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

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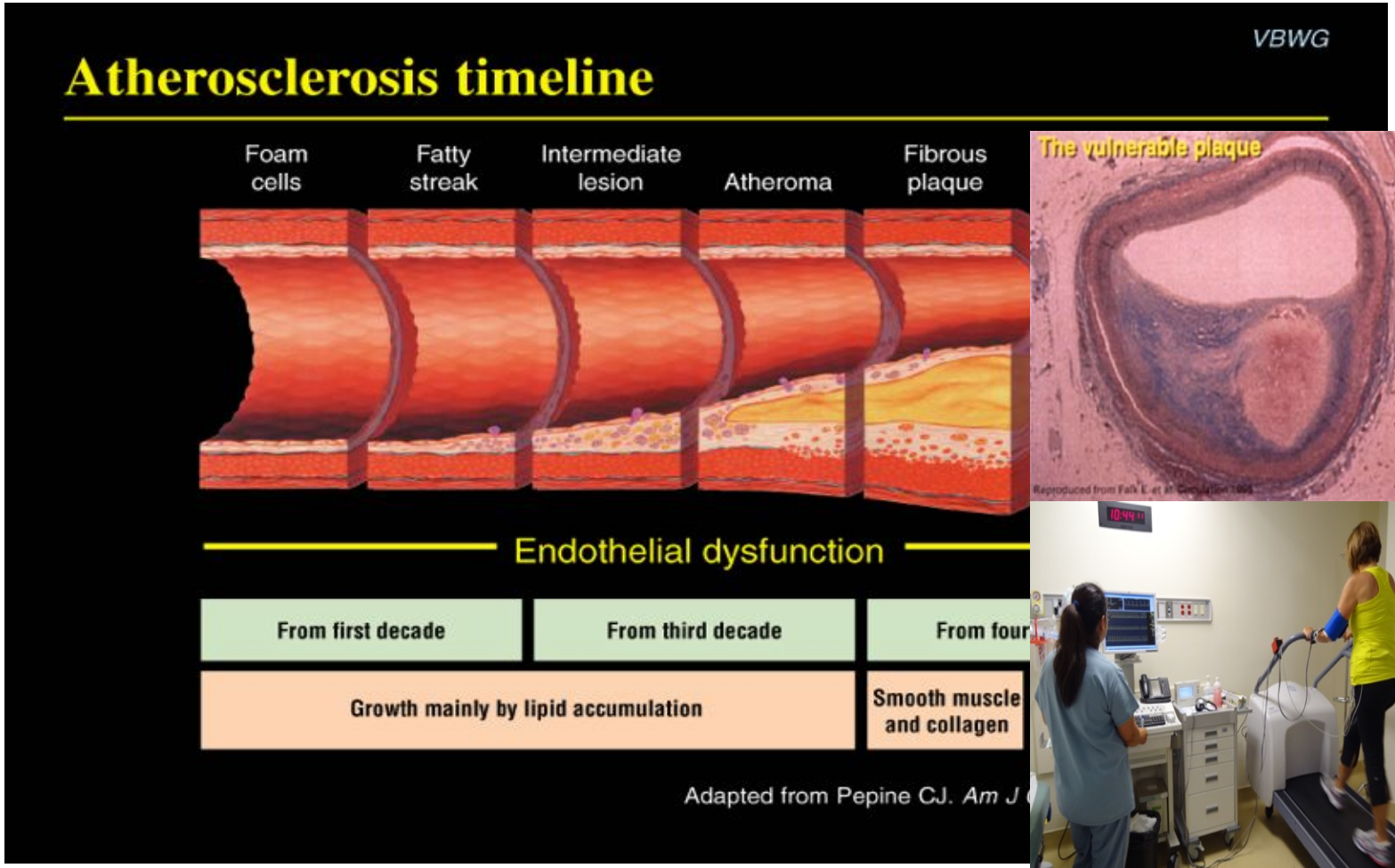
# Faculty/presenter disclosure

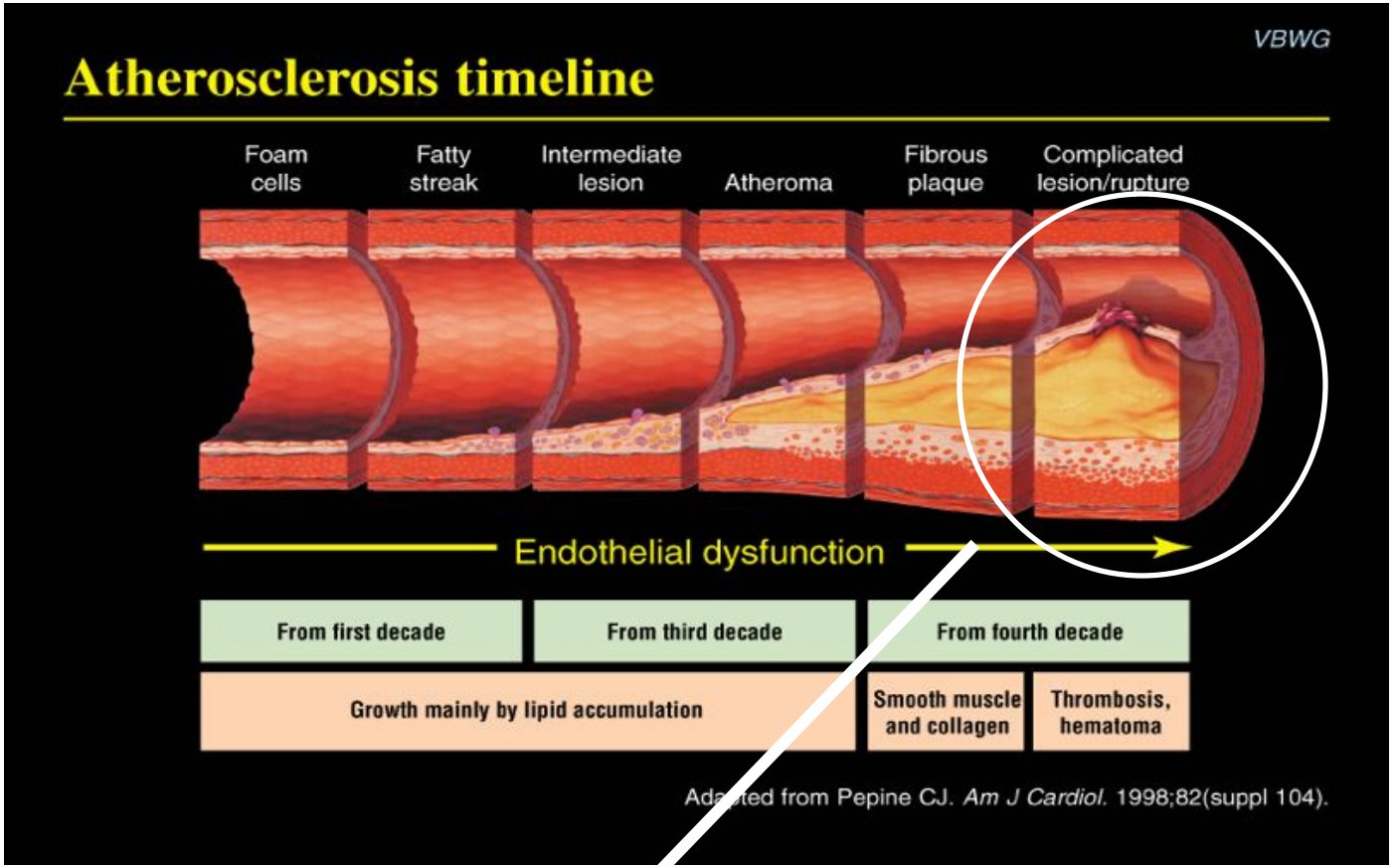
- Faculty: Jehonathan H. Pinthus MD, Ph.D.

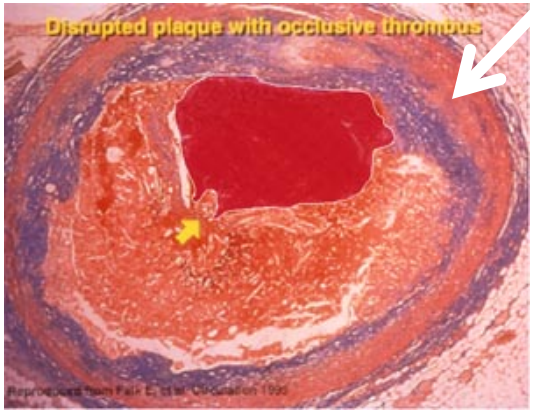
- Relationships with commercial interests:
  - Grants/Research Support: Ferring Inc.
  - Consulting Fees: Ferring Inc.

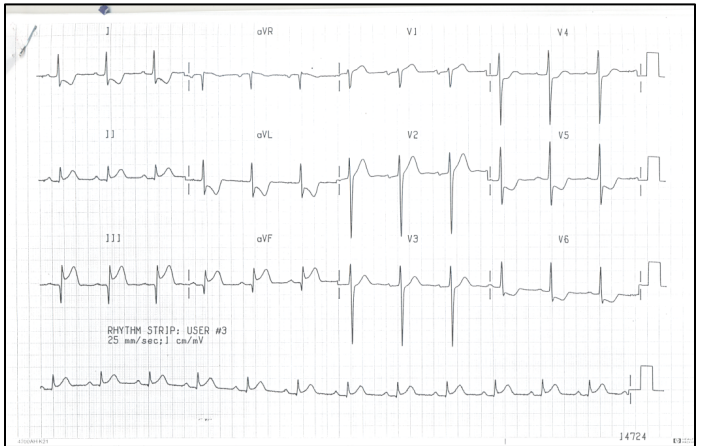
# Stable coronary artery disease



# Acute/ unstable coronary artery disease



# 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

Greenland *et al.* 2010 American Heart Association Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults. C*irculation* 2010; 122: e584

American Heart Association

# US Veterans with Locoregional PC

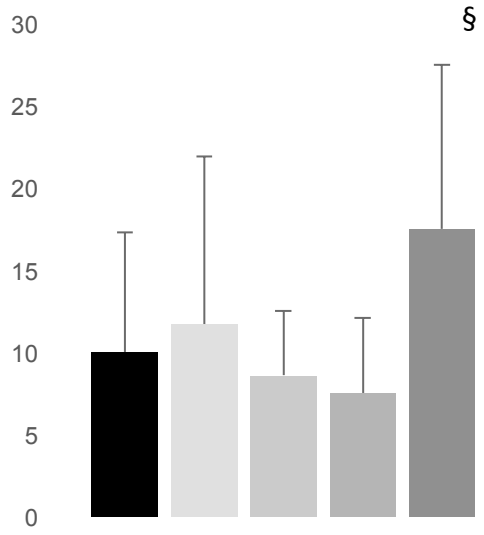
Incidence of CVD (% per year)

| Treatment | Coronary heart disease | MI | Sudden Cardiac Death | Stroke |
|---|---|---|---|---|
| No ADT | 8.1 | 0.73 | 1.15 | 1.08 |

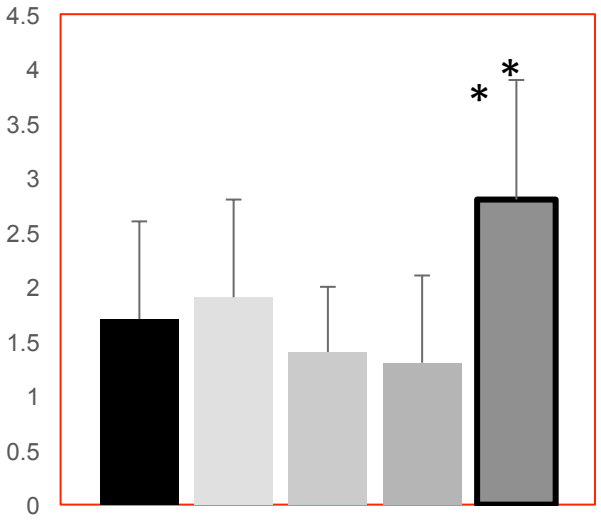
**Prostate cancer is a diagnosis that is associated with a high subsequent risk of cardiovascular disease**

Keating, *et al. JNCI* 2010; 102: 39

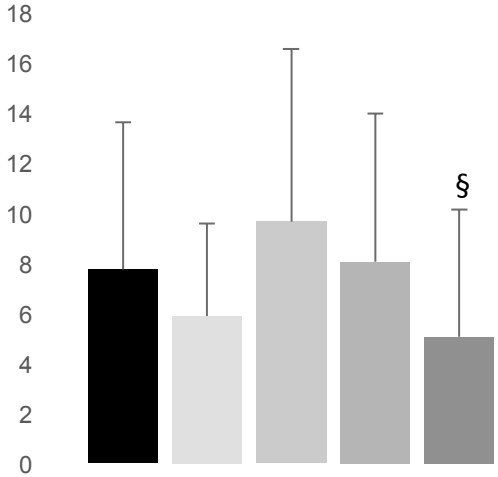
# Comprehensive prospective metabolic, antrophometric, nutritional and physical profiling of prostate cancer patients



