The Controversy About Androgen Deprivation Therapy and Cardiovascular Harm – How Do We Balance Risks and Benefits?

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Harvard Medical School
Disclosures

- Consulting:
  - Medivation
  - Ferring
  - Genome Dx
  - Nanobiotix
  - Dendreon
  - Bayer
  - Astellas
  - Blue Earth
  - Augmenix
  - Cota

- Research Funding
  - Janssen
  - Astellas

- Equity
  - Augmenix
Huggins and Hodges - 1941

- Castration induces dramatic responses in men w/metastatic prostate CA

- Nobel prize in 1966 (Huggins)
Modern Hormone Therapy

- Gonadotropin Releasing Hormone Agonist
  “GnRH Agonist”
  (e.g. Leuprolide)

- Androgen Receptor Antagonist
  (e.g. Bicalutamide)
Cure Rates with XRT Alone Depend on Risk Group

<table>
<thead>
<tr>
<th>XRT Cure Rate</th>
<th>Localized</th>
<th>Locally-Advanced</th>
<th>Node Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk</td>
<td>Interm Risk</td>
<td>High Risk</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>75%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20-40%</td>
</tr>
</tbody>
</table>
Randomized Trials Show Adding ADT to XRT Improves Overall Survival (Except in Low-Risk Disease)

<table>
<thead>
<tr>
<th></th>
<th>Localized</th>
<th>Locally-Advanced</th>
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</tr>
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<tr>
<td></td>
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<td>XRT Cure Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>75%</td>
<td>60%</td>
</tr>
<tr>
<td>ADT</td>
<td>X</td>
<td>☻</td>
<td>☻</td>
</tr>
</tbody>
</table>
Widespread Growth in Use of ADT For All Risk Groups

Use of ADT Among Patients Receiving XRT

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Low-Risk</td>
<td>5.4%</td>
<td>57.1%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4.9%</td>
<td>73.5%</td>
</tr>
<tr>
<td>High Risk</td>
<td>15.3%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Overall</td>
<td>9.8%</td>
<td>74.6%</td>
</tr>
</tbody>
</table>

Cooperberg et al JNCI 2003 CAPSURE data
In 1999, GnRH Agonists accounted for 23% of total Medicare drug spending!

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Share of total Medicare drug spending (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolide acetate (for depot suspension)</td>
<td>15.1</td>
</tr>
<tr>
<td>Epoetin alpha for non-ESRD use</td>
<td>9.5</td>
</tr>
<tr>
<td>Goserelin acetate implant</td>
<td>7.9</td>
</tr>
<tr>
<td>Ipratropium bromide, unit dose form</td>
<td>6.4</td>
</tr>
<tr>
<td>Albuterol, unit dose form</td>
<td>6.3</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>6.2</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>2.9</td>
</tr>
<tr>
<td>Pamidronate disodium</td>
<td>2.8</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>2.0</td>
</tr>
<tr>
<td>Gemcitabine HCl</td>
<td>1.9</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1.8</td>
</tr>
<tr>
<td>Filgrastim (G-CSF) 480 mcg</td>
<td>1.7</td>
</tr>
<tr>
<td>Leucovorin calcium</td>
<td>1.6</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>1.5</td>
</tr>
<tr>
<td>Factor VIII (antihemophilic factor, recombinant)</td>
<td>1.3</td>
</tr>
<tr>
<td>Technetium TC Sestamibi</td>
<td>1.2</td>
</tr>
<tr>
<td>Hylan G-F 20</td>
<td>1.2</td>
</tr>
<tr>
<td>Filgrastim (G-CSF) 300 mcg</td>
<td>1.2</td>
</tr>
<tr>
<td>Not otherwise classified antineoplastic drugs</td>
<td>1.2</td>
</tr>
<tr>
<td>Dolasetron mesylate, injection</td>
<td>1.2</td>
</tr>
<tr>
<td>Subtotal, 20 highest-expenditure drugs and biologicals</td>
<td>74.9</td>
</tr>
<tr>
<td>All other Medicare-covered drugs and biologicals</td>
<td>25.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Source: GAO analysis of data from the Medicare Part B Extract and Summary System (BESS).
Is There any Downside to ADT?
Adverse Side Effects of ADT
Bothersome & Worrisome

