Cardiovascular Complications of ADT: Reviewing Pre-clincal and Clinical Data and Introducing the RADICAL-PC Trial

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Associate professor
Department of Surgery-Urology
McMaster University
Faculty/presenter disclosure

• Faculty: Jehonathan H. Pinthus MD, Ph.D.

• Relationships with commercial interests:
  – Grants/Research Support: Ferring Inc.
  – Consulting Fees: Ferring Inc.
Stable coronary artery disease

Atherosclerosis timeline

- Foam cells
- Fatty streak
- Intermediate lesion
- Atheroma
- Fibrous plaque
- Complicated lesion/rupture

Endothelial dysfunction

- From first decade: Growth mainly by lipid accumulation
- From third decade: Smooth muscle and collagen
- From fourth decade: Thrombosis, hematoma

Adapted from Pepine CJ. Am J Cardiol. 1998;82(suppl 104).
Acute/ unstable coronary artery disease

Atherosclerosis timeline

- Foam cells
- Fatty streak
- Intermediate lesion
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From first decade
- Growth mainly by lipid accumulation

From third decade
- Smooth muscle and collagen

From fourth decade
- Thrombosis, hematoma

Adapted from Pepine CJ. Am J Cardiol. 1998;82(suppl 104).

Disrupted plaque with occlusive thrombus

ECG strips showing abnormal cardiac activity.
Epidemiology of CVD in PC patients

• patients are deemed to be high risk if they have a global risk estimate for hard CVD events of ≥2% per year

Prostate cancer is a diagnosis that is associated with a high subsequent risk of cardiovascular disease

Keating, *et al.* *JNCI* 2010; 102: 39
Comprehensive prospective metabolic, anthropometric, nutritional and physical profiling of prostate cancer patients

Fasting Insulin (uIU/mL)

Fasting C-Peptide (ng/mL)

Adiponectin (pg/mL)

Letpin: Adiponectin Ratio (AU)
US Veterans with Locoregional PC

Incidence of CVD (% per year)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Coronary heart disease</th>
<th>MI</th>
<th>Sudden Cardiac Death</th>
<th>Stroke</th>
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<tbody>
<tr>
<td>No ADT</td>
<td>8.1</td>
<td>0.73</td>
<td>1.15</td>
<td>1.08</td>
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<tr>
<td>GnRH agonist</td>
<td>14.4</td>
<td>1.28</td>
<td>2.16</td>
<td>1.85</td>
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# US Veterans with Locoregional PC

## Incidence of CVD (% per year)

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<tr>
<td>Orchietomy</td>
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<td>2.62</td>
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<td>Combined androgen blockade</td>
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<td>1.02</td>
<td>2.01</td>
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<td>Oral antiandrogen</td>
<td>14.3</td>
<td>1.12</td>
<td>1.88</td>
<td>1.49</td>
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Keating, *et al. JNCI* 2010; 102: 39
# Swedish population study

Incidence of CVD (% per year)

<table>
<thead>
<tr>
<th></th>
<th>Anti-androgen</th>
<th>GnRH agonist</th>
<th>Orchietomy</th>
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<td><strong>For the 2 years before ADT initiation</strong></td>
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<tr>
<td>Ischemic heart disease</td>
<td>1.58</td>
<td>2.24</td>
<td>2.20</td>
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<tr>
<td>Heart failure</td>
<td>0.59</td>
<td>1.09</td>
<td>1.44</td>
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<tr>
<td>Stroke</td>
<td>1.32</td>
<td>1.78</td>
<td>1.73</td>
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<tr>
<td><strong>For the 2 years after ADT initiation</strong></td>
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<tr>
<td>Ischemic heart disease</td>
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<tr>
<td>Heart failure</td>
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<tr>
<td>Stroke</td>
<td>1.58</td>
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<td>Any CVD</td>
<td>14.0</td>
<td>21.6</td>
<td>23.4</td>
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Novel ADT agents

### A

<table>
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<tr>
<th>Study or Subgroup</th>
<th>new HA</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tr>
<td>AFFIRM</td>
<td>49</td>
<td>30</td>
<td>12.9%</td>
<td>0.81 [0.53, 1.26]</td>
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<tr>
<td>COU-AA-301</td>
<td>126</td>
<td>46</td>
<td>18.9%</td>
<td>1.36 [1.00, 1.87]</td>
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<tr>
<td>COU-AA-302</td>
<td>126</td>
<td>96</td>
<td>23.9%</td>
<td>1.31 [1.03, 1.66]</td>
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<tr>
<td>ELM-PC 4</td>
<td>172</td>
<td>100</td>
<td>24.8%</td>
<td>1.69 [1.35, 2.12]</td>
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<tr>
<td>PREVAIL</td>
<td>88</td>
<td>66</td>
<td>19.5%</td>
<td>1.29 [0.95, 1.75]</td>
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</tbody>
</table>