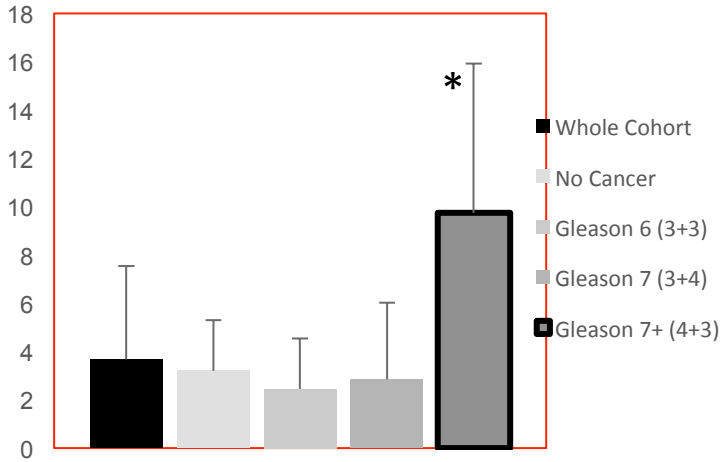

**Fasting Insulin (uIU/mL)**




**Fasting C-Peptide (ng/mL)**




**Adiponectin (pg/mL)**




**Letpin: Adiponectin Ratio (AU)**

***Di Sebastiano et al in preparation***

# PC patients are at high risk of CVD

- Risk of MI, stroke, or CV death in PC patients >2% per year[1, 2]
- Risk of MI, stroke, or CV death in PC patients on ADT >4% per year[1, 2]
- CVD risk considered high if global risk estimate for hard CVD events of ≥2% per year[3]


1. Keating, *et al. JNCI* 2010; 102: 39
2. O'Farrell, *et al. JCO* 2015; 102: 39
3. Greenland *et al.* 2010 American Heart Association Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults. C*irculation* 2010; 122: e584

# US Veterans with Locoregional PC

Incidence of CVD (% per year)

| Treatment | Coronary heart disease | MI | Sudden Cardiac Death | Stroke |
|---|---|---|---|---|
| No ADT | 8.1 | 0.73 | 1.15 | 1.08 |
| GnRH agonist | 14.4 | 1.28 | 2.16 | 1.85 |

Keating, *et al. JNCI* 2010; 102: 39

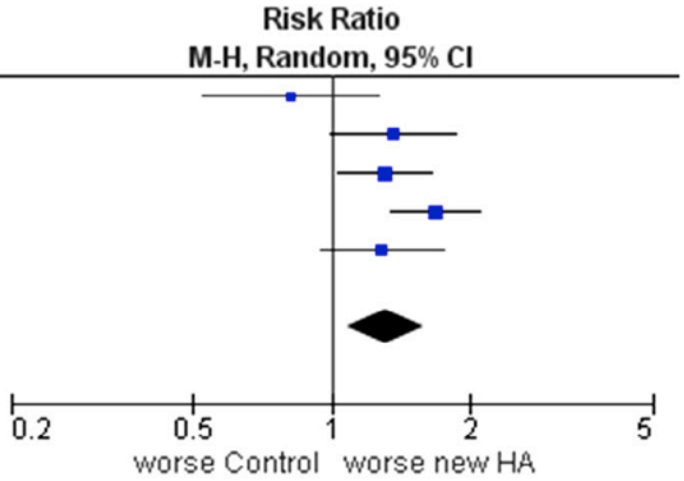
# Novel ADT agents

**A**

| Study or Subgroup | new HA Events | new HA Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| AFFIRM | 49 | 800 | 30 | 399 | 12.9% | 0.81 [0.53, 1.26] |
| COU-AA-301 | 126 | 791 | 46 | 394 | 18.9% | 1.36 [1.00, 1.87] |
| COU-AA-302 | 126 | 542 | 96 | 540 | 23.9% | 1.31 [1.03, 1.66] |
| ELM-PC 4 | 172 | 784 | 100 | 770 | 24.8% | 1.69 [1.35, 2.12] |
| PREVAIL | 88 | 871 | 66 | 844 | 19.5% | 1.29 [0.95, 1.75] |
| **Total (95% CI)** | | **3788** | | **2947** | **100.0%** | **1.32 [1.08, 1.60]** |
| Total events | 561 | | 338 | | | |

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 9.01$, df = 4 (P = 0.06); $I^2 = 56\%$

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

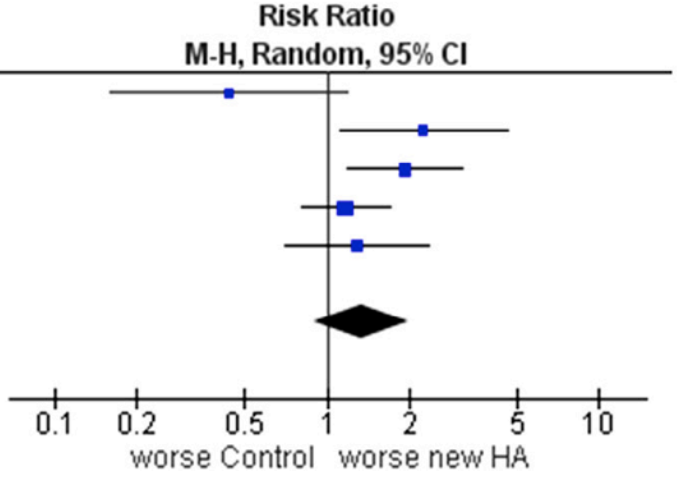



**B**

| Study or Subgroup | new HA Events | new HA Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| AFFIRM | 7 | 800 | 8 | 399 | 11.3% | 0.44 [0.16, 1.19] |
| COU-AA-301 | 41 | 791 | 9 | 394 | 17.2% | 2.27 [1.11, 4.62] |
| COU-AA-302 | 45 | 542 | 23 | 540 | 23.8% | 1.95 [1.20, 3.18] |
| ELM-PC 4 | 55 | 784 | 46 | 770 | 27.6% | 1.17 [0.80, 1.72] |
| PREVAIL | 24 | 871 | 18 | 844 | 20.2% | 1.29 [0.71, 2.36] |
| **Total (95% CI)** | | **3788** | | **2947** | **100.0%** | **1.35 [0.90, 2.03]** |
| Total events | 172 | | 104 | | | |

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 9.58$, df = 4 (P = 0.05); $I^2 = 58\%$

Test for overall effect: Z = 1.46 (P = 0.15)

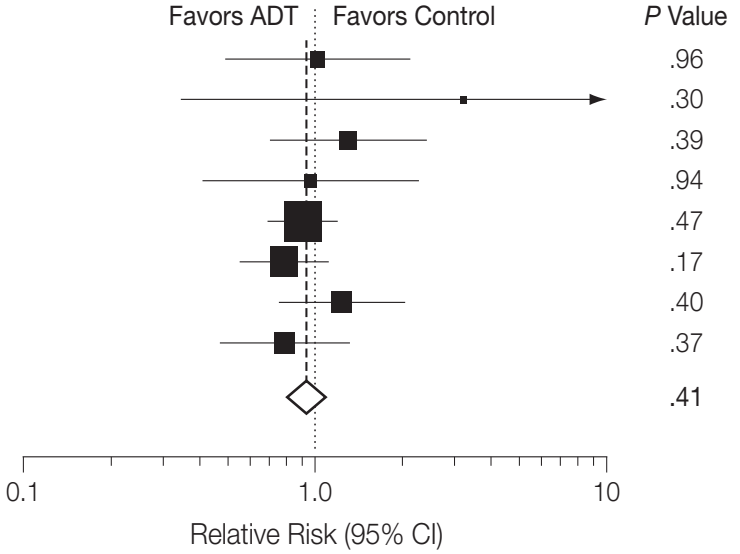



*Iacovelli R et al European Journal of Cancer 2015*

# Randomized Trials of ADT vs. Control: CV Mortality

| Source | No./Total No. of Events: ADT | No./Total No. of Events: Control | Relative Risk (95% CI) | *P* Value |
|---|---|---|---|---|
| D'Amico et al,[3] 2008 (DFCI 95-096) | 13/102 | 13/104 | 1.02 (0.50-2.09) | .96 |
| Messing et al,[12] 2006 (ECOG/EST 3886) | 3/47 | 1/51 | 3.26 (0.35-30.2) | .30 |
| Bolla et al,[13] 2010 (EORTC 22863) | 22/207 | 17/208 | 1.30 (0.71-2.38) | .39 |
| Schröder et al,[14] 2009 (EORTC 30846) | 10/119 | 10/115 | 0.97 (0.42-2.23) | .94 |
| Studer et al,[15] 2006 (EORTC 30891) | 88/492 | 97/493 | 0.91 (0.70-1.18) | .47 |
| Efstathiou et al,[8] 2009 (RTOG 85-31) | 52/477 | 65/468 | 0.78 (0.56-1.10) | .17 |
| Roach et al,[9] 2008 (RTOG 86-10) | 31/224 | 26/232 | 1.23 (0.76-2.01) | .40 |
| Denham et al,[16] 2011 (TROG 96.01) | 36/532 | 23/270 | 0.79 (0.48-1.31) | .37 |
| **Overall** | **255/2200** | **252/1941** | **0.93 (0.79-1.10)** | **.41** |

Test for heterogeneity: $Q = 5.12$; $P = .64$; $I^2 = 0\%$




Nguyen, *et al. JAMA* 306: 2359.

# 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 life style

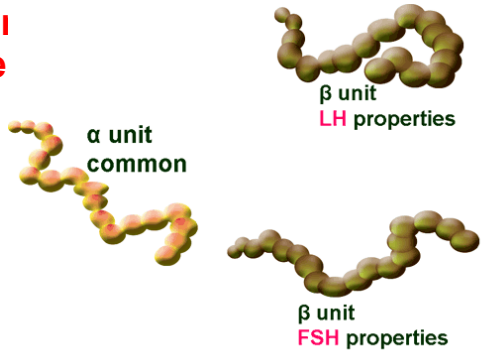

Testosterone
**FSH**
GnRH
Est

→ **Plaque vulnerability** →

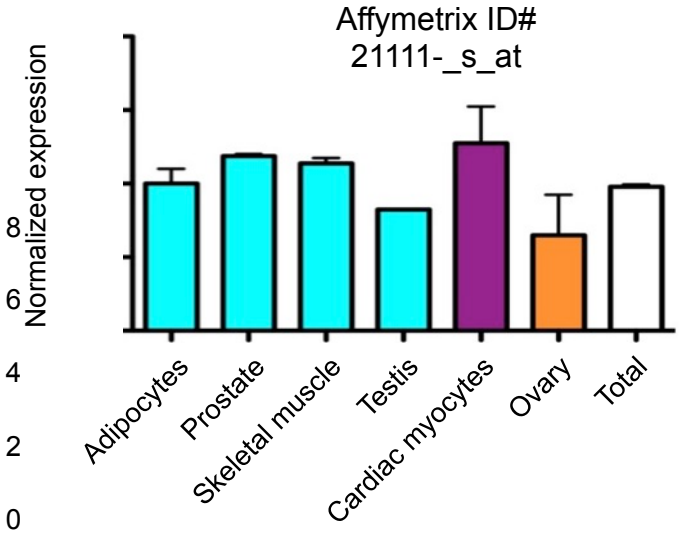
Cardiovascular event

# FSH is a trophic hormone

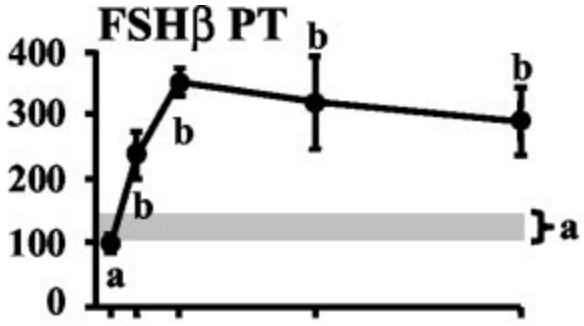
Males: stimulates seminiferous to produce sperm
Females: stimulates granulosa cells in the ovarian follicle
Common: **steroidogenesis, energy and metabolism, protein synthesis, cell division, gl and differentiation, calcium intake**