Bothersome:
- Hot flashes
- Fatigue
- Loss of Libido
- Gynecomastia
- Testicular atrophy
- Penile Shortening
Adverse Side Effects of ADT

Bothersome
- Hot flashes
- Fatigue
- Loss of Libido
- Gynecomastia
- Testicular atrophy
- Penile Shortening

Worrisome
- Weight gain (2.4% gain)
- More fat mass (10% up)
- Muscle loss (3% decline)
- Insulin resistance (26-65% higher fasting levels)
- Triglycerides (26% increase)
- Cholesterol (10% increase)
- Fracture risk
- Alzheimer’s
- Depression

Phil Saylor and M. Smith, J Urol 2009
Metabolic Changes Due to ADT
Adverse Side Effects of ADT

Healthy Young Man  Man Receiving ADT

- Subcutaneous Fat
- Muscle Atrophy

Phil Saylor & M. Smith, J Urol 2009
Metabolic Syndrome vs. ADT Syndrome

- Central obesity
- High blood pressure
- High triglycerides
- Low HDL-cholesterol
- Insulin resistance

Ravindranath, Indian J Psychol Med 2012;34:247-54
Evidence that ADT increases risk of CV death

Keating 2006 SEER-Medicare

Tsai et al 2007 CAPSURE database

D’Amico 2007 (DFCI 95-096 + TROG 96-01)
ADT for prostate cancer associated with increased risk of cardiovascular complications:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Excess Risk</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>44%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>16%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11%</td>
<td>0.03</td>
</tr>
<tr>
<td>Sudden death</td>
<td>16%</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Age < 65 (p=NS)  
Age > 65 (p<.05)  

Tsai et al 2007 JNCI Observational Data
D’Amico: Shorter Time to Fatal MI for Men on ADT

• Combined DFCI 95-096 (RT +/- 6m ADT) and ANZ’s TROG 96-01 (RT +/- 6m ADT)

• Among 546 men age >65,
  • ADT was associated with a shorter time to fatal MI (p=0.017)
  • Absolute number of events equal by 7 years
D’Amico: Shorter Time to Fatal MI for Men on ADT

Events began 18 months earlier in the ADT arm

Mechanism for very early events still unclear
Warnings from prominent groups about ADT and CV Events

1. Consensus statement
2. FDA Warning
“...At this point, it is reasonable, on the basis of the above data to state that there may be a relation between ADT and cardiovascular events and death.”
New labeling required on GnRH agonists
warning of

“increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke)”
Major studies showing no excess risk of CVD due to ADT

Randomized:
- Roach JCO 2008 (RTOG 86-10)
- Efstathiou JCO (RTOG 85-31)

Retrospective:
- Alibhai JCO 2009 (Canadian registry)
- Punnen JCO 2011 (CaPSURE)
Association of Androgen Deprivation Therapy With Cardiovascular Death in Patients With Prostate Cancer
A Meta-analysis of Randomized Trials

Paul L. Nguyen, MD  
Youjin Je, MS  
Fabio A. B. Schutz, MD  
Karen E. Hoffman, MD, MPH, MHSc  
Jim C. Hu, MD, MPH  
Arti Parekh, BA  
Joshua A. Beckman, MD, MSc  
Toni K. Choueiri, MD

Context  Whether androgen deprivation therapy (ADT) causes excess cardiovascular deaths in men with prostate cancer is highly controversial and was the subject of a joint statement by multiple medical societies and a US Food and Drug Administration safety warning.

Objective  To perform a systematic review and meta-analysis of randomized trials to determine whether ADT is associated with cardiovascular mortality, prostate cancer-specific mortality (PCSM), and all-cause mortality in men with unfavorable-risk, non-metastatic prostate cancer.

