Gemelli ART
Advanced Radiation Therapy
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

MRO . ART
INNOVATIVE TREATMENTS AND PATIENTS COMPLIANCE
31° RESIDENTIAL COURSE

Does drug innovation change compliance in combined treatments?

Androgen pathway therapy

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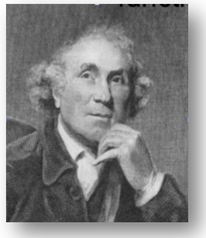
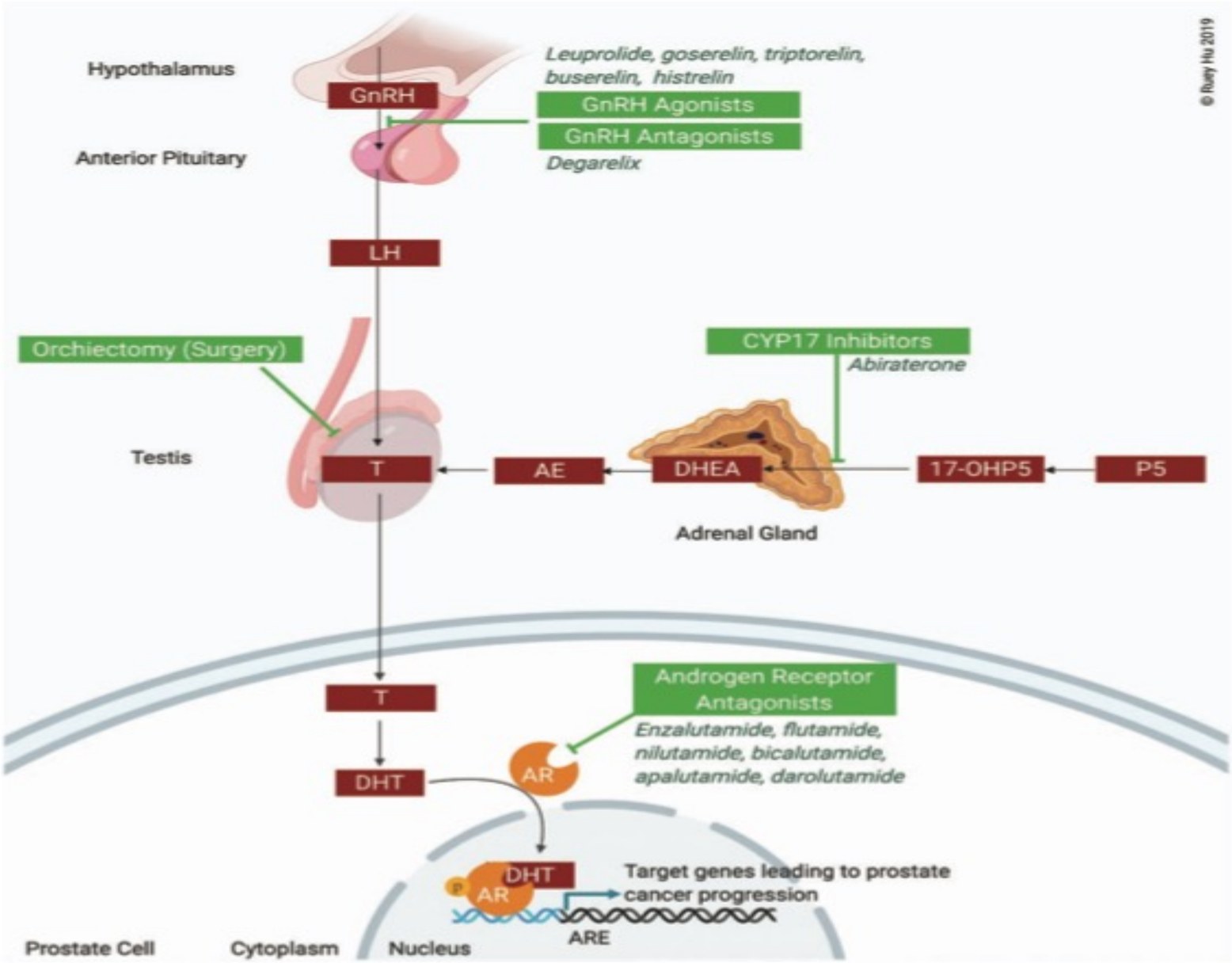
Androgen Deprivation Therapy: where we have come from



