ventricular arrhythmia in adult patients who initiated methylphenidate therapy
- A retrospective, population-based study of >150,000 adults on methylphenidate, amphetamine, or atomoxetine matched to non-users showed a lack of association between stimulant use and incidence of MI, sudden cardiac death (SCD), and stroke

Adult Sudden Death with ADHD Drugs

Drug	All Age Groups	Adult Age Group 0 – 18 Years		
	Total Prescriptions[1]	Adult Exposure (p-y)[2]	N[3]	Reporting Rate per 100,000 p-y
Methylphenidate	110,734,000	1,764,591	2	0.1
Amphetamine & Dextroamphetamine	70,699,000	1,857,056	6	0.3
Atomoxetine	9,419,000	142,855	4	2.8

[1] IMS Health, National Prescription Audit *Plus*™, January 1992 through December 2004. Data Extracted April 2005.
[2] Total person-years (p-y) times the percentage of drug appearances in the adult subgroup population (IMS Health, National Disease and Therapeutic Index™, January 1993 to December 2004, Data Extracted June 2005).
[3] N = sudden death cases identified in FDA AERS database received from January 1992 through February 2005.
Note: drugs include both branded and generic, all formulations available during respective time periods.

Stimulant Abuse

Recommendations

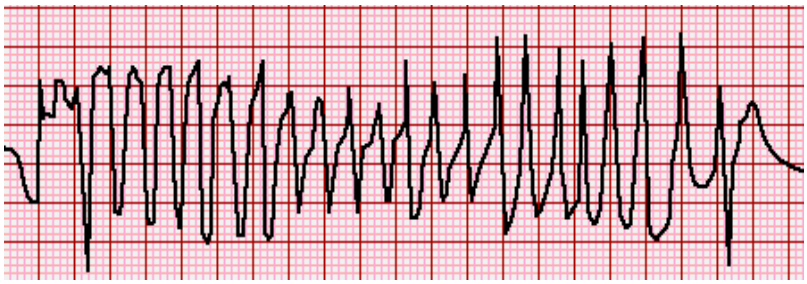
- If clinically significant HTN or Tachycardia, consider a dose reduction or cessation of drug
- The FDA issued a safety announcement in 2011 stating that stimulant products and atomoxetine should not be used in patients with serious heart problems, or for whom an increase in blood pressure (BP) or heart rate (HR) would be problematic.

"I have a question about my medication. Why is the couple in the commercial sitting outdoors in separate bathtubs?"

Grab Bag

Antibiotics

- Macrolides, fluoroquinolones, and antifungals can increase QTc interval and cause Torsades de Pointes in patients on anti-arrhythmics like Sotalol, Amiodarone, and Dofetilide



Herbals

- St. John's Wart
  - can affect the P450 system and decrease effects of antiarrhythmics, Warfarin, etc.
- Ginseng
  - can increase BP and decrease the effect of diuretics and Warfarin
- Echinacea
  - can increase QT interval
- Ginkgo and Garlic
  - can increase bleeding with W[illegible]

OTC Cold/Flu/Decongestants

- The key is to *avoid* PSEUDOEPHEDRINE which can cause hypertension with use

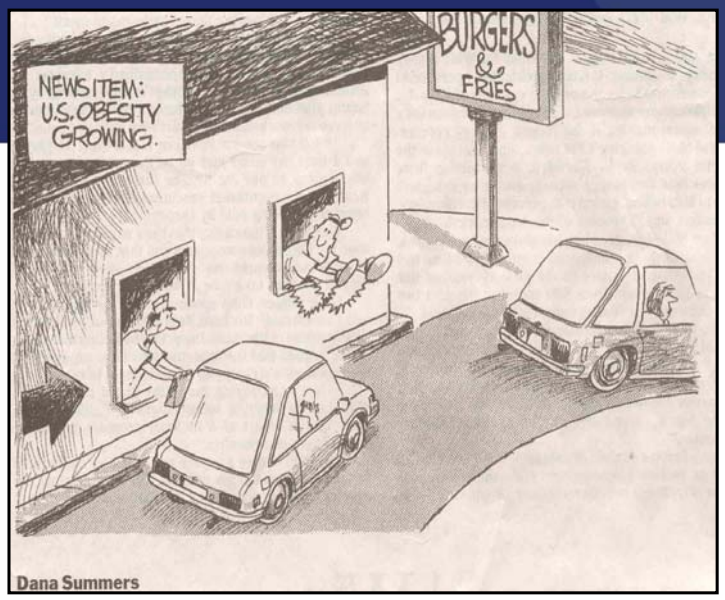
- "Look for the heart on the box"

Weight Loss Drugs

- Short-Term Agents
  - Phentermine
- Long-Term Agents
  - Liraglutide (reduced CV events in 1 trial)
  - Orlistat (lowers BP and lipids)
  - Lorcaserin (possibility of valvulopathy)