Data Sources  A search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases for relevant randomized controlled trials in English be-
Purpose

- To perform a meta-analysis of randomized trials to determine whether ADT causes excess cardiovascular death in men with unfavorable-risk non-metastatic prostate cancer.
Search Sources

PubMed from January 1966 to April 2011

Cochrane Central Register of Controlled Trials through April 2011

Embase through April 2011
Inclusion criteria

- Randomized
- GnRH-Agonist-based ADT vs. no ADT
- Reported CV Deaths
- Median follow-up > 1 year
- Excluded metastatic or hormone refractory disease
Papers Identified
N=1041

Unique Records After Duplicates Removed
N=655

Full Text Articles Assessed
N=18

Studies Included
N=8
4,141 Patients Total

Abstracts Excluded
N=637
- Metastatic/HRPC (242)
- Both arms got ADT (152)
- No GnRH agonist (91)
- Older version/second analysis (62)
- No randomized (62)
- Other (28)

Full Text Excluded
N=10 (1,905 pts)
- No CV Death Data (9)
- Follow up <1 yr (1)
Included Trials

8 trials, 4,141 patients

Median follow-up 7.6-13.2 yrs

Local therapy:
- Radiation (5)
- Surgery (1)
- No Local therapy (2)

ADT Duration:
- <=6 months (3)
- 3yrs-Lifelong (5)

Node Positive: Yes (3)
Included Trials

DFCI 95096 (D’Amico)
ECOG/EST 3886 (Messing)
EORTC 22863 (Bolla)
EORTC 30846 (Schroder)
EORTC 30891 (Studer)
RTOG 85-31 (Pilepich/Efstathiou)
RTOG 86-10 (Pilepich/Roach)
TROG 96.01 (Denham)
Results: No Excess CV Deaths

Risk of CV Death for ADT arms: 11.0%
Risk of CV Death for no ADT arms: 11.2%

RR of CV Death for ADT vs no ADT: 0.93 (95% CI=0.79 to 1.10), p=0.41
# RR of CV Death in Each Study

<table>
<thead>
<tr>
<th>Source</th>
<th>Relative Risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 22863 (Bolla)</td>
<td>1.30 (0.71-2.38)</td>
<td>.39</td>
</tr>
<tr>
<td>DFCI 95-096 (D’Amico)</td>
<td>1.02 (0.50-2.09)</td>
<td>.96</td>
</tr>
<tr>
<td>TROG 96.01 (Denham)</td>
<td>0.79 (0.48-1.31)</td>
<td>.37</td>
</tr>
<tr>
<td>RTOG 85-31 (Efstathiou)</td>
<td>0.79 (0.56-1.11)</td>
<td>.17</td>
</tr>
<tr>
<td>ECOG EST-3886 (Messing)</td>
<td>3.26 (0.35-30.2)</td>
<td>.30</td>
</tr>
<tr>
<td>RTOG 86-10 (Roach)</td>
<td>1.24 (0.76-2.01)</td>
<td>.40</td>
</tr>
<tr>
<td>EORTC 30846 (Schroder)</td>
<td>0.97 (0.42-2.24)</td>
<td>.94</td>
</tr>
<tr>
<td>EORTC 30891 (Studer)</td>
<td>0.91 (0.70-1.18)</td>
<td>.47</td>
</tr>
<tr>
<td>Overall (fixed-effects model)</td>
<td>0.93 (0.79-1.10)</td>
<td>.41</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q=5.12, p=.645, I-squared=0.0%
Results Same in All Subgroups

ADT Did not Cause Excess CV Death in any of the Subgroups of Trials:
- Short-Course ADT (<=6 mos) trials
- Long-Course ADT (3+ years) trials
- Trials with median age >70
- Trials using radiation
ADT Reduced PCSM and ACM

The RR for PC-Specific Mortality was 0.69 (0.56 to 0.84), p<0.001 favoring ADT

The RR for All-Cause Mortality was 0.86 (0.80 to 0.93), p<0.001 favoring ADT
PCSM Reduced by ADT

Source

Aus et al,17 2002 (Aus)
D'Amico et al,3 2008 (DFCI 95-096)
Messing et al,12 2006 (ECOG/EST 3886)
Bolla et al,13 2010 (EORTC 22863)
Schröder et al,14 2009 (EORTC 30846)
Studer et al,15 2006 (EORTC 30891)
Schulman et al,18 2000 (ESGNTPC)
Yee et al,19 2010 (MSKCC)
Efstathiou et al,8 2009 (RTOG 85-31)
Roach et al,9 2008 (RTOG 86-10)
Denham et al,16 2011 (TROG 96.01)