- 1780 John Hunter, castration
- 1938 Acid phosphatase
- 1940 Huggins, Orchiectomy and estrogen (Nobel Prize)
- 1965 Synthetic estrogens
- 1977 First generation non-steroidal anti-androgens
- 1989 2nd generation non-steroidal AA (Bicalutamide)
- 1985 Schally, LHRH agonists (Nobel Prize)
- 2003 LHRH antagonist (Abarelix)
- 2008 Degarelix
- 2009 Abiraterone
- 2010 Enzalutamide
- 2012 Apalutamide and Darolutamide

Hypothalamic-pituitary-gonadal axis and targets for ADT in PCa

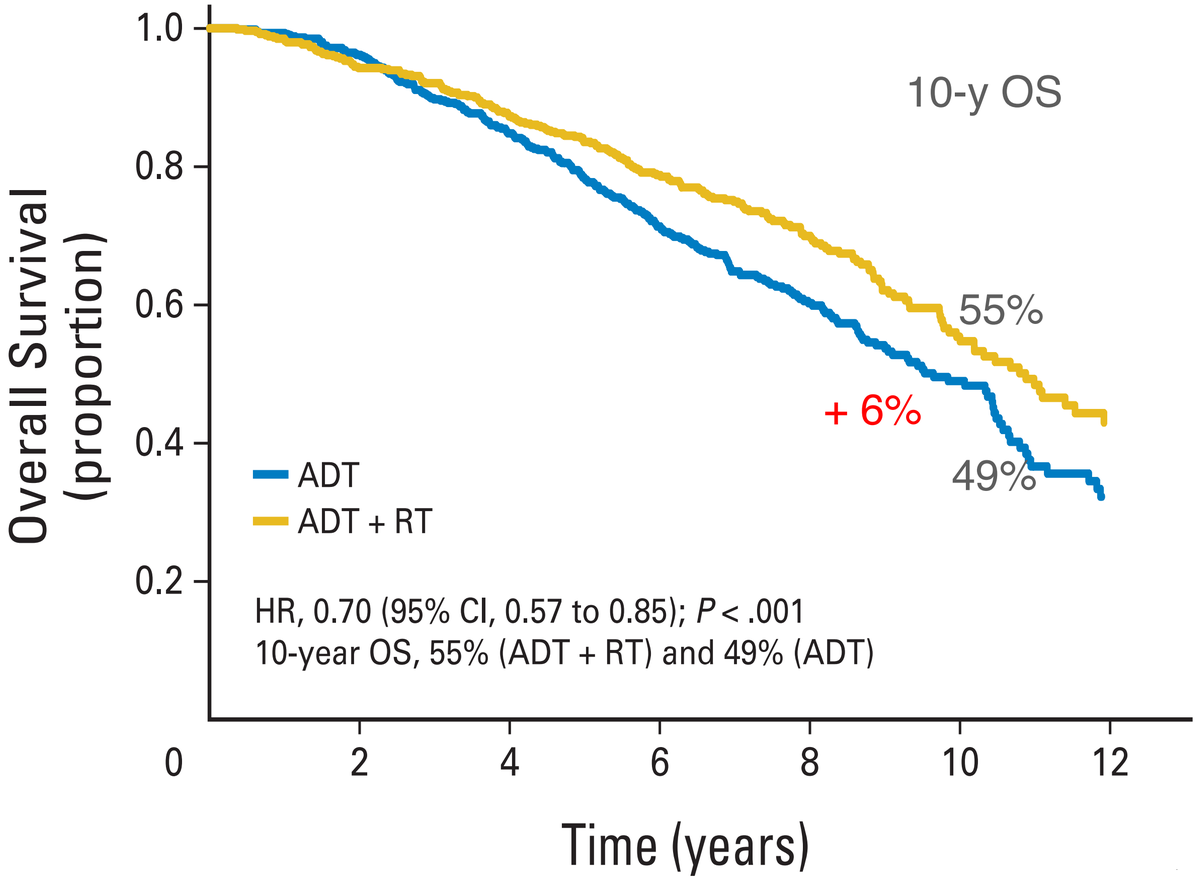


Integrating ADT with RT