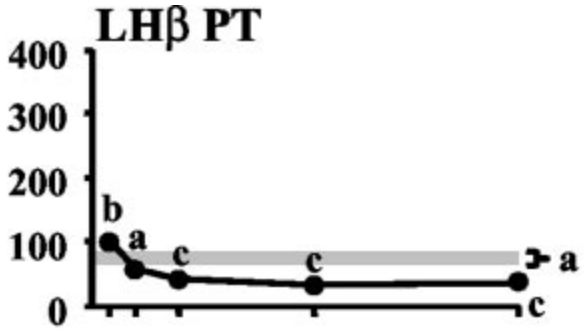



**Follicle-stimulating hormone receptor**
**Gene/RefSeq[2]:**
**FSHR (NP_000136)**




FSHR expression in different tissue



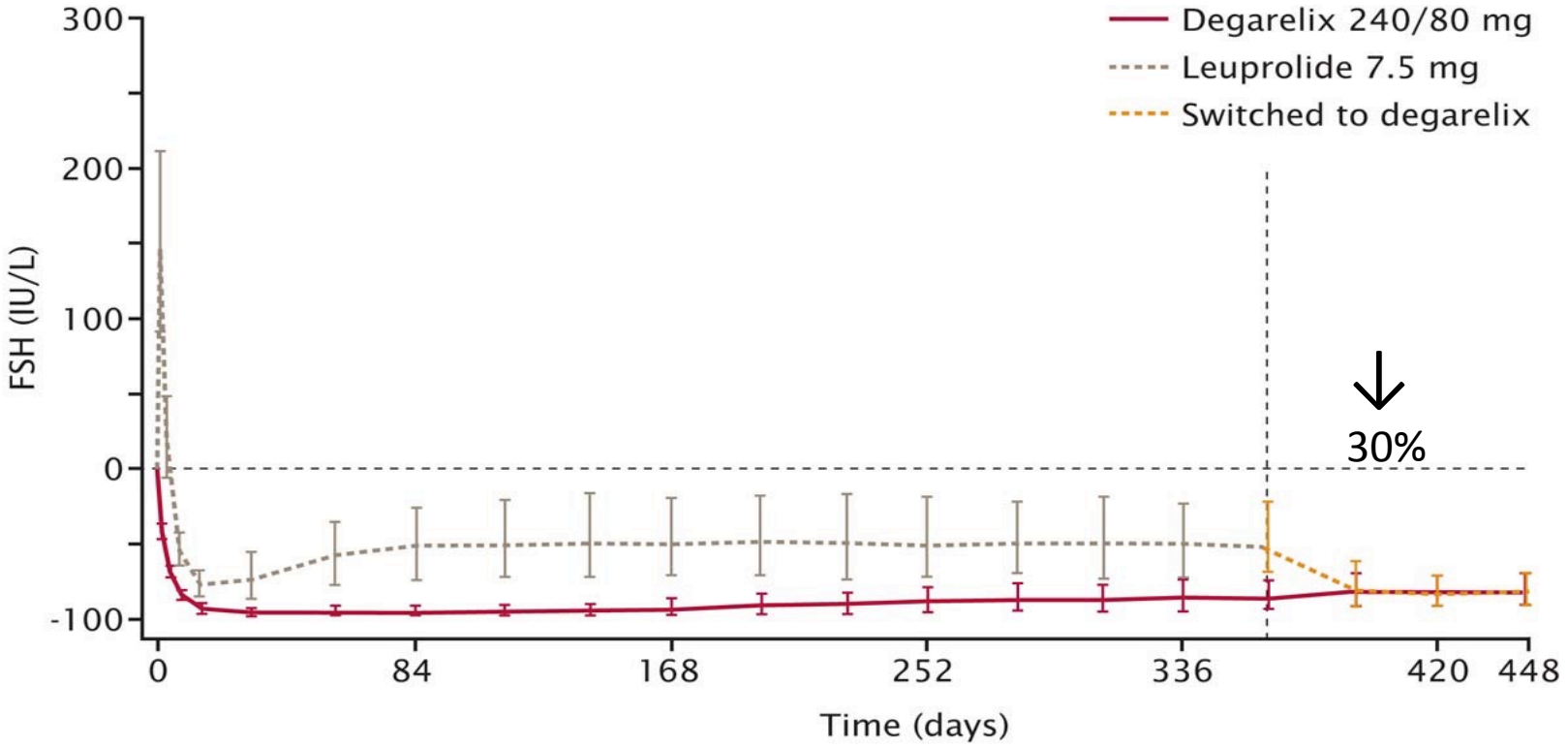




*Dalkin AC, et al. Endocrinol 2001;142:139–46*

1. Data source: www.biogps.org
2. Tivesten A, Pinthus J et al. Submitted 2014

# What happens to FSH with different modes of ADT?

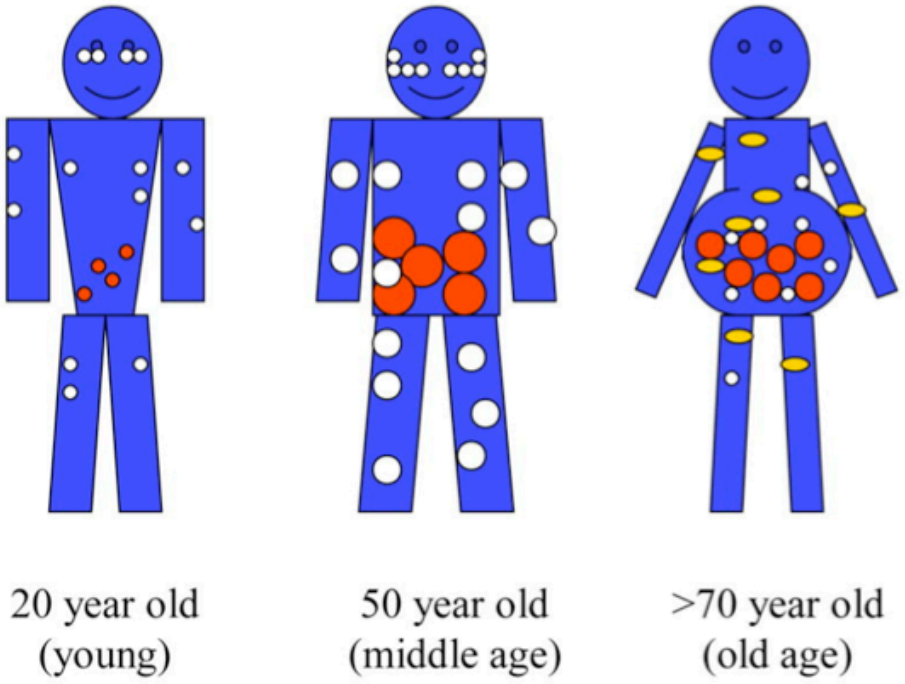
- Orchiectomy: ↑
- GNRH analogues: ↓ (~50%)/escape?
- GNRH antagonists: ↓↓ (90%)



# 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

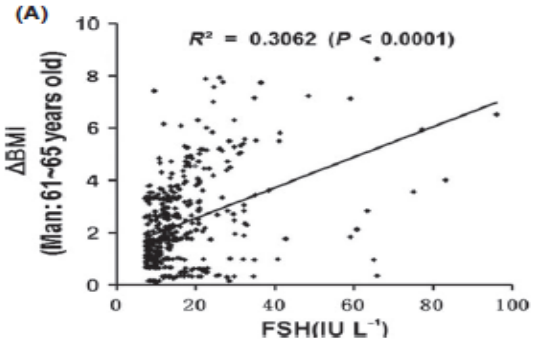



- Menopause occurs at an average age of 51
(range 44–59)
- Ovarian function declines before menopause (4–5 years) - reduced inhibin levels and increased FSH levels; Estrogen and progesterone levels maintained
- After the menopause, FSH levels rise 10-15-fold, with low estradiol

Burger HG. Eur J Endrorinol 1994;130:38–42

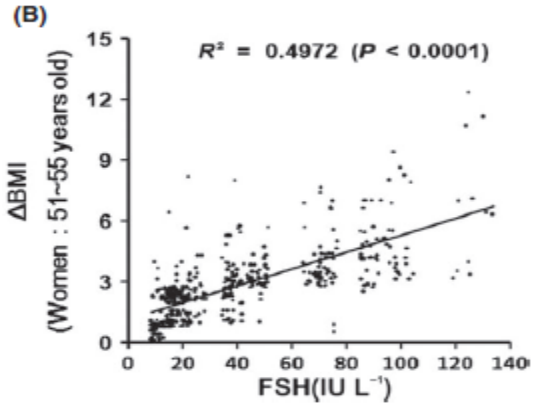
# Correlation between FSH levels and BMI in aging males and females

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




Δ BMI= BMI (present) – BMI (age 35-45)

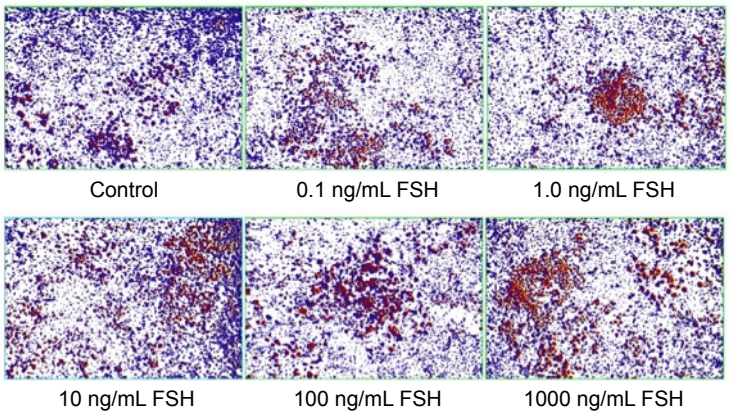
## Females (n=499, age 51-55 yrs)

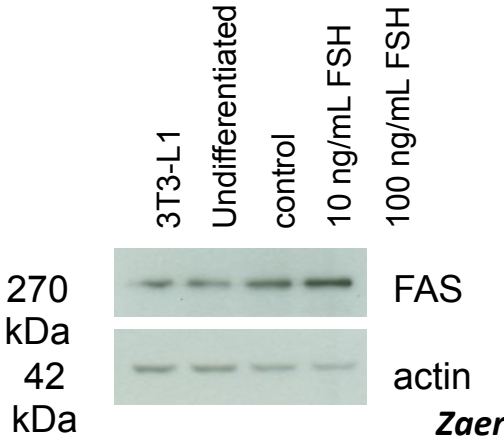



Δ BMI= BMI (post-menapausal) – BMI (pre-menapausal)

***Liu et al 2015***

# FSH induces adipogenesis *in vitro*




***Zaereba et al 2015***

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ELSEVIER

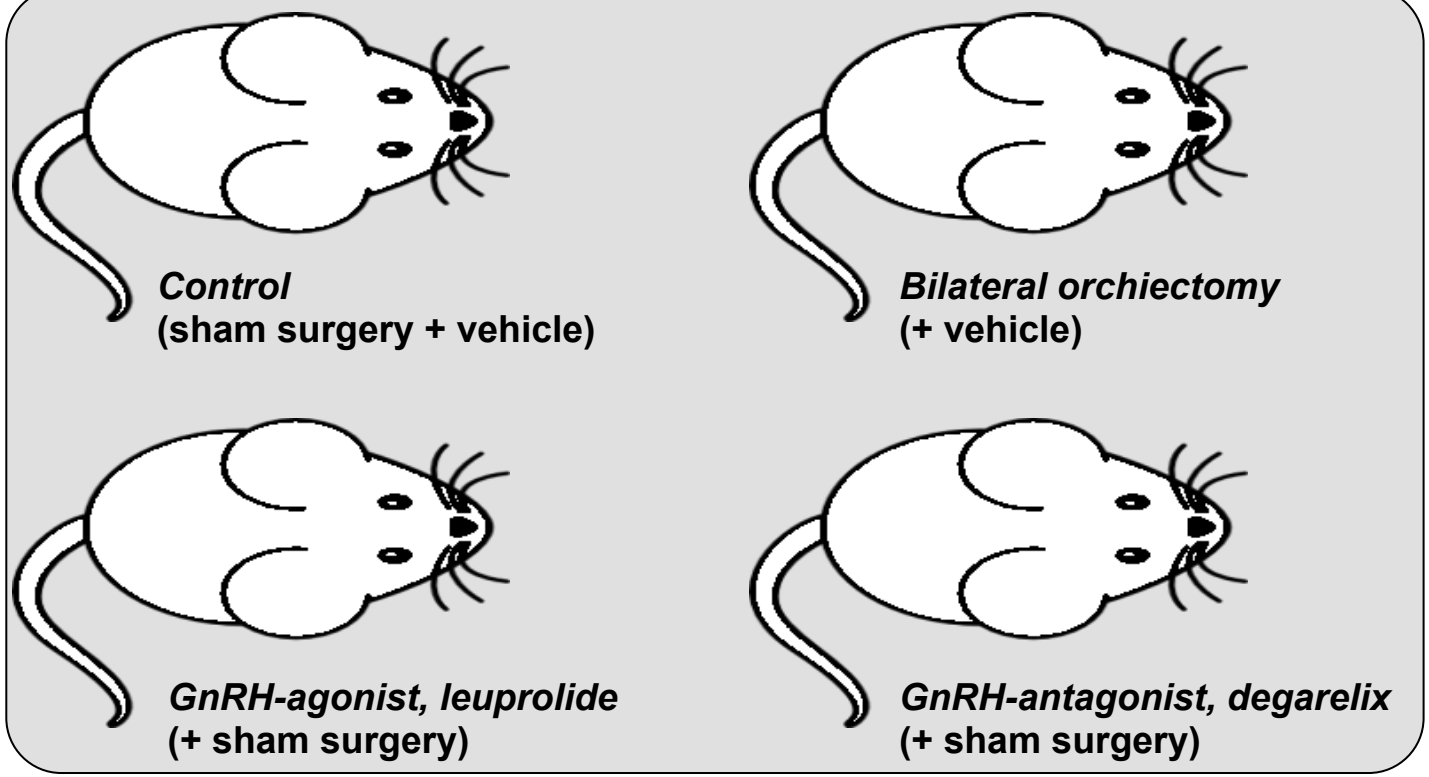
Urologic Oncology: Seminars and Original Investigations ▮ (2014) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

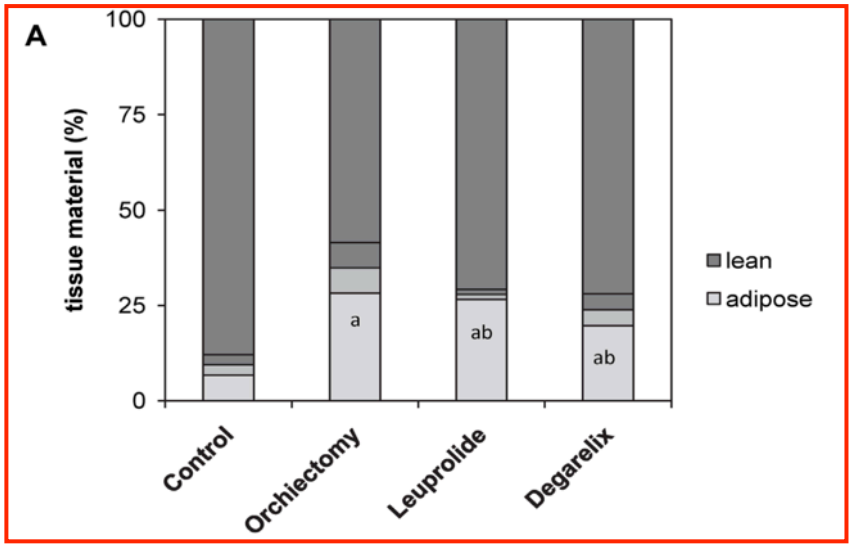
Original article

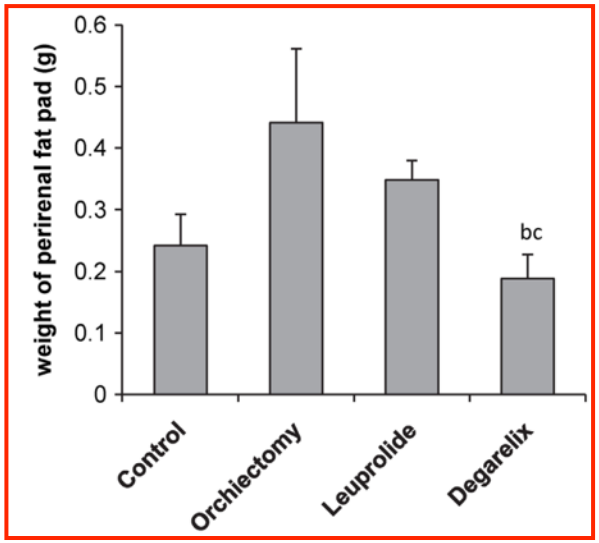
# GnRH antagonist associates with less adiposity and reduced characteristics of metabolic syndrome and atherosclerosis compared with orchiectomy and GnRH agonist in a preclinical mouse model