Overall
Test for heterogeneity: Q = 24.57; P = .006; 12

Relative Risk (95% CI)

Favors ADT
Favors Control

P Value

>.99
.03
.002
<.001
.65
.70
.55
.37
.009
.007
.002
<.001
OS Improved by ADT

<table>
<thead>
<tr>
<th>Source</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aus et al, 2002 (Aus)</td>
<td>1.22 (0.54-2.74)</td>
<td>.63</td>
</tr>
<tr>
<td>D’Amico et al, 2008 (DFCI 95-096)</td>
<td>0.70 (0.48-1.01)</td>
<td>.06</td>
</tr>
<tr>
<td>Messing et al, 2006 (ECOG/EST 3886)</td>
<td>0.66 (0.42-1.04)</td>
<td>.07</td>
</tr>
<tr>
<td>Bolla et al, 2010 (EORTC 22863)</td>
<td>0.72 (0.58-0.89)</td>
<td>.0002</td>
</tr>
<tr>
<td>Schröder et al, 2009 (EORTC 30846)</td>
<td>0.96 (0.85-1.08)</td>
<td>.46</td>
</tr>
<tr>
<td>Studer et al, 2006 (EORTC 30891)</td>
<td>0.91 (0.81-1.02)</td>
<td>.09</td>
</tr>
<tr>
<td>Schulman et al, 2000 (ESGNTPC)</td>
<td>1.09 (0.42-2.86)</td>
<td>.86</td>
</tr>
<tr>
<td>Yee et al, 2010 (MSKCC)</td>
<td>1.78 (0.64-4.93)</td>
<td>.27</td>
</tr>
<tr>
<td>Efstathiou et al, 2009 (RTOG 85-31)</td>
<td>0.86 (0.78-0.96)</td>
<td>.005</td>
</tr>
<tr>
<td>Roach et al, 2008 (RTOG 86-10)</td>
<td>0.92 (0.83-1.02)</td>
<td>.13</td>
</tr>
<tr>
<td>Denham et al, 2011 (TROG 96.01)</td>
<td>0.74 (0.63-0.87)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>0.86 (0.80-0.93)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Conclusion

ADT appears to reduce PCSM and improve OS for men with unfavorable risk prostate cancer without causing excess cardiovascular mortality
Androgen deprivation therapy for prostate cancer doesn’t boost fatal risk, Dana-Farber study says

By DAVID ROGERS
DAILY NEWS STAFF WRITER

Updated: 7:27 p.m. Saturday, Dec. 17, 2011
Posted: 6:41 p.m. Saturday, Dec. 17, 2011

A new report from two Dana-Farber Cancer Institute physicians indicates there is no evidence that androgen deprivation therapy raises the risk of fatal heart attacks in prostate cancer.
Prostate cancer drugs from AstraZeneca Plc (AZN), Watson Pharmaceuticals Inc. (WPI) and others don’t increase the risk of heart attacks in men with no history of the disease, a study said, contradicting earlier reports.

The prescription medicines used to lower male hormones, a treatment known as androgen deprivation therapy, didn’t result in more cases of...
New Hope for Prostate Cancer

by Christien Brownlee  December 6, 2011, 04:00 pm EST

Androgen deprivation therapy (ADT) has been a mainstay for prostate cancer treatment since the 1950s. But a warning last year from the FDA based on recent studies showing that ADT might cause deadly heart attacks really put the kibosh on this treatment with some doctors.

While most docs thought the risk was worth the benefit for the most serious patients—those with metastatic disease, or tumors that spread—they were unclear whether ADT was worth it for patients whose disease was aggressive but hadn’t spread.