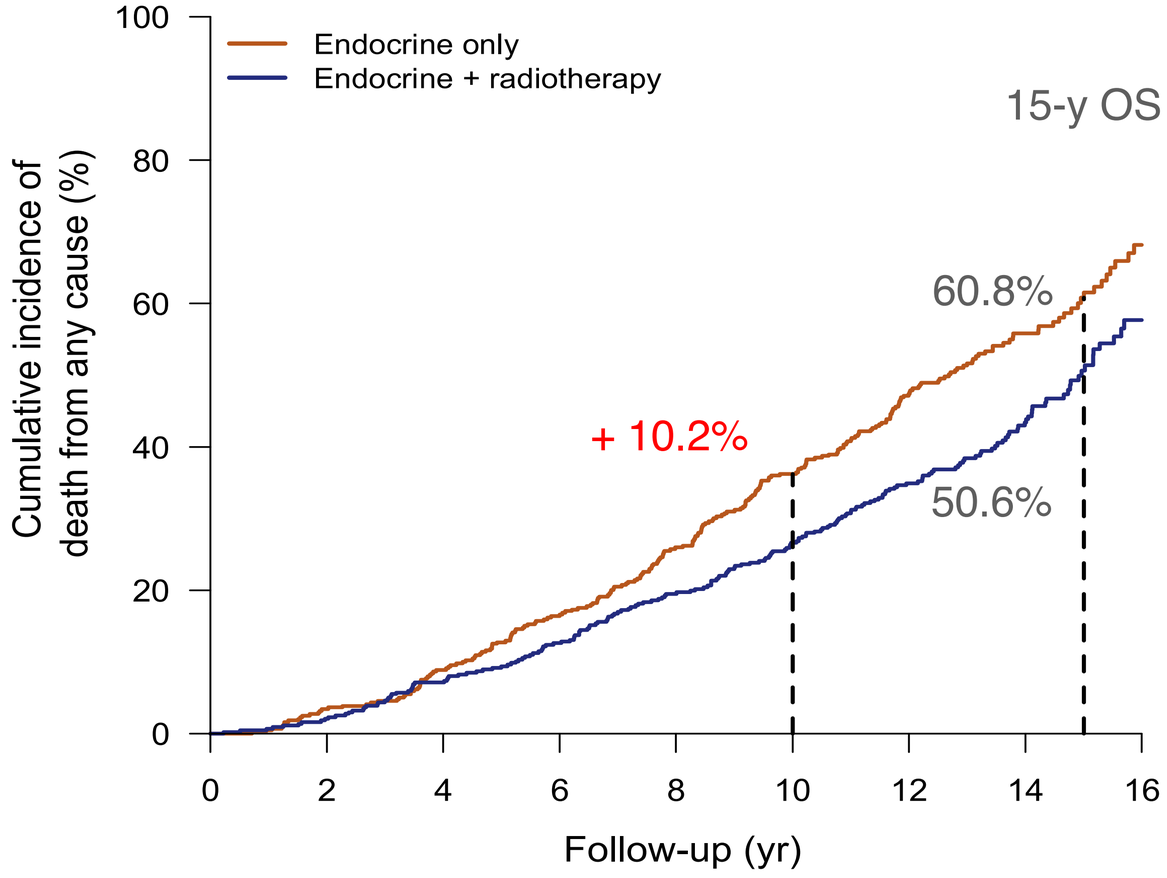
0 months	4-6 months	18 months	24-36 months
Low Risk	Unfavorable Intermediate Risk	High Risk	Very High Risk
Favorable Intermediate Risk			LN+

Courtesy of Dr. Tendulkar

OS improved when ADT is combined with RT in locally advanced PCa



NCI-MRC, JCO 2015

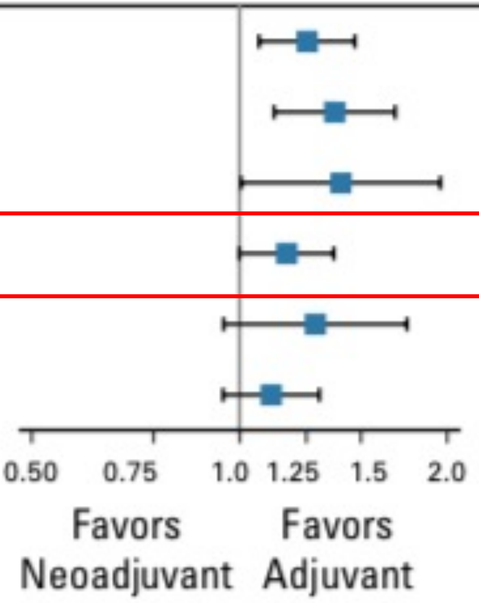


SPC-G7, Eur Urol 2016

original reports

Prostate Radiotherapy With Adjuvant Androgen Deprivation Therapy (ADT) Improves Metastasis-Free Survival Compared to Neoadjuvant ADT: An Individual Patient Meta-Analysis