Total (95% CI) 3788 2947 100.0% 1.32 [1.08, 1.60]

Total events 561 338

Heterogeneity: Tau² = 0.03; Chi² = 9.01, df = 4 (P = 0.06); I² = 56%

Test for overall effect: Z = 2.77 (P = 0.006)

### B

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>new HA</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>AFFIRM</td>
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<td>8</td>
<td>11.3%</td>
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<tr>
<td>COU-AA-301</td>
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<td>17.2%</td>
<td>2.27 [1.11, 4.62]</td>
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<tr>
<td>COU-AA-302</td>
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<td>23</td>
<td>23.8%</td>
<td>1.95 [1.20, 3.18]</td>
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<tr>
<td>ELM-PC 4</td>
<td>55</td>
<td>46</td>
<td>27.6%</td>
<td>1.17 [0.80, 1.72]</td>
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<tr>
<td>PREVAIL</td>
<td>24</td>
<td>18</td>
<td>20.2%</td>
<td>1.29 [0.71, 2.36]</td>
</tr>
</tbody>
</table>

Total (95% CI) 3788 2947 100.0% 1.35 [0.90, 2.03]

Total events 172 104

Heterogeneity: Tau² = 0.12; Chi² = 9.58, df = 4 (P = 0.05); I² = 58%

Test for overall effect: Z = 1.46 (P = 0.15)
Take home massage #1

• CVS disease and its risk factors are common among PC patients.
• Higher risk in more aggressive disease?
• Observational data suggest that the risk significantly increase with all forms of ADT.
How might ADT accelerate CVD?

CVS (atherosclerosis) risk factors

- Dysglycemia
- Central adiposity
- Dyslipidemia
- Changes in lifestyle

Cardiovascular event

Testosterone
FSH
GnRH
Est

Plaque vulnerability

Disrupted plaque with occlusive thrombus
FSH is a trophic hormone

Males: stimulates seminiferous to produce sperm
Females: stimulates granulosa cells in the ovarian follicle
Common: steroidogenesis, energy and metabolism, protein synthesis, cell division, growth and differentiation, calcium intake


1. Data source: www.biogps.org
What happens to FSH with different modes of castration?

- Orchiectomy: \(\uparrow\)
- GNRH analogues: \(\downarrow\) (~50%)/escape?
- GNRH antagonists: \(\downarrow\downarrow\) (90%)

*Dalkin AC, et al. Endocrinol 2001;142:139–46*
What happens to FSH with different modes of ADT?

- Orchietomy: \( \uparrow \)
- GNRH analogues: \( \downarrow (\sim 50\%)/\text{escape?} \)
- GNRH antagonists: \( \downarrow \downarrow (90\%) \)
FSH may facilitate pro-atherogenic risk factors and effect the development of CVS events

• Development of dysfunctional fat tissue

• Effects on atherosclerotic plaque stability
Lessons learnt from menopause

- Menopause occurs at an average age of 51 (range 44–59)
- Ovarian function declines before menopause (4–5 years) - reduced inhibin levels and increased FSH levels; Estrogen and progesterone levels maintained
- After the menopause, FSH levels rise 10-15-fold, with low estradiol

![Diagram showing depot distribution at different ages:](image-url)
Correlation between FSH levels and BMI in aging males and females

Males (n=414, age 61-65 yrs)

\[ \Delta \text{BMI} = \text{BMI (present)} - \text{BMI (age 35-45)} \]

Females (n=499, age 51-55 yrs)

\[ \Delta \text{BMI} = \text{BMI (post-menapausal)} - \text{BMI (pre-menapausal)} \]

\[ R^2 = 0.3062 \ (P < 0.0001) \]

\[ R^2 = 0.4972 \ (P < 0.0001) \]

FSH induces adipogenesis \textit{in vitro}

\[ \text{Zaereba et al 2015} \]
GnRH antagonist associates with less adiposity and reduced characteristics of metabolic syndrome and atherosclerosis compared with orchiectomy and GnRH agonist in a preclinical mouse model

Sarah N. Hopmans, M.Sc. a,1, Wilhelmina C.M. Duivenvoorden, Ph.D. a,1, Geoff H. Werstuck, Ph.D. b,c, Laurence Klotz, M.D. d, Jehonathan H. Pinthus, M.D., Ph.D. a,*

- Control (sham surgery + vehicle)
- Bilateral orchiectomy (+ vehicle)
- GnRH-agonist, leuprolide (+ sham surgery)
- GnRH-antagonist, degarelix (+ sham surgery)
ADT induced obesity

N = 6 per group

ADT induced glucose intolerance

Fig. 7. (A) Blood glucose and (B) glucose tolerance measured after overnight fasting of LDLR<sup>−/−</sup> mice receiving different modes of ADT (n = 9–13/group) at 14 weeks. Data shown represent mean ± SEM. 