If this is the boat you’re in, rest assured: A new study in this week’s Journal of the American Medical Association suggests that all that drama might have been for nothing. Results show that ADT doesn’t appear to raise the risks of cardiac death, and it might increase your chances of living longer.
Is this the end of the story?
Limitations

Pts in RCTs tend to be healthier than average

Cannot exclude possibility that subset of men with significant comorbidity harmed by ADT

Doesn’t let ADT off the hook for metabolic events/diabetes and non-fatal CV events
Quantifying Observational Evidence for Risk of Fatal and Nonfatal Cardiovascular Disease Following Androgen Deprivation Therapy for Prostate Cancer: A Meta-analysis

Cecilia Bosco\textsuperscript{a,}\textsuperscript{*}, Zsolt Bosnyak\textsuperscript{b}, Anders Malmberg\textsuperscript{b}, Jan Adolfsson\textsuperscript{c}, Nancy L. Keating\textsuperscript{d}, Mieke Van Hemelrijck\textsuperscript{a}

\textsuperscript{a}King's College London, Division of Cancer Studies, Cancer Epidemiology Group, London, UK; \textsuperscript{b}Ferring Pharmaceuticals, Clinical R&D, Copenhagen, Denmark; \textsuperscript{c}Karolinska Institute, Stockholm, Sweden; \textsuperscript{d}Harvard Medical School and Brigham and Women's Hospital, Boston, MA, USA

Meta-analysis of observational data shows significantly increased risk of harm from ADT
ADT and Fatal or Non-Fatal Myocardial Infarction
Pooled HR = 1.57 (95% CI 1.26-1.94)
ADT and Fatal or Non-Fatal Stroke
Pooled HR = 1.51 (95% CI 1.24 - 1.84)
So What Can Explain the Discrepancy Between Randomized and Observational Data?

- **Randomized Data:**
  - HR for ADT and CVD = 0.93 (0.79-1.10)

- **Observational Data:**
  - HR for ADT and CVD = 1.57 (1.26-1.94)
Possible Explanations

1) The results from observational data reflect confounding (sicker pts get ADT)

2) The observational results included non-fatal MIs while randomized only looked CV Death

3) Perhaps ADT causes harm mainly in men with pre-existing comorbidities, who are under-represented in randomized trials
Evidence that a subgroup of men who could be harmed by ADT
D’Amico/DFCI 6 vs 0 Mos Update
16 yrs follow-up, Int/High risk localized

ADT no longer significantly improves OS, possibly due to harms of ADT in some men

JAMA: Sept 22 2015
P=0.04
Benefit in healthy men

P=0.07
?Harm in sick men?
Increased CV Death for Sicker Men on ADT

<table>
<thead>
<tr>
<th></th>
<th>Cardiac</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Deaths</td>
<td>AHR (95% CI)</td>
</tr>
<tr>
<td><strong>No. of Men</strong></td>
<td><strong>No. of Deaths</strong></td>
<td></td>
</tr>
<tr>
<td>Age at randomization, per year</td>
<td>206$^a$</td>
<td>39</td>
</tr>
<tr>
<td><strong>Interaction Terms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or minimal comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT and ADT</td>
<td>78</td>
<td>7</td>
</tr>
<tr>
<td>RT alone</td>
<td>79</td>
<td>11</td>
</tr>
<tr>
<td>Moderate or severe comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT and ADT</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>RT alone</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>ADT x comorbidity</td>
<td>206</td>
<td>39</td>
</tr>
</tbody>
</table>

D’Amico
JAMA 2015
Risk and Timing of Cardiovascular Disease After Androgen-Deprivation Therapy in Men With Prostate Cancer

Sean O’Farrell, Hans Garmo, Lars Holmberg, Jan Adolfsson, Pär Stattin, and Mieke Van Hemelrijck

See accompanying editorial on page 1232

ABSTRACT

Purpose
Findings on the association between risk of cardiovascular disease (CVD) and the duration and type of androgen-deprivation therapy (ADT) in men with prostate cancer (PCa) are inconsistent.

Methods
By using data on filled drug prescriptions in Swedish national health care registers, we investigated the risk of CVD in a cohort of 14,882 men with PCa who received ADT, compared with men matched...
O’Farrell JCO 2015: Highest ADT-related CV event rate in men with ≥2 recent CV events.
Which Specific Comorbidities Place Men at Highest Risk of Harm by ADT?
Which Comorbidities Put Men at Highest Risk of Death After ADT?