Migraine Medications

- Triptans
  - inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem
  - should be avoided in patients with ischemic stroke, heart disease, Prinzmetal's angina, uncontrolled hypertension, and pregnancy
- Ergots
  - bind to 5HT 1b/d receptors and promote vasoconstriction
  - avoid in patients with coronary artery disease, peripheral vascular disease, hypertension, and hepatic/renal disease.
  - have been associated with cerebrovascular, cardiovascular, and peripheral ischemic complications



Thank You

References

1 https://www.endocrine.org/news-room/press-release-archives/2014/endocrine-society-calls-for-large-scale-studies-to-evaluate-testosterone-therapy-risks (Accessed on January 23, 2015).
2 http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm436280.htm (Accessed on April 14, 2015).
3 Shores MM, Smith NL, Forsberg CW, et al. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012; 97:2050.
4 Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 2010; 95:639.
5 Basaria S, Harman SM, Travison TG, et al. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial. JAMA 2015; 314:570.
6 Baillargeon J, Urban RJ, Kuo YF, et al. Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy. Ann Pharmacother 2014; 48:1138.
7 Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J 2015; 36:2706.
8 Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med 2013; 11:108.
9 Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010; 363:109.
10 Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013; 310:1829.
11 Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014; 9:e85805.
12 Layton JB, Meier CR, Sharpless JL, et al. Comparative Safety of Testosterone Dosage Forms. JAMA Intern Med 2015; 175:1187.
13 Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007; 115:1634.
`4 Caughey GE, Cleland LG, Penglis PS, et al. Roles of cyclooxygenase (COX)-1 and COX-2 in prostanoid production by human endothelial cells: selective up-regulation of prostacyclin synthesis by COX-2. J Immunol 2001; 167:2831.
`5 Cheng Y, Austin SC, Rocca B, et al. Role of prostacyclin in the cardiovascular response to thromboxane A2. Science 2002; 296:539.
`5 Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011; 342:c7086.
`7 Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 2005; 365:475.
`8 Haag MD, Bos MJ, Hofman A, et al. Cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs and risk of stroke. Arch Intern Med 2008; 168:1219.
19 McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006; 296:1633.
20 Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005; 330:1366.
21 Johnsen SP, Larsson H, Tarone RE, et al. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study. Arch Intern Med 2005; 165:978.
22 Kimmel SE, Berlin JA, Reilly M, et al. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. Ann Intern Med 2005; 142:157.
23 Andersohn F, Schade R, Suissa S, Garbe E. Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: a nested case-control study. Stroke 2006; 37:1725.
24 Roumie CL, Mitchel EF Jr, Kaltenbach L, et al. Nonaspirin NSAIDs, cyclooxygenase 2 inhibitors, and the risk for stroke. Stroke 2008; 39:2037.
25 FitzGerald GA. Imprecision: Limitations to Interpretation of a Large Randomized Clinical Trial. Circulation 2017; 135:113.
26 Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2006; 368:1771.
27 Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005; 352:1081.
28 White WB, Strand V, Roberts R, Whelton A. Effects of the cyclooxygenase-2 specific inhibitor valdecoxib versus nonsteroidal antiinflammatory agents and placebo on cardiovascular thrombotic events in patients with arthritis. Am J Ther 2004; 11:244.
29 Farkouh ME, Kirshner H, Harrington RA, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 2004; 364:675.
30 Merck news release. www.merck.com/newsroom/press_releases/product/2004_0930.html (Accessed on September 30, 2004).
31 Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005; 352:1092.
32 Kerr DJ, Dunn JA, Langman MJ, et al. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. N Engl J Med 2007; 357:360.
33 Ray WA, Stein CM, Daugherty JR, et al. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. Lancet 2002; 360:1071.
34 Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004; 109:2068.
35 Baron JA, Sandler RS, Bresalier RS, et al. Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. Lancet 2008; 372:1756.
36 Heerdink ER, Leufkens HG, Herings RM, et al. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med 1998; 158:1108.
37 Whelton A, Fort JG, Puma JA, et al. Cyclooxygenase-2--specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther 2001; 8:85.
38 Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000; 343:1520.
39 Alsalameh S, Burian M, Mahr G, et al. Review article: The pharmacological properties and clinical use of valdecoxib, a new cyclo-oxygenase-2-selective inhibitor. Aliment Pharmacol Ther 2003; 17:489.
40 Curtis SP, Ng J, Yu Q, et al. Renal effects of etoricoxib and comparator nonsteroidal anti-inflammatory drugs in controlled clinical trials. Clin Ther 2004; 26:70.
41 Wolfe F, Zhao S, Pettitt D. Blood pressure destabilization and edema among 8538 users of celecoxib, rofecoxib, and nonselective nonsteroidal antiinflammatory drugs (NSAID) and nonusers of NSAID receiving ordinary clinical care. J Rheumatol 2004; 31:1143.
42 Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. JAMA 2006; 296:1619.
43 De Caterina R, Ruigómez A, Rodríguez LA. Long-term use of anti-inflammatory drugs and risk of atrial fibrillation. Arch Intern Med 2010; 170:1450.