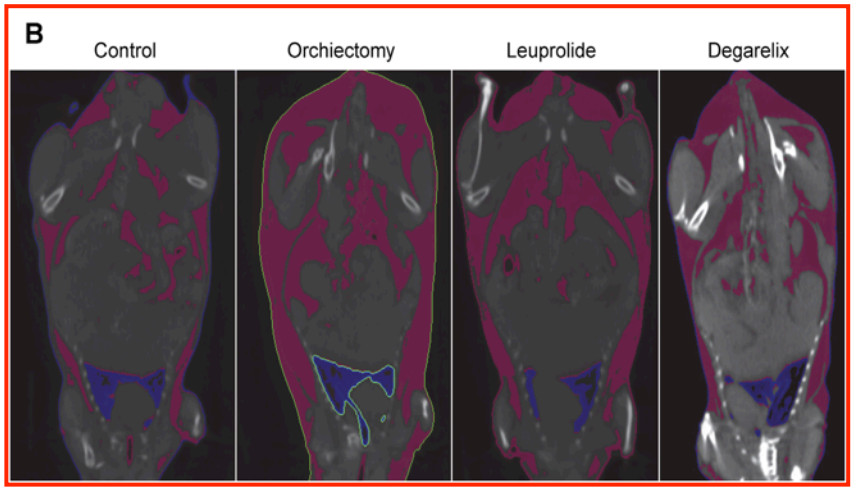
Sarah N. Hopmans, M.Sc.[a,1], Wilhelmina C.M. Duivenvoorden, Ph.D.[a,1], Geoff H. Werstuck, Ph.D.[b,c], Laurence Klotz, M.D.[d], Jehonathan H. Pinthus, M.D., Ph.D.[a,*]

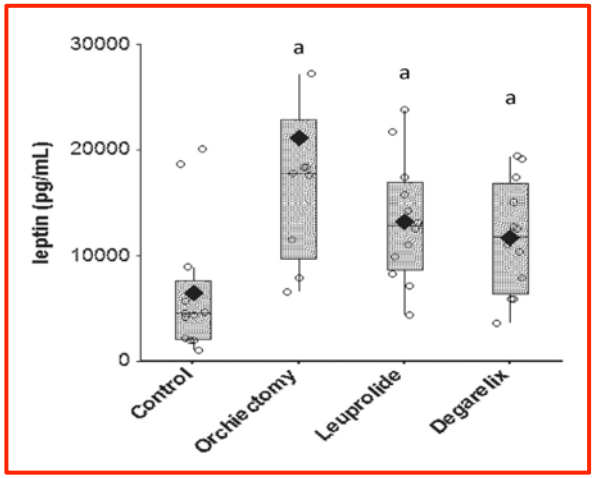


# ADT induced obesity



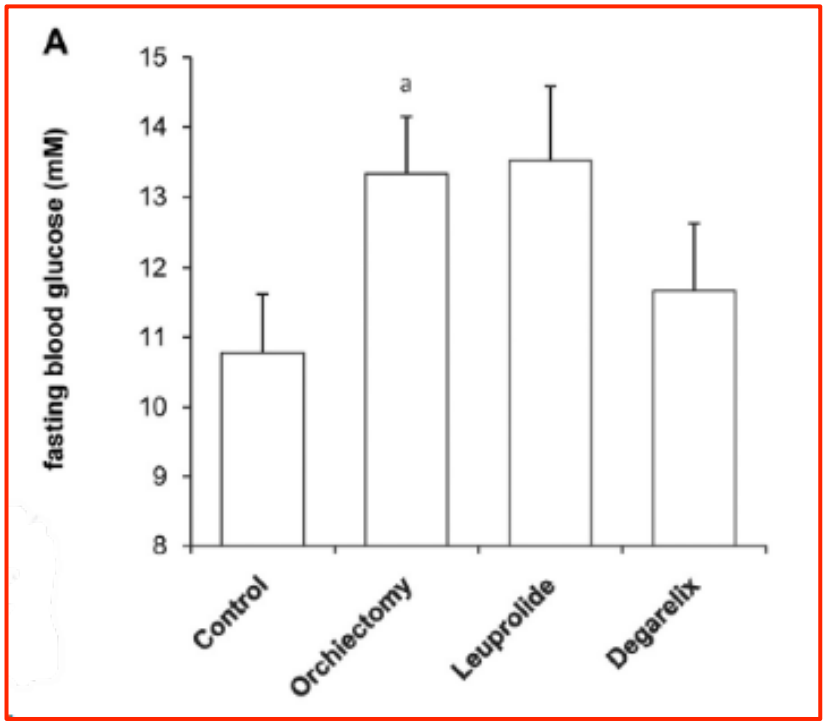




N = 6 per group

Hopmans SN, et al. Urol Oncol 2014;32:1126–34

# ADT induced glucose intolerance



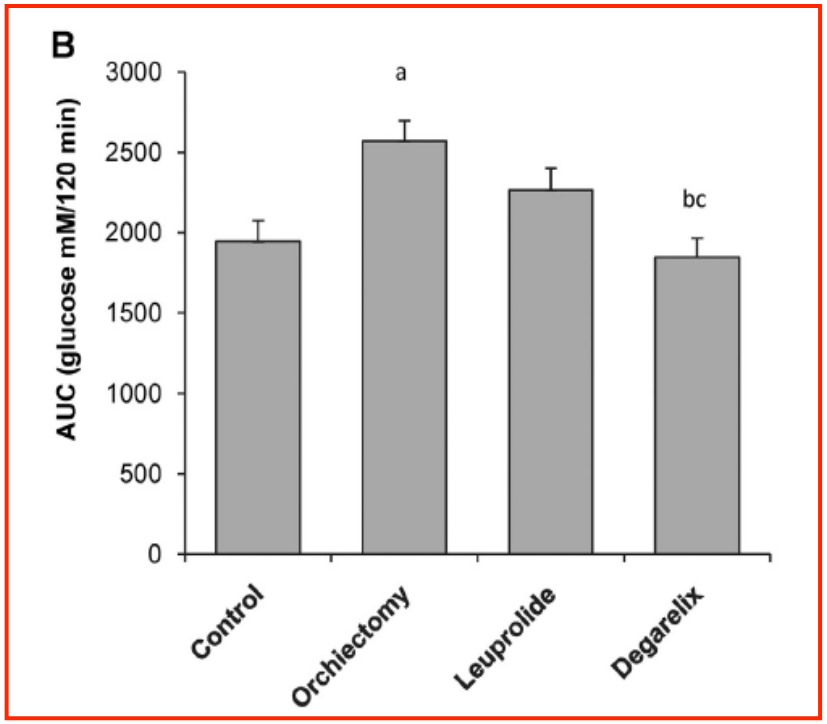




Fig. 7. (A) Blood glucose and (B) glucose tolerance measured after overnight fasting of LDLR$^{-/-}$ mice receiving different modes of ADT ($n$ = 9–13/group) at 14 weeks. Data shown represent mean ± SEM. $^{a}P < 0.05$ vs. control; $^{b}P < 0.05$ vs. orchiectomy; $^{c}P < 0.05$ vs. leuprolide.

Hopmans SN, et al. Urol Oncol 2014;32:1126–34

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

- Mice are relatively atheroprtected (High HDL).
- In-order to induce atherosclerosis one needs to manipulate lipoproteins (Apo E-/- , LDLr-/-) and stimulate with high fat diet.

**ADT an atheroogenic (enough) stimulus**

# ADT induced (de-novo) atherosclerosis

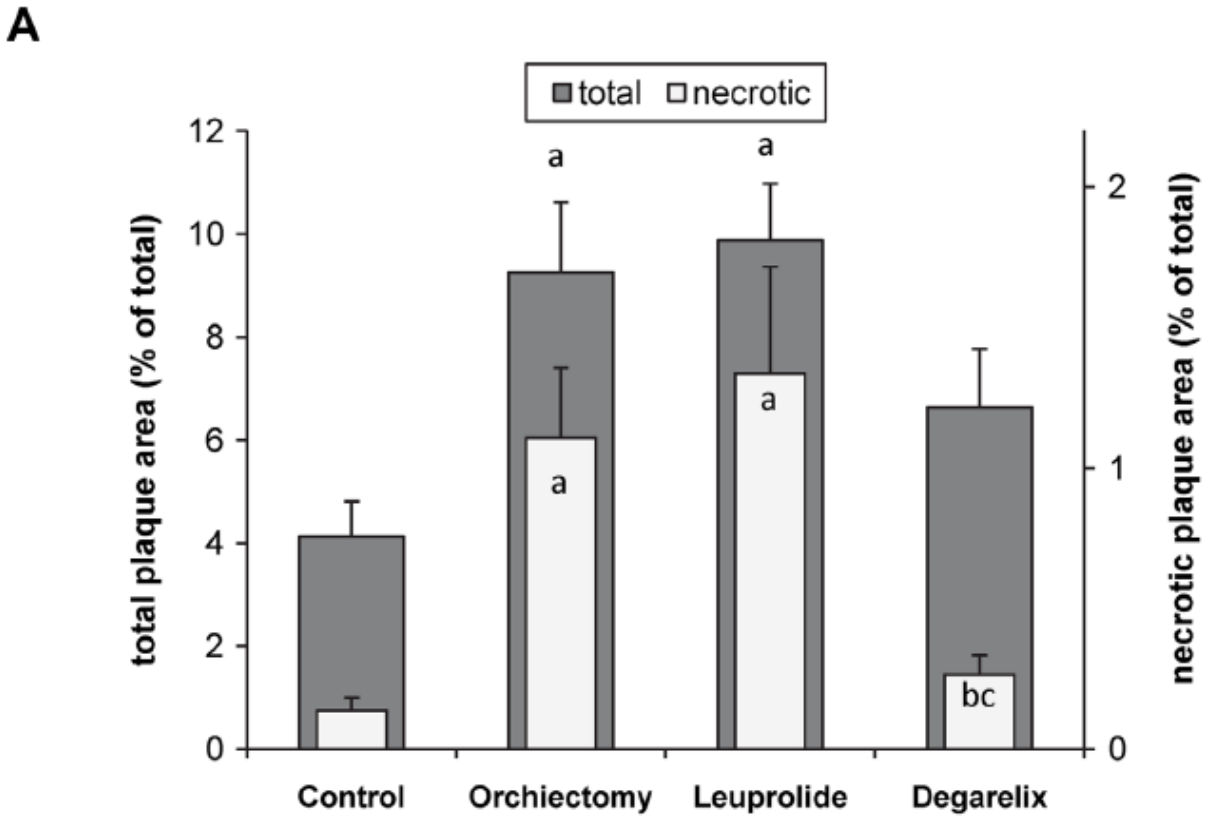



Fig. 8. (A) Aortic atherosclerotic plaque area in LDLR$^{-/-}$ mice receiving different modes of ADT ($n$ = 9–13/group) at 4 months calculated as percentage of plaque and necrotic plaque area of aortic tissue. Data shown represent mean ± SEM. [a] $P < 0.05$ vs. control; [b] $P < 0.05$ vs. orchiectomy; [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.)