Nanda (JAMA 2009)

Review of 5077 men who got XRT (brachytherapy) +/- ADT

Mainly low and intermediate risk

Endpoint was all-cause mortality

Median f/u 5.1 yrs

Median HT duration = 4 months
No Adverse Impact of ADT in Men with No Comorbidity

Nanda (JAMA 2009)
No Adverse Impact of ADT in Men with a Single CV Risk Factor (HTN, HChol, or Diabetes)

Nanda (JAMA 2009)
Significantly Worse Survival For Men w/CAD-Induced CHF or MI After ADT

26% vs. 11% at 5 years
p=0.004

Adjusted Hazard Ratio = 1.96 (1.04-3.71), p=0.04

This group represented only 5% (256/5077) of the patients

Nanda (JAMA 2009)
Decision-Making in the Clinic

Risk of Prostate Cancer Death

Comorbidity Level

Low Risk | Intermediate Risk | High Risk | Locally Advanced | Node Positive

CHF/MI | Multiple CM | Single CM | No CM

Mild CM | Mod/Severe CM

Avoid ADT | ?????????????? | Give ADT
Should ADT be used in high risk men with CHF or MI?

CLINICAL INVESTIGATION

INFLUENCE OF ANDROGEN DEPRIVATION THERAPY ON ALL-CAUSE MORTALITY IN MEN WITH HIGH-RISK PROSTATE CANCER AND A HISTORY OF CONGESTIVE HEART FAILURE OR MYOCARDIAL INFARCTION


IJROBP April 2012
Even men with high-risk prostate CA had poorer overall survival with ADT if they had a history of CHF or MI (HR= 2.57, p=0.01) (retrospective data)
## Decision-Making in the Clinic

<table>
<thead>
<tr>
<th>Comorbidity Level</th>
<th>Risk of Prostate Cancer Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Locally Advanced</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>Node Positive</td>
</tr>
<tr>
<td>High Risk</td>
<td></td>
</tr>
<tr>
<td>CHF/MI</td>
<td></td>
</tr>
<tr>
<td>Multiple CM</td>
<td></td>
</tr>
<tr>
<td>Mod/Severe CM</td>
<td></td>
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<tr>
<td>Single CM</td>
<td></td>
</tr>
<tr>
<td>Mild CM</td>
<td></td>
</tr>
<tr>
<td>No CM</td>
<td></td>
</tr>
</tbody>
</table>

- **Avoid ADT**
- **Give ADT**

### Risk of Prostate Cancer Death
- **Low Risk**
- **Intermediate Risk**
- **High Risk**
- **Locally Advanced**
- **Node Positive**

### Comorbidity Level
- **CHF/MI**
- **Multiple CM**
- **Mod/Severe CM**
- **Single CM**
- **Mild CM**
- **No CM**
Should diabetics receive ADT?

ADT worsens survival for men w/Low Risk Pr CA & diabetes

ADT does not harm men w/Int-High risk PrCA &/diabetes

Parekh, Brachytherapy 2013

Fig. 4. Impact of ADT in diabetics with low-risk disease. ADT = androgen deprivation therapy; AHR = adjusted hazard ratio; CI = confidence interval.

Fig. 5. Impact of ADT in diabetics with intermediate/high risk disease. ADT = androgen deprivation therapy; AHR = adjusted hazard ratio; CI = confidence interval.
### Risk of Prostate Cancer Death

<table>
<thead>
<tr>
<th>Comorbidity Level</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
<th>Locally Advanced</th>
<th>Node Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF/MI</td>
<td></td>
<td></td>
<td></td>
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<td>No CM</td>
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</tr>
</tbody>
</table>

### Decision-Making in the Clinic

- **Avoid ADT**
- **Give ADT**

- **Low Risk**
- **Intermediate Risk**
- **High Risk**
- **Locally Advanced**
- **Node Positive**
Unanswered Questions

- What is the mechanism by which ADT may be harming men with CHF/MI?

- What can we do to reduce this harm?
Mechanism?

- Insulin resistance, increased lipids, leading to accelerated atherosclerosis?
  - However, excess events appear to occur *too early* for this mechanism
All Excess Deaths Occur *Early* Within <2 Years of ADT Exposure
Mechanism?

- Involvement of androgen receptors on cardiac myocytes?
GnRH agonists directly affected contractility of isolated mouse cardiomyocytes
Could explain Keating SEER-Medicare (JCO 2006) and Jespersen Danish (Eur Urol 2013) finding of excess CV risk from GnRH agonists
but not orchiectomy
Could ADT be Inducing Endothelial Dysfunction?