End Point	Neoadjuvant Incidence/N	Adjuvant Incidence/N	15-yr Absolute Benefit of Adjuvant ADT (%, CI 95%)	15-yr RMST Benefit of Adjuvant ADT (Months, CI 95%)	HR (95%)	*P* value
Progression-free survival	316/531	292/534	7.4 (–0.1, 14.8)	10.8 (2.7, 18.8)	1.25 (1.07, 1.47)	.01
Biochemical failure	214/531	168/534	10.1 (3.8, 16.3)	12.4 (3.7, 21.1)	1.37 (1.12, 1.68)	.002
Distant metastasis	82/531	60/534	5.3 (0.5, 10.1)	2.9 (–2.6, 8.4)	1.40 (1.00, 1.95)	.04
Metastasis-free survival	324/531	298/534	7.2 (0.3, 14.1)	3.9 (–3.1, 10.8)	1.17 (1.00, 1.37)	.050
Prostate cancer-specific mortality	91/531	73/534	5.8 (0.5, 11.0)	3.5 (–1.6, 8.6)	1.29 (0.95, 1.75)	.10
Overall survival	307/531	291/534	5.4 (–1.6, 12.3)	2.7 (–4.0, 9.3)	1.11 (0.95, 1.30)	.20



Spratt et al. J Clin Oncol 2021

NEWS RELEASE 27-OCT-2021

ASTRO: International meta-analysis quantifies impact of three prostate cancer therapy intensification strategies

Individual patient data analysis from MARCAP Consortium may be the strongest evidence to date on androgen deprivation therapy use and duration

data from 10,853 patients enrolled in 12 radiation therapy trials

- After a median follow-up of 12 years, the addition of ADT to RT improved 12-year OS by **7%**

Kishan et al. ASTRO 2021

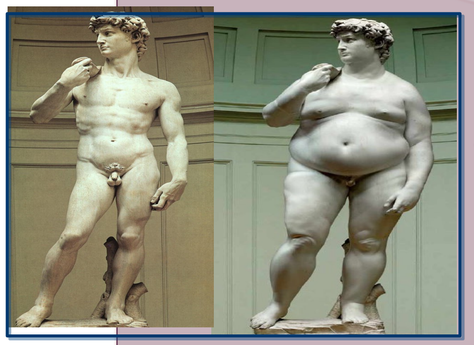
ADT side effects

- Loss of libido and sexual interest, erectile dysfunction, impotence
- Fatigue
- Hot flushes
- Decline in intellectual capacity, emotional liability, depression
- Decrease in muscular strength
- Increase in (abdominal) fat apposition
- Osteoporosis
- Cardiovascular

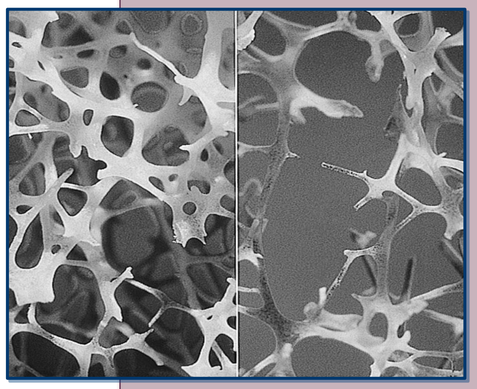
Conditions

Side-effects

Complications



Sarcopenic obesity



Bone loss

CV events

Osteoporosis

CV death

Fracture (SREs)

Courtesy of Dr. Crawford

Cardiovascular Effects of Androgen Deprivation Therapy in Prostate Cancer

Contemporary Meta-Analyses

Table 1. Cardiovascular Mortality and Cardiovascular Disease Associated With ADT as a Pooled Group Compared With Non-ADT, According to Results of Meta-Analyses From 2010 to 2019