Hopmans SN, et al. Urol Oncol 2014;32:1126–34

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 >/= GnRH angonists > GnRH antagonists

**But,**

**in subjects with established atherosclerosis (CVD) …**

**ADT induced plaque instability hence CVS events**

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# 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*

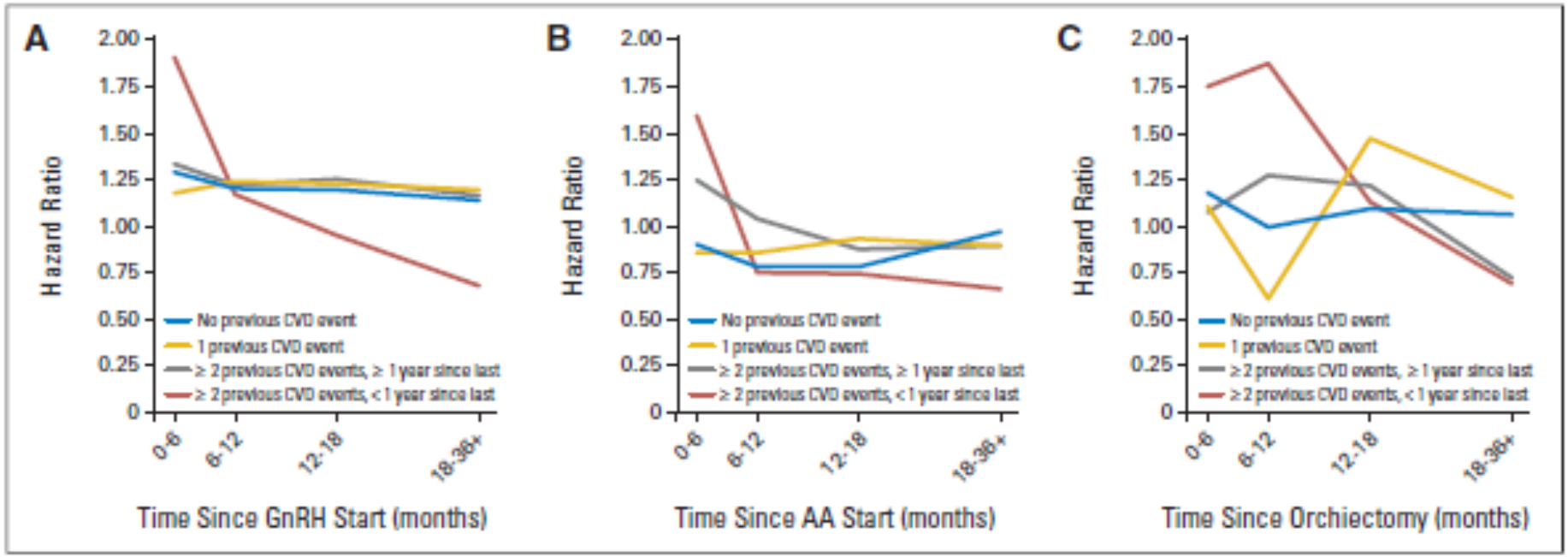
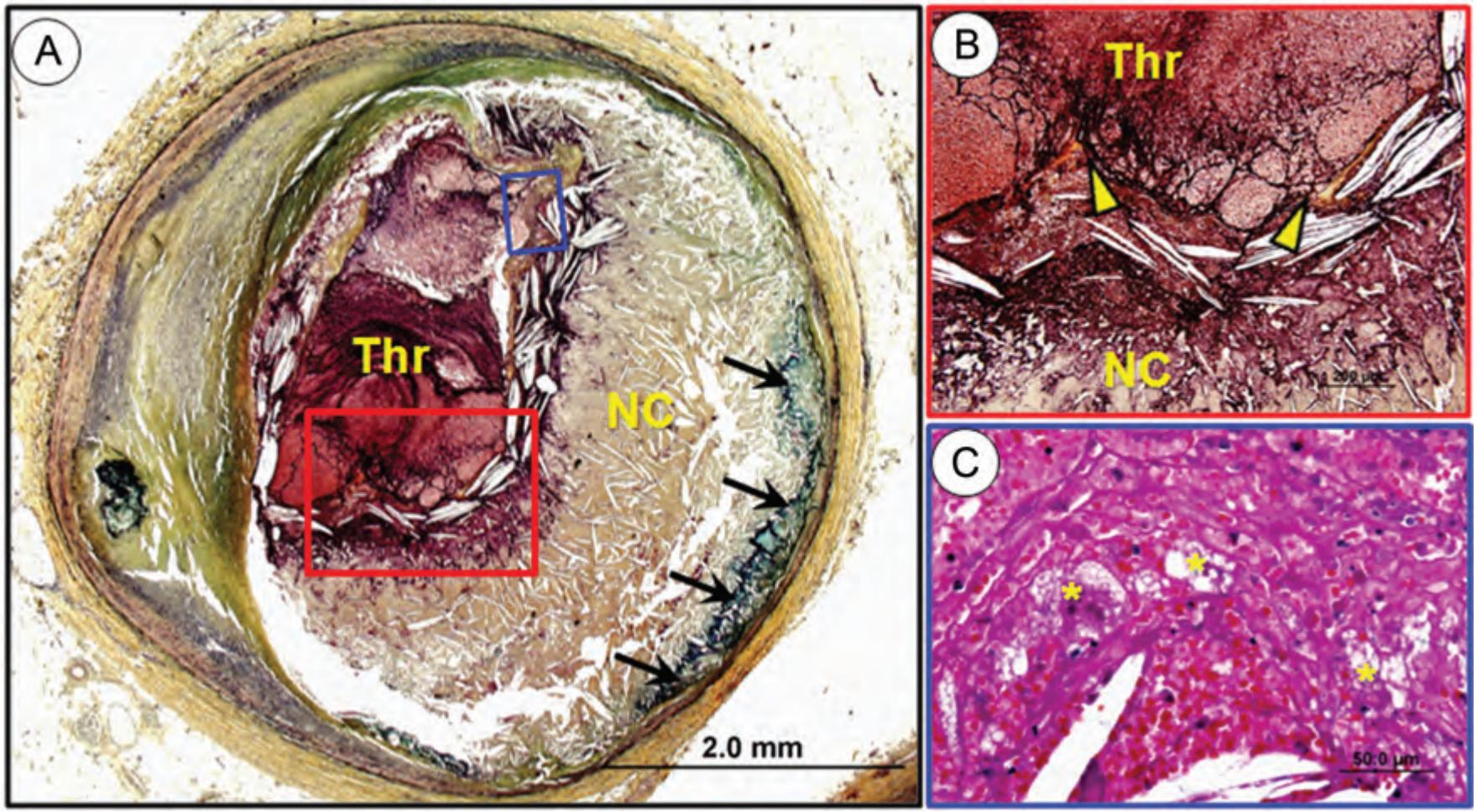


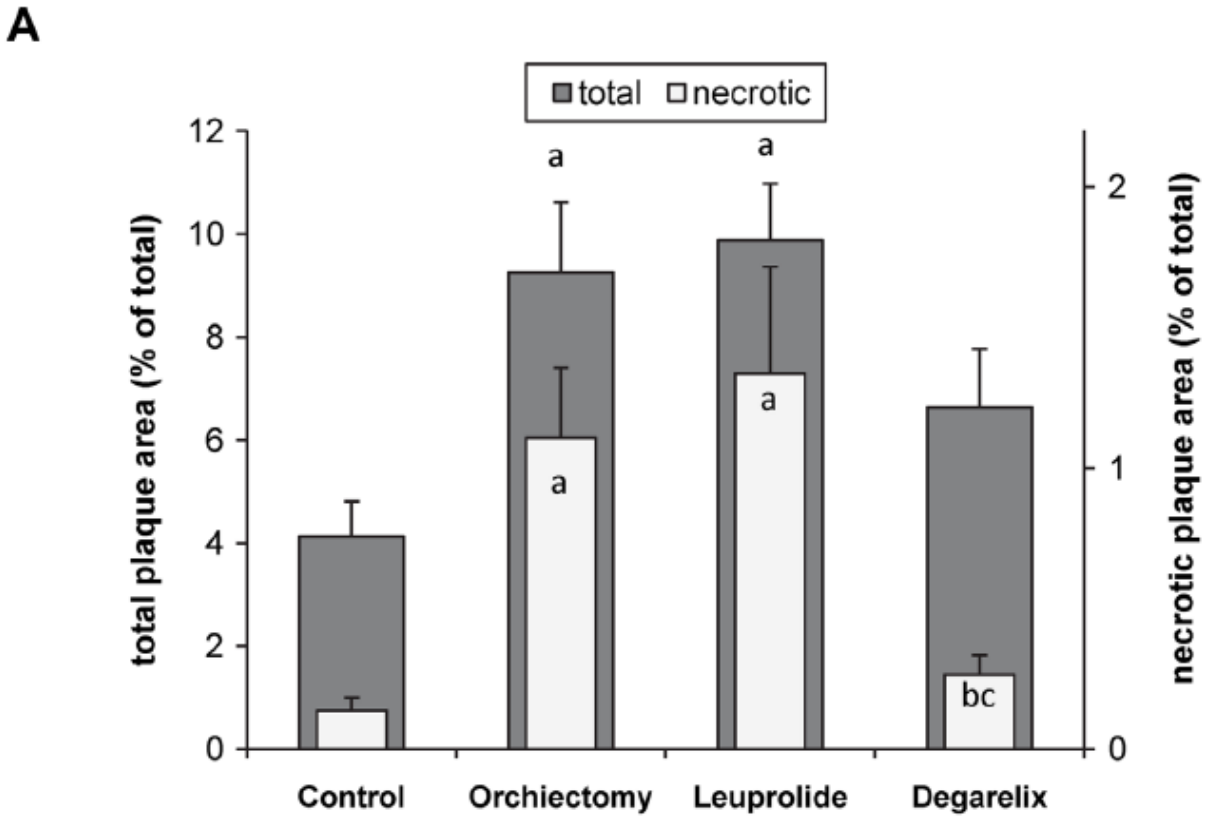

**Fig 2.** Hazard ratios at selected time intervals since the start of androgen-deprivation therapy for first cardiovascular disease (CVD) event in men with differing baseline CVD over duration of (A) gonadotropin-releasing hormone (GnRH) agonist, (B) antiandrogen (AA) therapy, and (C) surgical orchiectomy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

# Plaque rupture




Falk et al. Eur Heart J 2013;34:719–28

# ADT induced (de-novo) atherosclerosis

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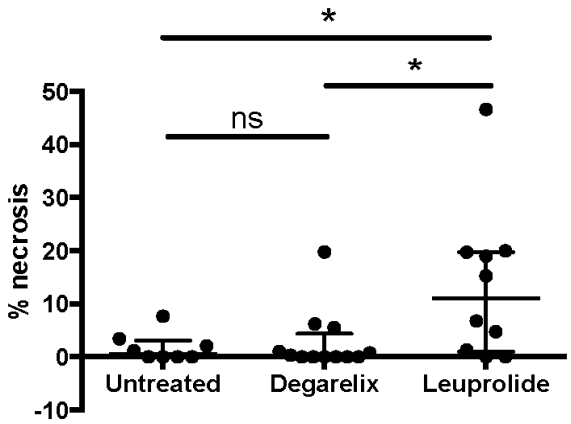
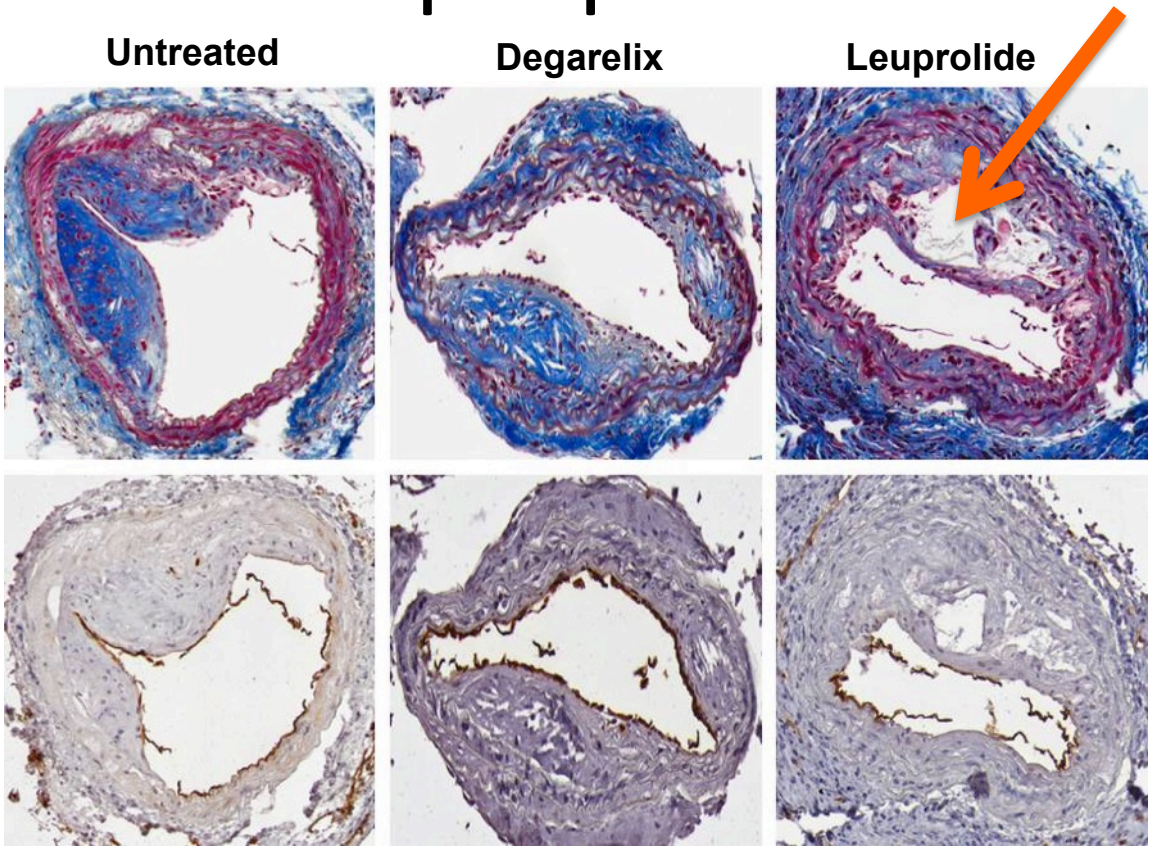
Hopmans SN, et al. Urol Oncol 2014;32:1126–34