- Prospective DFCI study of 17 consecutive men about to receive ADT
- Pre-ADT and 3 months after ADT we measured labs and endothelial function using a vascular ultrasound

Nguyen PL, et al JAHA 2015
## Labs Changes as Expected

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>3 Months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (µIU/ml)</td>
<td>5.6 [4.6,8.6]</td>
<td>10.0 [6.5,14.8]</td>
<td>0.005</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>96 [85,99]</td>
<td>100 [95,123]</td>
<td>0.037</td>
</tr>
<tr>
<td>HOMA&lt;sub&gt;IR&lt;/sub&gt;</td>
<td>1.3 [1.1,1.7]</td>
<td>2.6 [1.6,3.6]</td>
<td>0.005</td>
</tr>
<tr>
<td>HOMA&lt;sub&gt;B&lt;/sub&gt;</td>
<td>65 [53,112]</td>
<td>76 [57,127]</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>159 [131,194]</td>
<td>200 [158,219]</td>
<td>0.005</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>45 [39,53]</td>
<td>59 [39,53]</td>
<td>0.028</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>101 [70,125]</td>
<td>126 [87,149]</td>
<td>0.005</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>78 [69,104]</td>
<td>95 [71,118]</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Hs-CRP</td>
<td>0.4 [0.2,1.7]</td>
<td>0.8 [0.5,1.6]</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>22.9 [19.3,40]</td>
<td>5.0 [5.0,12.2]</td>
<td>0.005</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>451 [317,794]</td>
<td>6 [3,14]</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Nguyen PL, et al JAHA 2015
### Endothelial Function Actually Improved After ADT

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Arterial Diameter (mm)</td>
<td>3.93 [3.39,4.36]</td>
<td>3.79 [3.45,4.12]</td>
<td>0.031</td>
</tr>
<tr>
<td>Reactive Hyperemic Stimulus (Fold Increase, VTI)</td>
<td>4.3 [2.6,6.8]</td>
<td>6.0 [3.8,7.1]</td>
<td>0.18</td>
</tr>
<tr>
<td>Diameter increase (mm)</td>
<td>.34 [0.14,0.48]</td>
<td>0.36 [0.29,0.55]</td>
<td>0.047</td>
</tr>
<tr>
<td>Flow-Mediated Vasodilation (%)</td>
<td>8.9 [4.0,12.6]</td>
<td>10.8 [7.7,14.6]</td>
<td>0.046</td>
</tr>
<tr>
<td>Nitroglycerin-Mediated Vasodilation (%)</td>
<td>16.7 [12.8,25.9]</td>
<td>19.2 [13.9,25.7]</td>
<td>&gt;0.2</td>
</tr>
</tbody>
</table>

Acute Endothelial dysfunction does not appear to be the culprit

Nguyen PL, et al JAHA 2015
Mechanism?

- Could the problem be related to an abrupt *change* in testosterone levels?

- TOM Trial (Basaria NEJM 2010) was RCT of testosterone supplementation vs. placebo in hypogonadal men
  - Halted early due to excess cardiac deaths in the testosterone arm
How Can We Prevent CV Harm?
Could Intermittent ADT Be Safer Than Continuous?

- SEER-Medicare Analysis of Intermittent vs. Continuous ADT finds Intermittent had LOWER risk for serious cardiac events (HR 0.64, 95% CI 0.53–0.77)
  
- Mostly driven by less Heart Failure
  
- (HR 0.62, 95% CI 0.49–0.78)

Tsai et al J Urol 2017
Could Intermittent ADT Be More Dangerous Than Continuous?

- Reanalysis of Randomized SWOG Intermittent vs. Continuous Trial found 10-year rate of ischemic and thrombotic events was:
  - 24% continuous
  - 33% intermittent (p=0.02)

Suggesting intermittent was worse
  Possibly related to change in T levels?