	Type	Treatment Agent (No. of Patients)	Comparator Agent (No. of Patients)	CV Mortality	Any Nonfatal CVD	Myocardial Infarction	Stroke
Nguyen et al[19]	RCT	ADT (n=2200)	Nonimmediate ADT (n=1941)	RR, 0.93 (CI, 0.79–1.10; *P*=0.41; I^2=0%; N=8)			
Bourke et al[20]	RCT	ADT (n=1065)	Nonimmediate ADT (n=814)	RR, 1.06 (CI, 0.80–1.40; *P*=0.69; I^2=0%; N=4)			
Zhao et al[18]	Obs.	ADT (n=129 802)*	Non-ADT (n=165 605)*	HR, 1.17† (CI, 1.04–1.32; *P*=0.01; I^2=57%; N=6)	HR, 1.10 (CI, 1.00–1.21; *P*=0.06; I^2=72%; N=6)	HR, 1.10 (CI, 0.97–1.26; *P*=0.14; I^2=68%; N=6)	
Zhao et al[18]	Obs.	ADT (n=39 465)*	Watchful waiting (n=43 648)*	HR, 1.30† (CI, 1.13–1.50; *P*=0.0003; I^2=0%; N=4)	HR, 1.19† (CI, 1.08–1.30; *P*=0.0004; I^2=0%; N=3)		
Carneiro et al[16]	Obs.	ADT (n=52 308)	Non-ADT (n=74 590)	OR, 1.92 (CI, 0.79–4.68; *P*=0.15; I^2=97%; N=3)	OR, 1.06 (CI, 0.70–1.61; *P*<0.78; I^2=100%; N=2)	OR, 2.05† (CI, 1.93–2.17; *P*<0.00001; I^2=100%; N=2)	OR, 1.07 (CI, 0.66–1.72; *P*=0.79; I^2=99%; N=2)
Carneiro et al[16]	RCT	ADT (n=8388)	Non-ADT (n=8411)	OR, 0.97 (CI, 0.81–1.18; *P*=0.79; I^2=0%; N=6)	OR, 1.55† (CI, 1.09–2.20; *P*=0.01; I^2=0%; N=3)	OR, 1.23 (CI, 0.92–1.64; *P*=0.16; I^2=0%; N=2)	OR, 1.02 (CI, 0.71–1.46; *P*=0.93; I^2=0%; N=2)
Meng et al[17]	Obs.	ADT (n=74 538)	Non-ADT (n=85 947)				HR, 1.12 (CI, 0.95–1.32; *P*=0.16; I^2=85%; N=6)
Meng et al[17]	Obs.	ADT (n=39 029)	Watchful waiting (n=42 073)				HR, 1.16† (CI, 1.03–1.31; *P*=0.01; I^2=0%; N=2)

Hu, et al. Arterioscler Thromb Vasc Biol. 2020

Cardiovascular Effects of Androgen Deprivation Therapy in Prostate Cancer

Contemporary Meta-Analyses

Table 3. Cardiovascular Events Associated With Abiraterone (a CYP17 Inhibitor) Compared With Non-ADT, According to Results of Meta-Analyses From 2010 to 2019

	Type	Treatment Agent (No. of Patients)	Comparator Agent (No. of Patients)	Any Cardiac Events	CTCAE Grade ≥3 Cardiac Events	Any Hypertension	CTCAE Grade ≥3 Hypertension
Moreira et al[26]	RCT	Abiraterone and prednisone (n=1343)	Prednisone (n=940)	RR, 1.28* (CI, 1.06–1.55; *P*=0.01; I^2=0%; N=2)	RR, 1.76* (CI, 1.12–2.75; *P*=0.01; I^2=0%; N=2)		
Iacovelli et al[25]	RCT	Abiraterone and prednisone (n=2878)	Prednisone (n=2496)	RR, 1.41* (CI, 1.21–1.64; *P*<0.001; I^2=0%; N=4)	RR, 2.22* (CI, 1.60–3.27; *P*<0.001; I^2=0%; N=4)	RR, 1.79* (CI, 1.45–2.21; *P*<0.001; I^2=68%; N=4)	RR, 2.19* (CI, 1.73–2.78; *P*<0.001; I^2=34%; N=4)