<sup>a</sup><sub>P < 0.05</sub> vs. control;  

<sup>b</sup><sub>P < 0.05</sub> vs. orchietomy;  

<sup>c</sup><sub>P < 0.05</sub> vs. leuprolide.

The effect of ADT on the development of atherosclerotic plaques in mice

• Mice are relatively atheroprotected (High HDL).

• In-order to induce atherosclerosis one needs to manipulate lipoproteins (Apo E-/-, LDLr-/-) and stimulate with high fat diet.

ADT an atheroogenenic (enough) stimulus
ADT induced (de-novo) atherosclerosis

Fig. 8. (A) Aortic atherosclerotic plaque area in LDLR⁻/⁻ mice receiving different modes of ADT ($n = 9-13$ group) at 4 months calculated as percentage of plaque and necrotic plaque area of aortic tissue. Data shown represent mean ± SEM. $^a$ $P < 0.05$ vs. control; $^b$ $P < 0.05$ vs. orchietomy; $^c$ $P < 0.05$ vs. leuprolide. (B) Representative images of H&E-stained sections. The width of the lesions is indicated. Magnification $\times 600$. Bar = 100 $\mu$m. H&E = hematoxylin and eosin. (Color version of figure is available online.)
So,
in subjects without pre established atherosclerosis (CVD)
ADT induces risk factors for CVD (over and above those that are associated with PC) and thus atherosclerosis

- Adiposity and dysfunctional fat
- Dysglycemia
- Dyslipidemia
- Hypertension

**Mode specific extent:**
Orchiectomy $\geq$ GnRH agonists $> \text{GnRH antagonists}$
But, in subjects with established atherosclerosis (CVD) ... 

ADT induced plaque instability hence CVS events
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

Fig 2. Hazard ratios at selected time intervals since the start of androgen-deprivation therapy for first cardiovascular disease (CVD) event in men with differing baseline CVD over duration of (A) gonadotropin-releasing hormone (GnRH) agonist, (B) antiandrogen (AA) therapy, and (C) surgical orchietomy versus the comparison cohort.
Plaque rupture
ADT induced (de-novo) atherosclerosis

Fig. 8. (A) Aortic atherosclerotic plaque area in LDLR−/− mice receiving different modes of ADT (n = 9–13/group) at 4 months calculated as percentage of plaque and necrotic plaque area of aortic tissue. Data shown represent mean ± SEM. a P < 0.05 vs. control; b P < 0.05 vs. orchiectomy; c P < 0.05 vs. leuprolide. (B) Representative images of H&E-stained sections. The width of the lesions is indicated. Magnification ×600. Bar = 100 μm. H&E = hematoxylin and eosin. (Color version of figure is available online.)
GnRH-receptor agonists induce necrosis in pre-established atherosclerotic plaques

Untreated

Degarelix

Leuprolide
Among men with prior CVD, the 1-year event risk with GnRH antagonist was reduced compared with GnRH agonist.

Effects of ADT on macrophage plasticity in atherosclerosis

**M1 macrophages**
- Classically activated
- Pro-inflammatory, pro-atherogenic
- Cause tissue injury and promote lesion development as well as enhance plaque vulnerability

**M2 macrophages**
- Alternatively activated
- Anti-inflammatory, athero-protective
  - M2a: involved in tissue repair and can stabilize vulnerable plaques
  - M2b and M2c: regulatory and anti-inflammatory and stabilize or even regress atherosclerotic plaques

**Mannose Receptor (anti-inflammatory M2 macrophages)**

**Mac3-IHC of atherosclerotic plaque in hearts of ADT mice**

**Graph:**
- MR-positive area (% of total plaque)
- Leuprolide: 0.005
- Degarelix: 0.01
An increase in macrophage content is seen in plaques from mice treated with a GnRH-R agonist.
Foam cells play a significant role in plaque progression and instability.

Jan Steffel et al. Circulation. 2006;113:722-731
GnRH agonist

GnRH antagonists

Monocyte

Increased RANK

GnRH receptors

T Cell

Th1 Cell

Secrete RANKL

IFN-γ

TNFα

Chronic Inflammation

Plaque Instability

Rupture

Platelets

Platelet Activation

Clot fragmentation

Lumen

Osteoclast

Macrophage

Reduced collagen synthesis

Collagenases

Thromboembolic Event

Atherosclerotic Plaque
Take home massages (#2)

- ADT induce obesity, metabolic syndrome and atherosclerosis (CVD) to a mode specific extent.

- FSH levels may have a role in this effect.

- In patients with pre-existing atherosclerosis ADT may induce plaque instability (changes in macrophage plasticity?, calcium deposition and tear? plaque hemorrhage?)