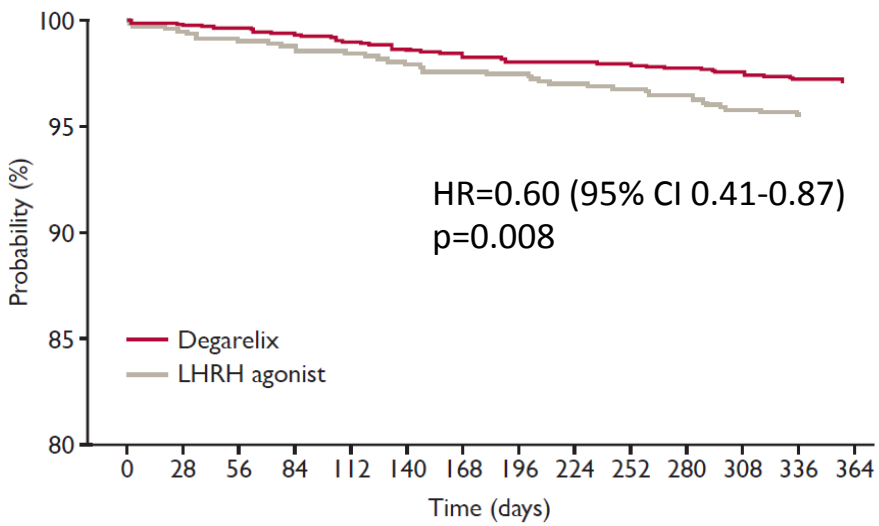
# GnRH-receptor agonists induce necrosis in pre-established atherosclerotic plaques



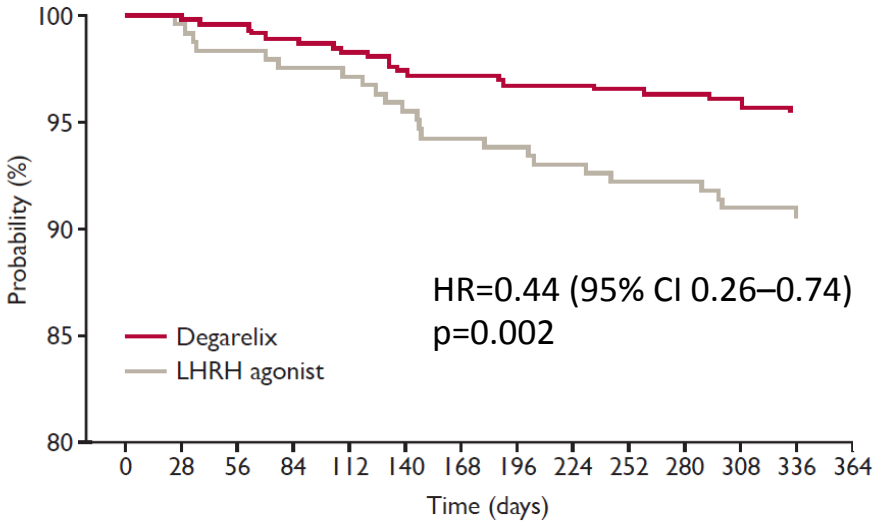




*Anki Knutsson et al EAU meeting 2015Abstract #558*

## Risk of CV event or death (all patients)




## Risk of CV event or death in men with baseline CVD



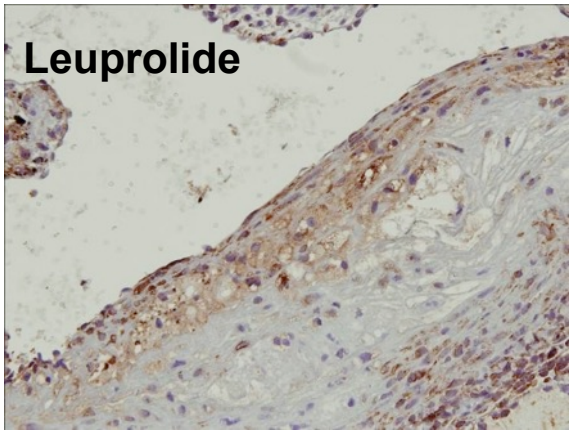

## Selected baseline demographics relating to CV risk

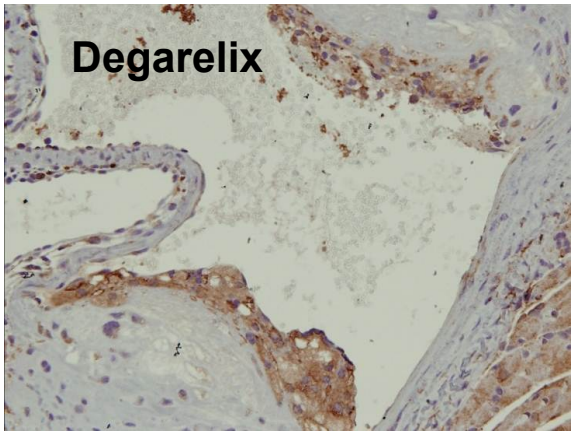
| Variable | Degarelix n=1491 | LHRH agonist n=837 |
|---|---|---|
| Age (yrs) | 71.7 | 71.6 |
| Body mass index<br>BMI >30, n (%) | 27.2<br>334 **(22)** | 27.5<br>200 **(24)** |
| History of cardiovascular disease, n (%) | 463 **(31)** | 244 **(29)** |
| Smoking, n (%) | 707 **(47)** | 432 **(52)** |
| Alcohol, n (%) | 889 **(60)** | 475 **(57)** |
| Elevated blood pressure, n (%) | 1117 **(75)** | 615 **(73.5)** |
| Cholesterol >6.2 mmol/ L, n (%) | 399 **(27)** | 247 **(30)** |
| Statin medication, n (%) | 400 **(27)** | 234 **(28)** |
| Diabetes, n (%) | 221 **(15)** | 128 **(15)** |

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

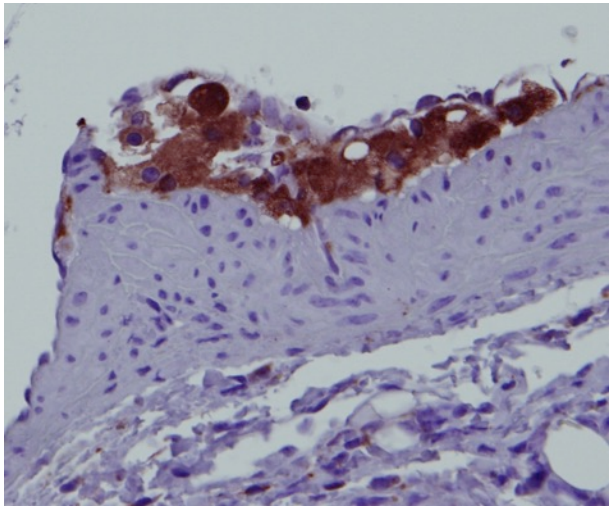
Albertsen PC, et al. Eur Urol 2014;653:565–73

# Effects of ADT on macrophage plasticity in atherosclerosis




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



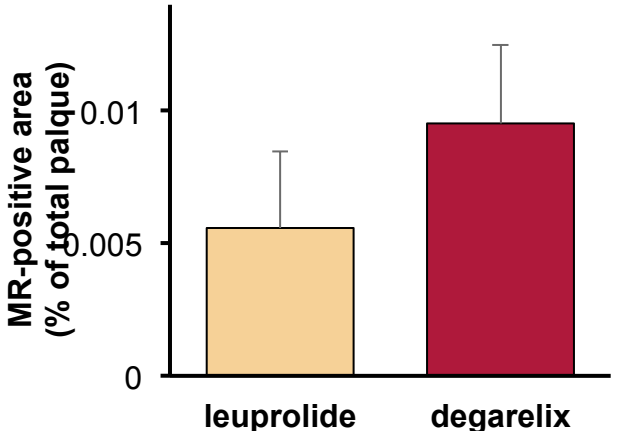
*Mac3-IHC of atherosclerotic plaque in hearts of ADT mice*

***M1 macrophages***

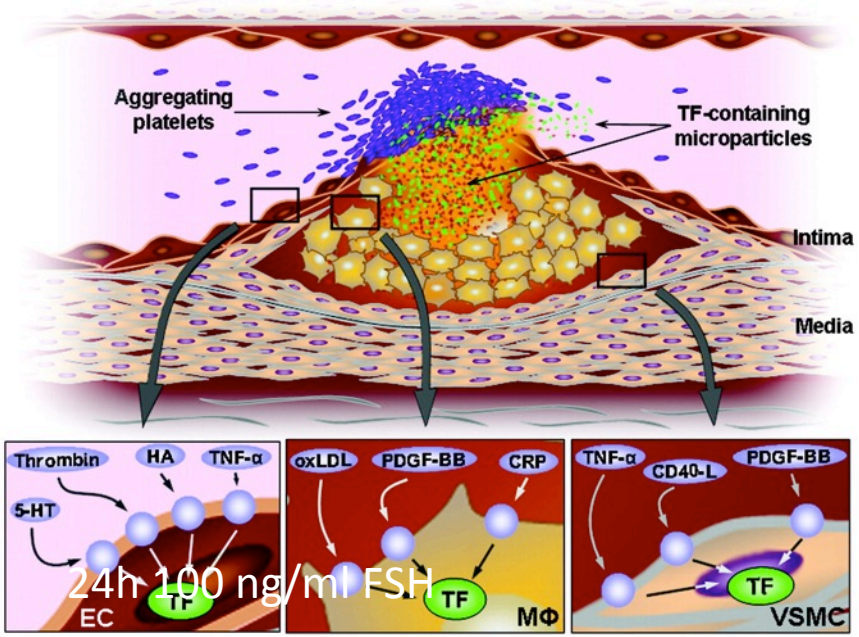
- Classically activated
- Pro-inflammatory, **pro-atherogenic**
- Cause tissue injury and **promote lesion development as well as enhance plaque vulnerability**

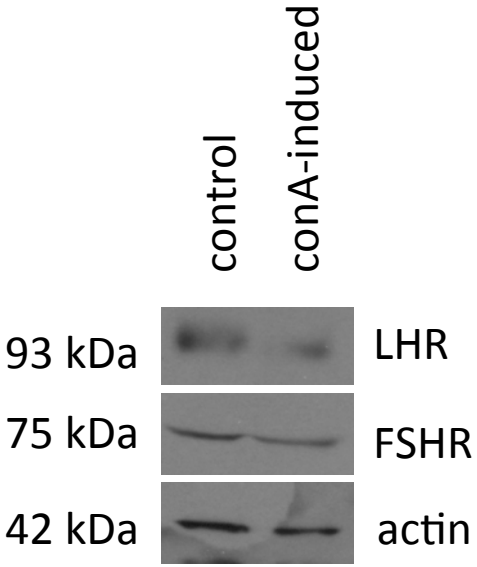
***M2 macrophages***

- 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**

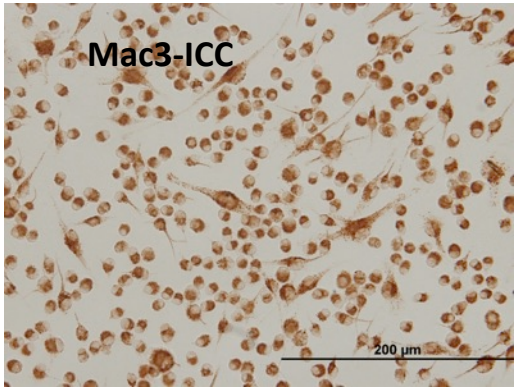


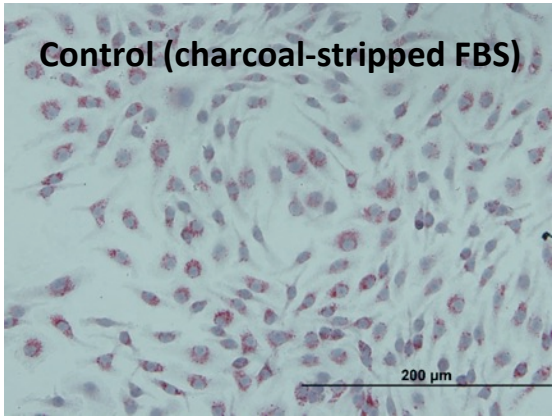
# Foam cells play a significant role in plaque progression and instability