Hershman et al JAMA Onc 2016
Should patients with CHF/MI Be Revascularized Prior to ADT?
Coronary Revascularization and Mortality in Men With Congestive Heart Failure or Prior Myocardial Infarction Who Receive Androgen Deprivation

Paul L. Nguyen, MD1,2; Ming H. Chen, PhD3; Samuel Z. Goldhaber, MD2,4; Neil E. Martin, MD, MPH1,2; Clair J. Beard, MD1,2; Daniel E. Dosoretz, MD5; Michael J. Katin, MD5; Rudi Ross, BS5; Sharon A. Salenius, MPH5; and Anthony V D'Amico, MD, PhD1,2

Cancer, 2011
7839 men who received radiation with or without a median of 4 months of ADT for PC from 1991 to 2006

495 (6.3%) had CAD-induced CHF or MI and formed the study cohort; 50% (n=250) had stent or CABG before PC treatment
Revascularization Did not Completely Eliminate Excess Mortality from ADT Among CHF/MI
Should patients on ADT take metformin?

- May prevent some of the effects of insulin resistance
- May also have anti-neoplastic properties
  - Associated with reduced PC-mortality in a population study (JCO 2013)
Metformin + Exercise Trial

- Nobes, BJUI 2012
- RCT of 6 mos of metformin + exercise vs. observation in 40 men starting ADT
- significant improvements in
  - abdominal girth (P = 0.05),
  - weight (P < 0.001), BMI (P < 0.001),
    systolic BP (P = 0.01)
- no difference in the biochemical markers of insulin resistance
Are GnRH Antagonists Safer than GnRH Agonists?

No Excess CV Events or Death for GnRH Agonist Overall
Among Men w/Prior CV Disease, GnRH Agonist Had More CV Events Than Antagonist
Among Men w/CV Disease

Table 4 – Hazard ratios from a Cox regression for predictors of a cardiac event or death among trial participants with a baseline cardiovascular history (n = 707)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH antagonist vs GnRH agonist</td>
<td>0.438</td>
<td>0.260–0.736</td>
<td>0.0018</td>
</tr>
<tr>
<td>Statin medication use</td>
<td>0.539</td>
<td>0.282–1.030</td>
<td>0.0614</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>0.433</td>
<td>0.243–0.774</td>
<td>0.0047</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.088</td>
<td>1.075–4.055</td>
<td>0.0296</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.259</td>
<td>0.722–2.193</td>
<td>0.4169</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>1.136</td>
<td>0.619–2.083</td>
<td>0.6807</td>
</tr>
<tr>
<td>Type 2 diabetes treated</td>
<td>0.825</td>
<td>0.340–1.997</td>
<td>0.6689</td>
</tr>
<tr>
<td>Hypertension treated</td>
<td>0.632</td>
<td>0.322–1.239</td>
<td>0.1816</td>
</tr>
<tr>
<td>Baseline age</td>
<td>1.027</td>
<td>0.990–1.066</td>
<td>0.1524</td>
</tr>
<tr>
<td>Baseline testosterone level</td>
<td>0.786</td>
<td>0.656–0.941</td>
<td>0.0089</td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>0.970</td>
<td>0.909–1.035</td>
<td>0.3571</td>
</tr>
</tbody>
</table>

BMI = body mass index; CI = confidence interval; GnRH = gonadotropin-releasing hormone.
Authors’ Hypothesis for Why Only GnRH Agonists Cause Harm

- Vulnerable plaques rupture due to macrophages breaking down fibrous cap
- T-Helper 1 (Th1) lymphocytes activate macrophages and are the dominant T-cell in atherosclerotic plaques
- Activation of GnRH receptors on T-cells leads to their differentiation into the Th1 phenotype
Current Status

- Concerns about potential cardiovascular harm of ADT has reduced ADT use despite overall survival benefits in high risk
  - 23% of High Risk Prostate CA do not receive ADT
  - Chen YW, Brachytherapy 2014
Summary

- ADT has not been shown to increase CV Death in Randomized Trials
  But there may be a vulnerable 5% with prior CHF/MI who might have excess CV death from ADT

- ADT Probably increases CV events

- ADT should not be withheld from men in whom a survival benefit has been proven (high risk)

- Recommend exercise and referral to cardiology for “optimization”, especially in men with pre-existing CV disease
MOVEMBER

A Survivorship Action Partnership

USA Workshop
March
2014
>$1 Billion raised for prostate and testicular cancer since 2003
“Random Task” from the Austin Powers movie
Thank you!