Hu, et al. Arterioscler Thromb Vasc Biol. 2020

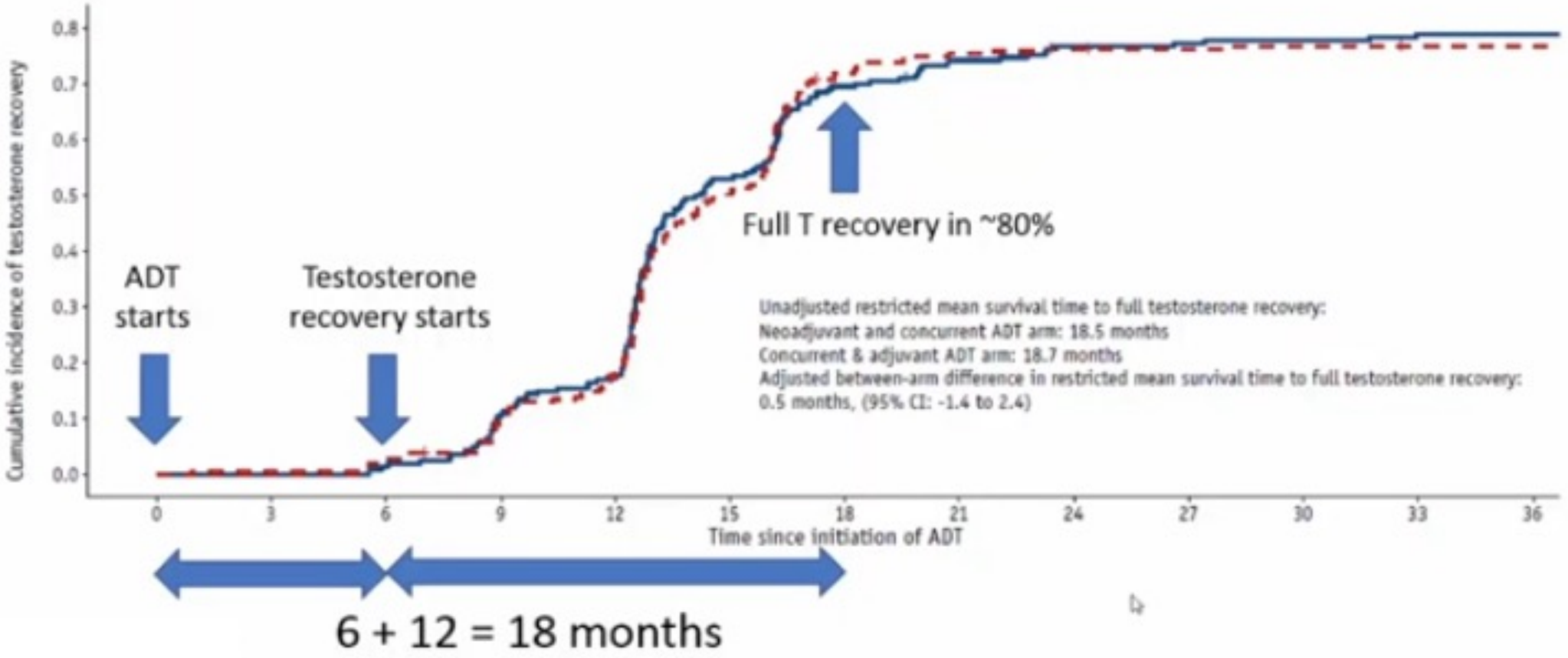
Delayed Testosterone Recovery after LHRHa

Trial	LHRHa Duration	Median T Recovery	% T Normalized
PCS III	0 months	NA	~80%
PCS III	6 months	20 months	~70%
PCS IV	18 months	3.6 years	~60%
PCS IV	36 months	6.6 years	~50%

Nabid, et al. EJC 2021

Delayed Testosterone Recovery after LHRHa

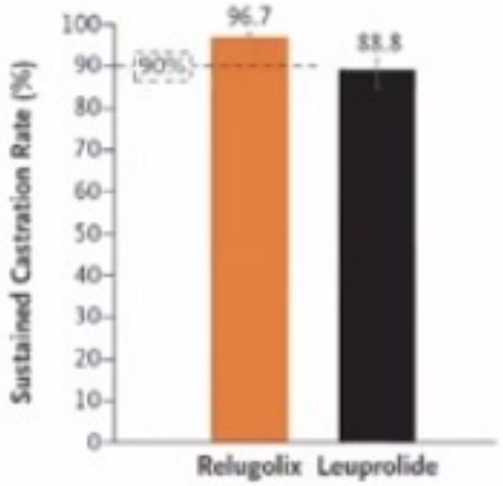
After 6m LHRHa it can take a full extra year to recover T (Ottawa 0101)