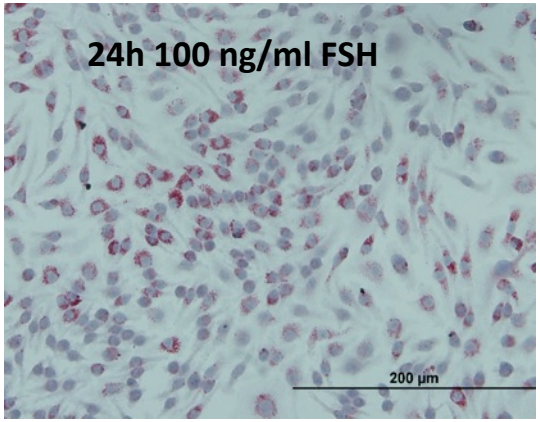


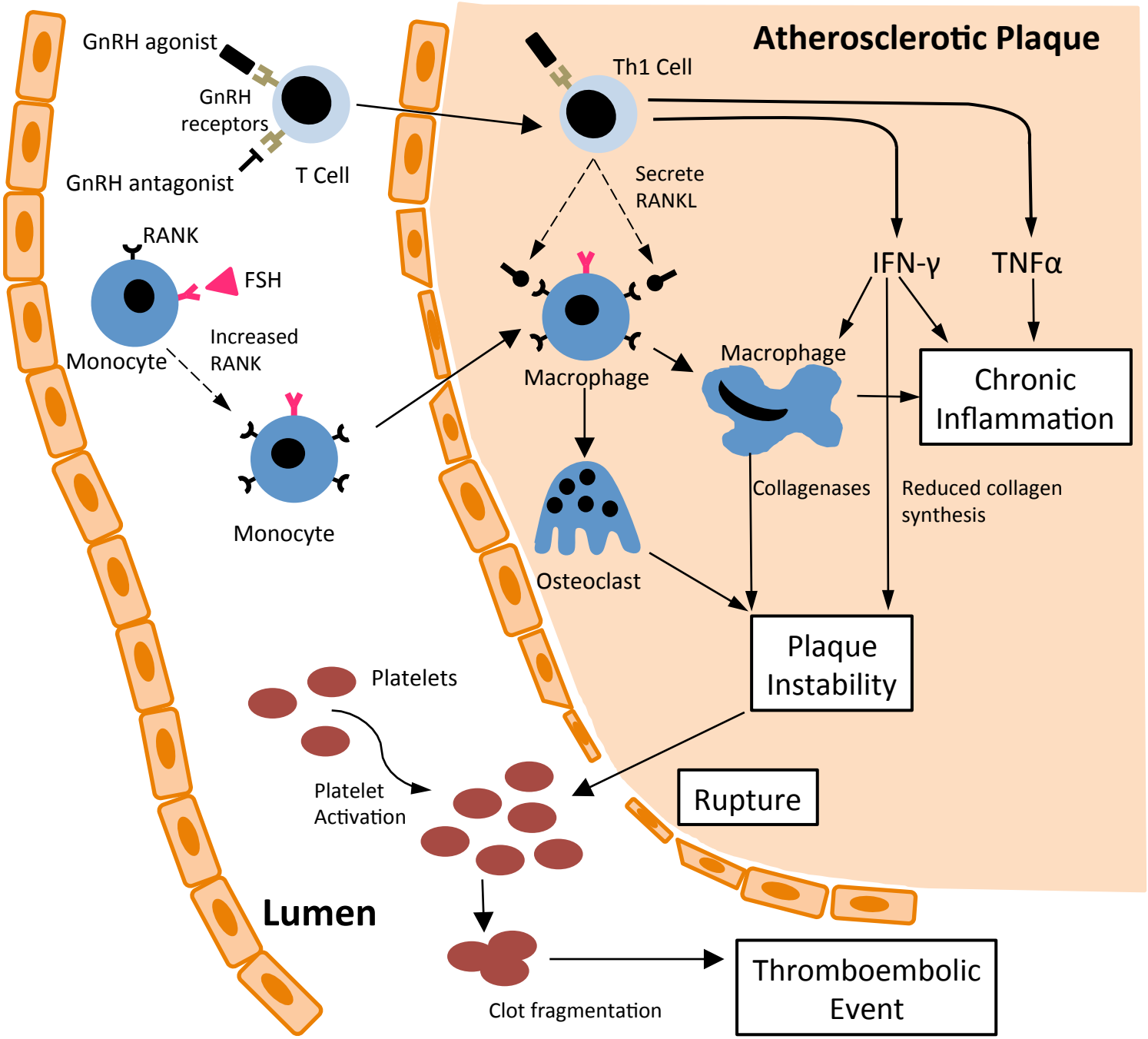




Jan Steffel et al. Circulation. 2006;113:722-731

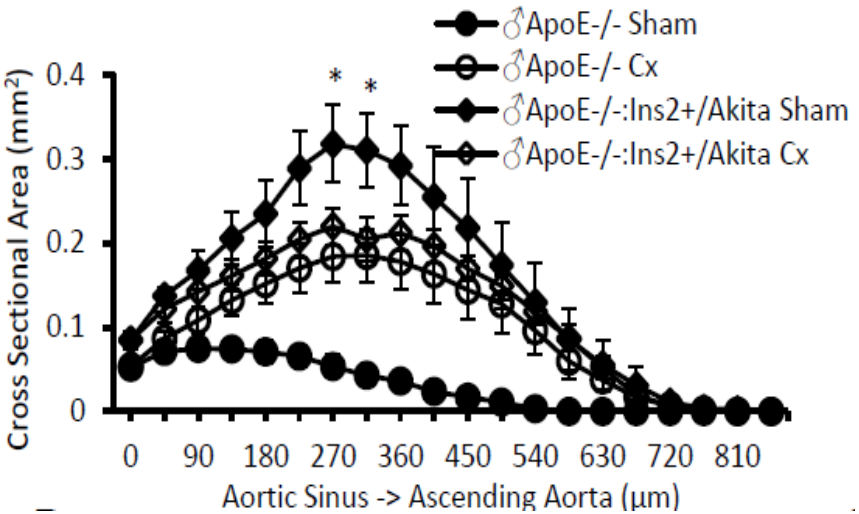


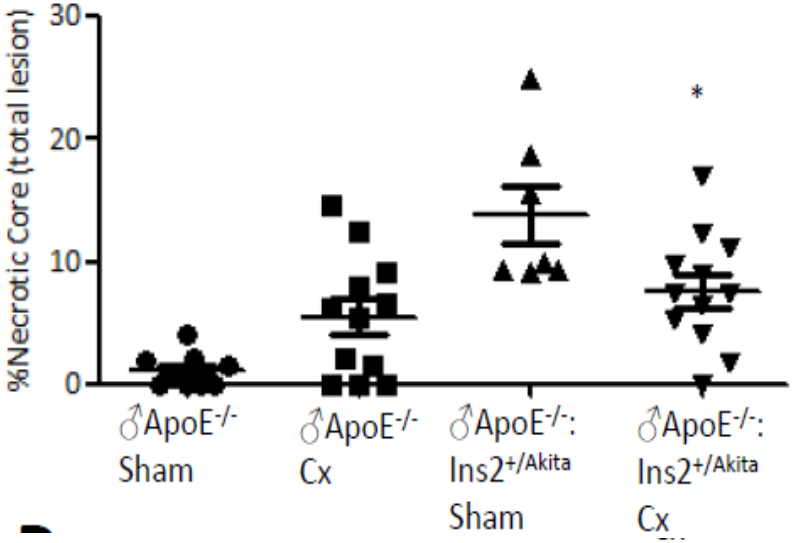



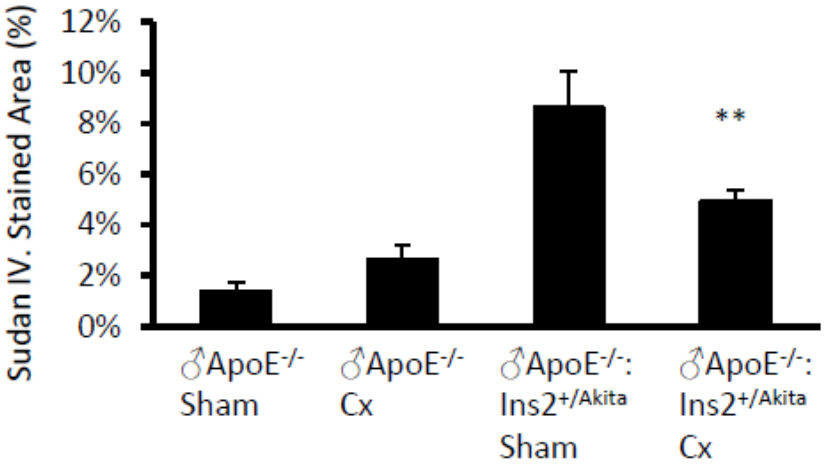

Atherosclerotic Plaque
GnRH agonist
GnRH receptors
GnRH antagonist
T Cell
Th1 Cell
Secrete RANKL
IFN-γ
TNFα
RANK
FSH
Monocyte
Increased RANK
Monocyte
Macrophage
Macrophage
Chronic Inflammation
Collagenases
Reduced collagen synthesis
Osteoclast
Plaque Instability
Platelets
Platelet Activation
Rupture
Lumen
Clot fragmentation
Thromboembolic Event

# ApoE-/-:Ins2+/Akita Mouse Model of Accelerated Atherosclerosis



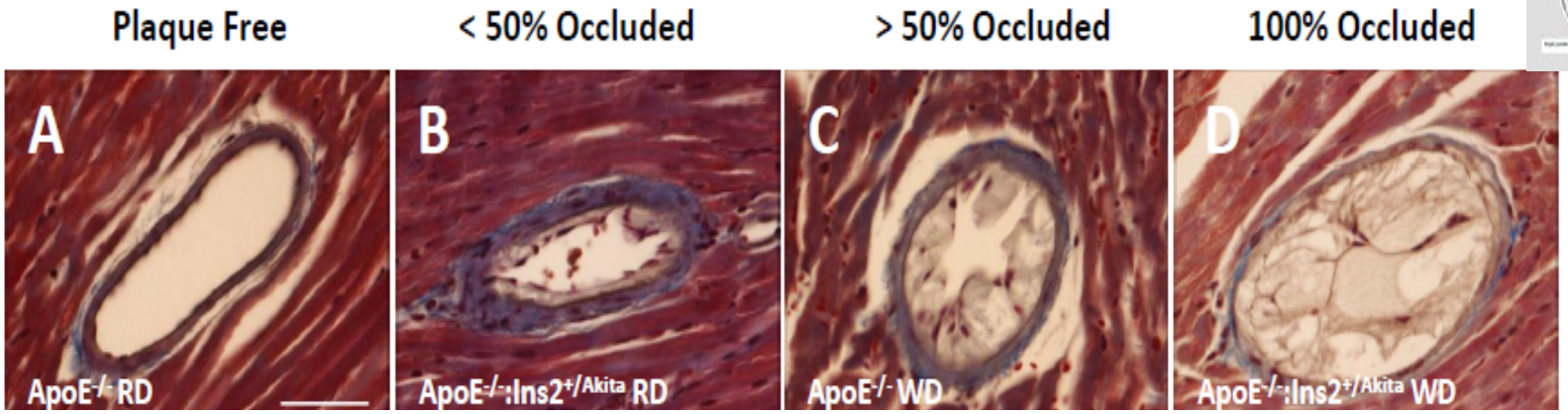



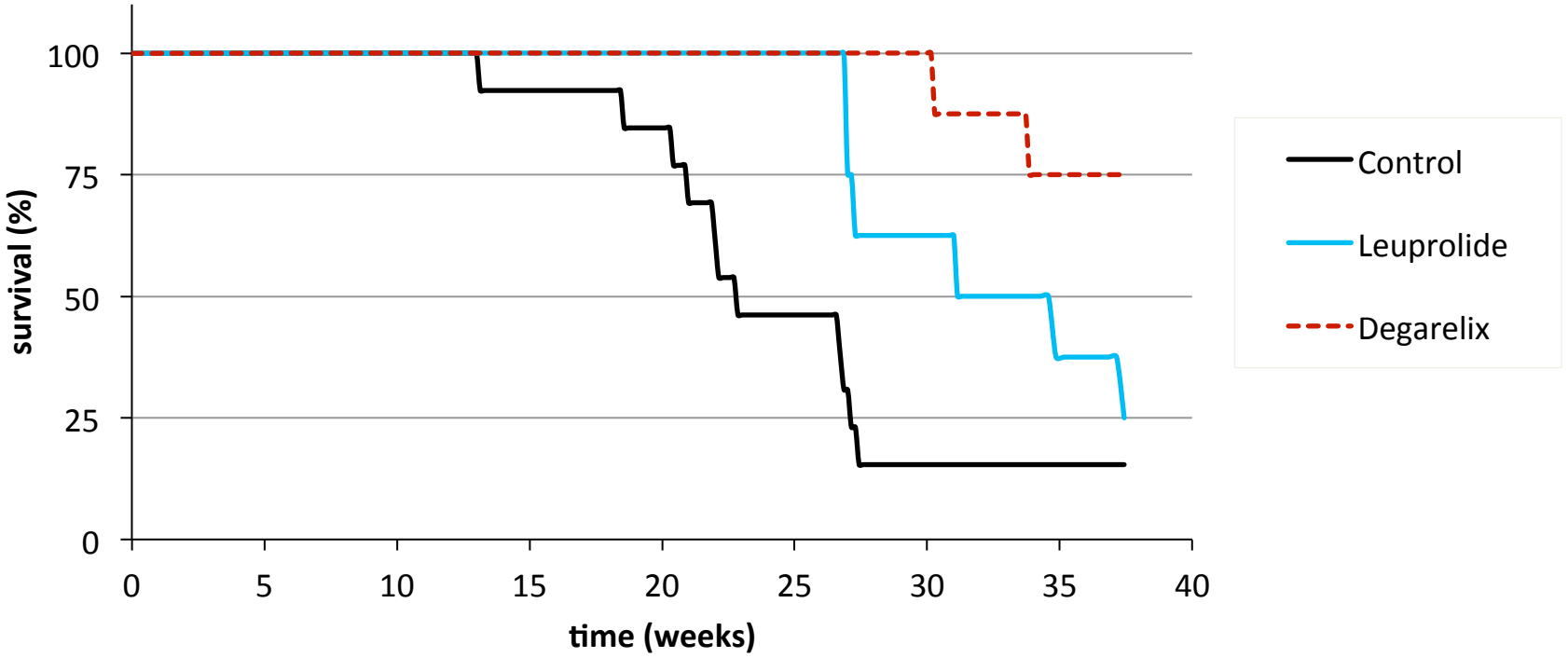





*Venegas-Pino et al 2015 (in press)*

# Survival of Ins2$^{+/Akita}$:apoE$^{-/-}$ mice



# 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.**


**No previous CVD**

- **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?**


**+ previous CVD**

# Role of Androgen Deprivation Therapy In Cardiovascular Disease – A Longitudinal Prostate Cancer

| Principal Investigator | Institution | Project Title | Funded Amount |
|---|---|---|---|
| Jehonathan Pinthus | McMaster University | *Role of androgen deprivation therapy in cardiovascular disease - a longitudinal prostate cancer study (RADICAL PC)* | $3,449,136 |