- Opportunity for selection of more “cardio-friendly” ADT?
Role of Androgen Deprivation Therapy In Cardiovascular Disease – A Longitudinal Prostate Cancer

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institution</th>
<th>Project Title</th>
<th>Funded Amount</th>
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<td>Jehonathan Pinthus</td>
<td>McMaster University</td>
<td>Role of androgen deprivation therapy in cardiovascular disease - a longitudinal prostate cancer study (RADICAL PC)</td>
<td>$3,449,136</td>
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The Role of Androgen Deprivation Therapy in Cardiovascular Disease – A Longitudinal Prostate Cancer Study (RADICAL PC1) – prospective cohort study

A Randomized Intervention for Cardiovascular And Lifestyle Risk Factors in Prostate Cancer Patients (RADICAL PC2) – prospective randomized controlled (prevention) trial
RADICAL PC1 - Objectives

• To determine in a representative, contemporary sample of men with PC (and in particular men treated with ADT):  
  a) the prevalence of CVD risk factors and disease, and  
  b) the incidence of adverse CVD events  
• To evaluate the relationship of ADT with adverse CVD events  
• To identify factors (clinical factors and PC treatments) that are independently associated with the development of CVD in men with PC, and in particular in men treated with ADT
Allow to clot at room temperature for ~30 minutes

Transfer serum from tube evenly into each of 8 cryovials (~1.0 mL ea.)

Carefully draw EDTA plasma off cells & transfer into 1 cryovial

Transfer 1.8 ml of urine to each vial (4)

Transfer 1.8 ml of whole blood into each vial (2)

Centrifuge

Transfer respun plasma from evenly into each of 2 cryovials (~1.0 mL ea.)

Buffy coat, Genetics

Cryovials should be placed in the freezer boxes provided and frozen within 2 hours of collection if possible. Collection tubes are discarded after completion of processing.

R&D

Coagulation
Mega bio-bank

- Blood
- Urine
- DNA
- CVS markers (HSTP, Pro-BNP)
- Renal markers (Cystatin C)
- Metabolic markers (adipokines, inflammatory markers)
- Coagulation markers
VISION Study

- 15,133 patients undergoing non-cardiac surgery
- Troponin measured 6-12 hours, 1, 2, and 3 days post-op

Kaplan-Meier Estimates of 30-Day Mortality Based on Peak Troponin T Values

<table>
<thead>
<tr>
<th>Peak troponin T, ng/mL</th>
<th>No. at risk</th>
<th>Cumulative Hazard</th>
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<tbody>
<tr>
<td>≥0.30</td>
<td>142</td>
<td>0.00</td>
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<tr>
<td>0.03-0.29</td>
<td>1121</td>
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<tr>
<td>0.02</td>
<td>494</td>
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</tr>
<tr>
<td>≤0.01</td>
<td>13376</td>
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</tbody>
</table>

RADICAL PC2 - Objectives

Primary
To determine whether a systematic CV and lifestyle risk factor modification strategy reduces the risk of CVD in men with a new diagnosis of PC or who are commencing ADT

Secondary
In men with a new diagnosis of PC or who are commencing ADT:
• To determine whether a systematic CV and lifestyle risk factor modification strategy improves the CV risk profile
• To estimate the incremental cost-effectiveness ratio of a systematic CV and lifestyle risk factor modification strategy
New prostate cancer (diagnosed within 1 year) or commencing ADT for the 1st time
N=6000

RADICAL PC1
Observational registry
N=1884

RADICAL PC2
Randomized, controlled trial
N=4116

Intervention:
Systematic CV risk factor management
N=2058

Control:
Usual care
N=2058

Clinical outcomes (N=6000) at average 3 years’ follow-up
<table>
<thead>
<tr>
<th>Study procedure</th>
<th>Baseline visit</th>
<th>3-month phone*</th>
<th>6-month phone*</th>
<th>12-month visit</th>
<th>18-month phone*</th>
<th>24-month visit</th>
<th>Close-out visit</th>
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Outcomes

Co-primary efficacy outcomes:

• Composite of cardiovascular death, myocardial infarction, stroke, heart failure, or arterial revascularization

• Composite of cardiovascular death, myocardial infarction, stroke, or heart failure
Power Calculation

RADICAL PC1
N=6000 has 90% power to detect hazard ratio as large as 0.86, assuming 30% primary outcome event rate and 5% loss-to-follow-up

RADICAL PC2
N=4116, experiencing 434 primary outcome events will have 85% power to detect hazard ratio of 0.75 in intervention group, assuming 30% drop-in, 15% drop-out, 5% loss-to-follow-up
Significance of Findings

• First prospective cohort study of PC/ADT with defined CVD end points
• Potential discovery of risk stratification methods
• Large biobank
Thanks to

Geoff Werstuck, PhD

Helga Duivenvoorden, PhD

Sarah Hopmans, MSc