The Role of Androgen Deprivation Therapy in CArdiovascular Disease – A Longitudinal Prostate Cancer Study (RADICAL PC1)- prospective cohort study

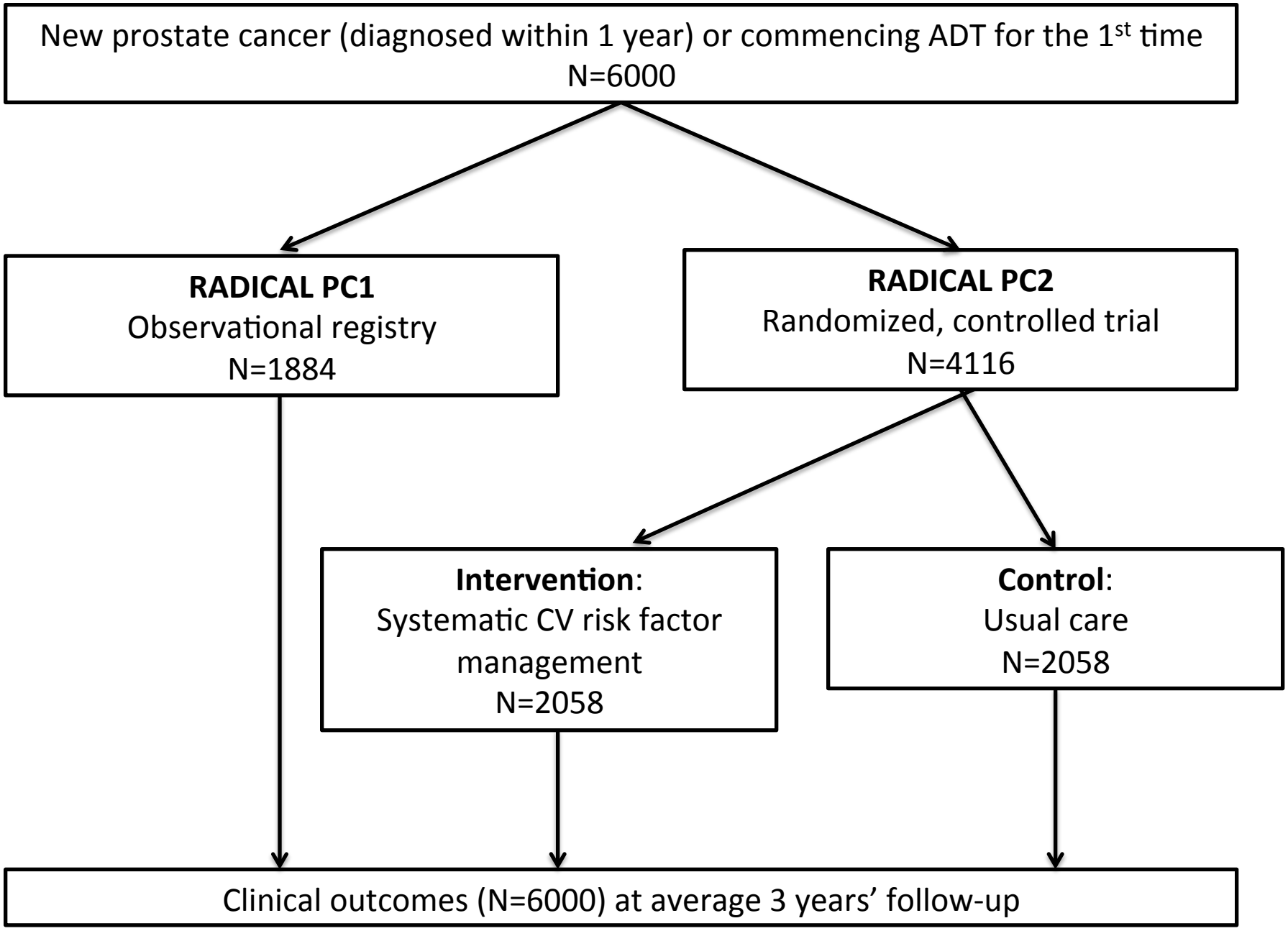
A RAndomizeD Intervention for Cardiovascular And Lifestyle Risk Factors in Prostate Cancer Patients (RADICAL PC2) – prospective randomized controlled (prevention) trial

# Key Epidemiologic Observations

- Men with PC are at high risk of CVD
- The role of ADT in promoting CVD remains uncertain

# Unanswered Questions

- What are the most important determinants of CVD in men with PC?
- How can we prevent CVD in men with PC?


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

# 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

# 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

# Inclusion Criteria

PC that is either:

- New (i.e. the diagnosis was made within 1 year), or
- Treated with ADT for the first time within 1 month prior to the baseline visit, or
- To be treated with ADT for the first time within 1 month after the baseline visit

# Exclusion Criteria

- Unwilling to provide consent, or
- <45 years of age

Patients will be eligible for RADICAL PC1, but will not be eligible for RADICAL PC2 if:

1) they see a cardiologist every year; or
2) if they are undertaking all of:
   - aspirin use
   - statin use
   - ACE-I or ARB use
   - exercise ≥4 times per week

# Intervention in RADICAL PC2

- Randomized in an open manner to usual care or
- Systematic risk factor management
  - Aspirin
  - Statin
  - ACE-I for BP >130/80
  - ARB
  - Dietary counseling
  - Exercise advice
  - Support to quit smoking

# RADICAL PC Procedures

| Study procedure | Baseline visit | 3-month phone | 6-month phone | 12-month visit | 18-month phone | 24-month visit | 36-month phone | Close-out visit |
|---|---|---|---|---|---|---|---|---|
| Past medical history | X | | | | | | | |
| Medications | X | X | X | X | X | X | X | X |
| Vital signs<br>Anthropometrics<br>Handgrip strength<br>Timed get-up-and-go test<br>Six-minute walk test | X | | | X | | X | | X |
| Results of routine blood tests | X | | | X | | X | | |
| FFQ | X | Abridged | Abridged | X | Abridged | X | Abridged | X |
| PAQ | X | Abridged | Abridged | X | Abridged | X | Abridged | X |
| ECOG<br>DSS test<br>PHQ-9<br>SAGE<br>IIEF5 | X | | | | | X | | |
| Urinalysis | X | | | X | | X | | |
| Clinical outcome events | | X | X | X | X | X | X | X |
| Drug adverse effects | | X | X | X | X | X | X | X |
| MMAS4 (RADICAL PC2 only) | | X | X | X | X | X | X | X |

# 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

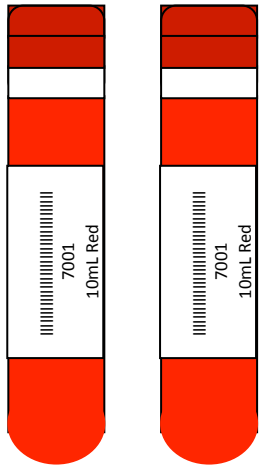
RADICAL PC1

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

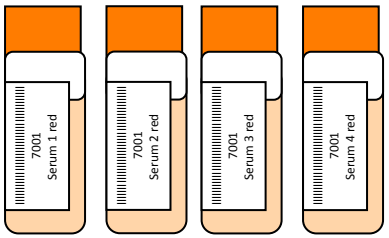
N=4116, experiencing 434 primary outcome events will have 85% power to detect hazard ratio of 0.75 in intervention group, assuming 30% drop-in, 15% drop-out, 5% loss-to-follow-up

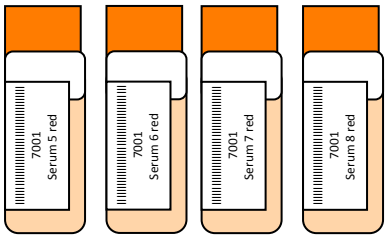
# Specimen Processing



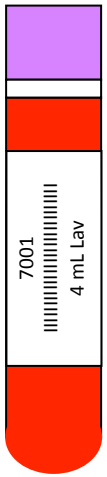

Allow to clot at room temperature for ~30 minutes

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

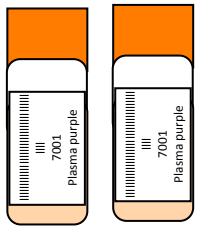


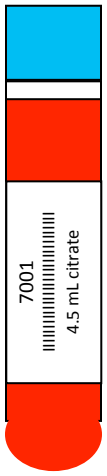




R&D




Carefully draw EDTA plasma off cells & transfer into1cryovials



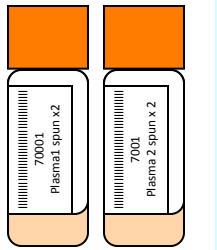



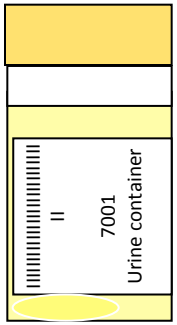


Centrifuge

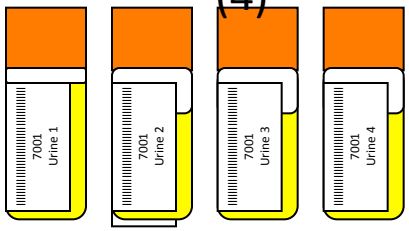
Transfer respun plasma from evenly into each of 2 cryovials (~1.0 mL ea.)

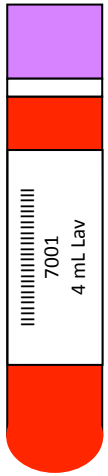
Coagulation



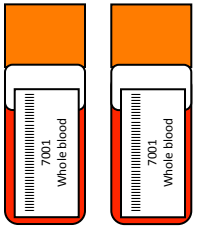




Transfer 1.8 ml of urine to each vial (4)




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




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.

# Mega bio-bank

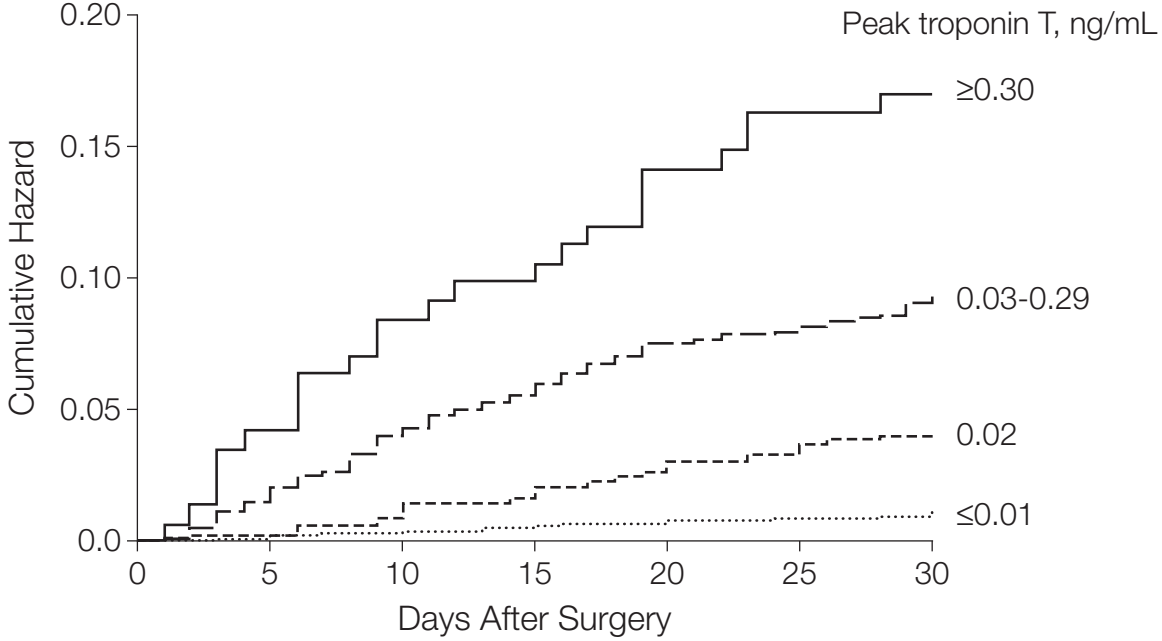
- Blood
- Urine
- DNA

R&D

- Hormonal markers (FSH, Estrogen)
- 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




No. at risk

| Peak troponin T, ng/mL | | | | | | | |
|---|---|---|---|---|---|---|---|
| ≥0.30 | 142 | 136 | 129 | 127 | 121 | 118 | 117 |
| 0.03-0.29 | 1121 | 1103 | 1075 | 1058 | 1036 | 1030 | 1018 |
| 0.02 | 494 | 492 | 489 | 485 | 480 | 477 | 473 |
| ≤0.01 | 13376 | 13348 | 13300 | 13271 | 13250 | 13230 | 13209 |

Devereaux, *et al. JAMA* 2012; 307: 2295.

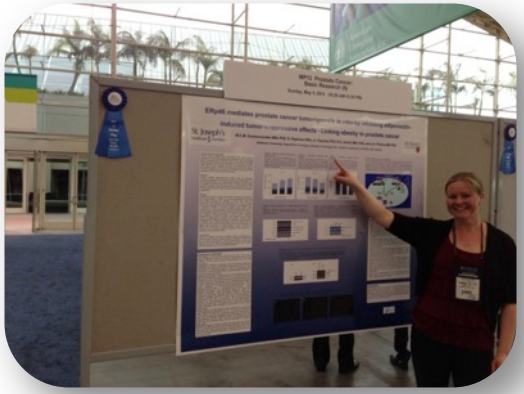
# Significance of Findings

- First prospective cohort study of PC/ADT with defined CVD end points
- Potential discovery of risk stratification methods
- Large bio-bank

# Thanks to

**Geoff Werstuck, PhD**

**Helga Duivenvoorden, PhD**



**Sarah Hopmans, MSc**