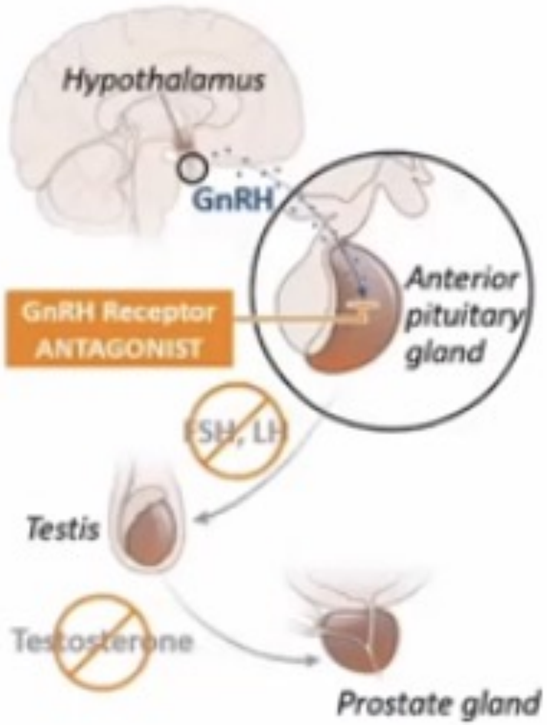


Roy, et al. IJROBP 2020

Alternatives to LHRHa ?

- Alternatives to LHRHa are desired
- **Relugolix is an oral GnRH <u>antagonist</u>**
- Tested on **HERO trial** vs. leuprolide (2:1)
- Met 1° endpoint: sustained castration (48 weeks)

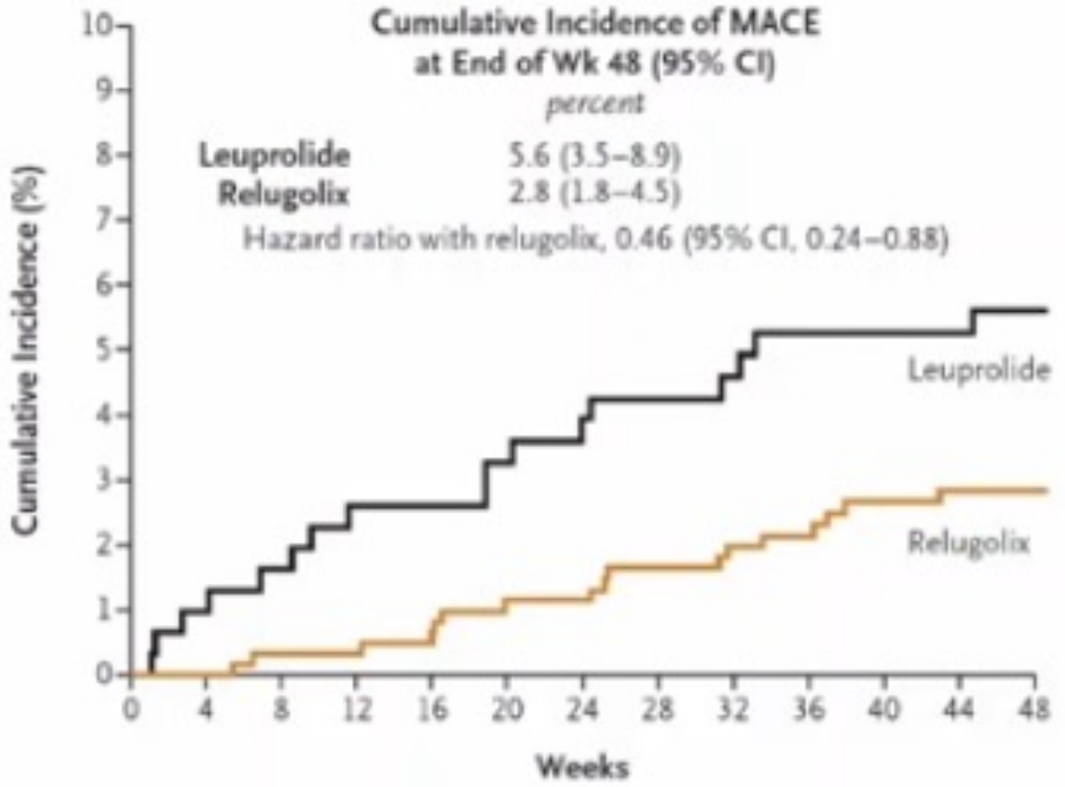




Shore, et al. NEJM 2020

Alternatives to LHRHa → HERO trial

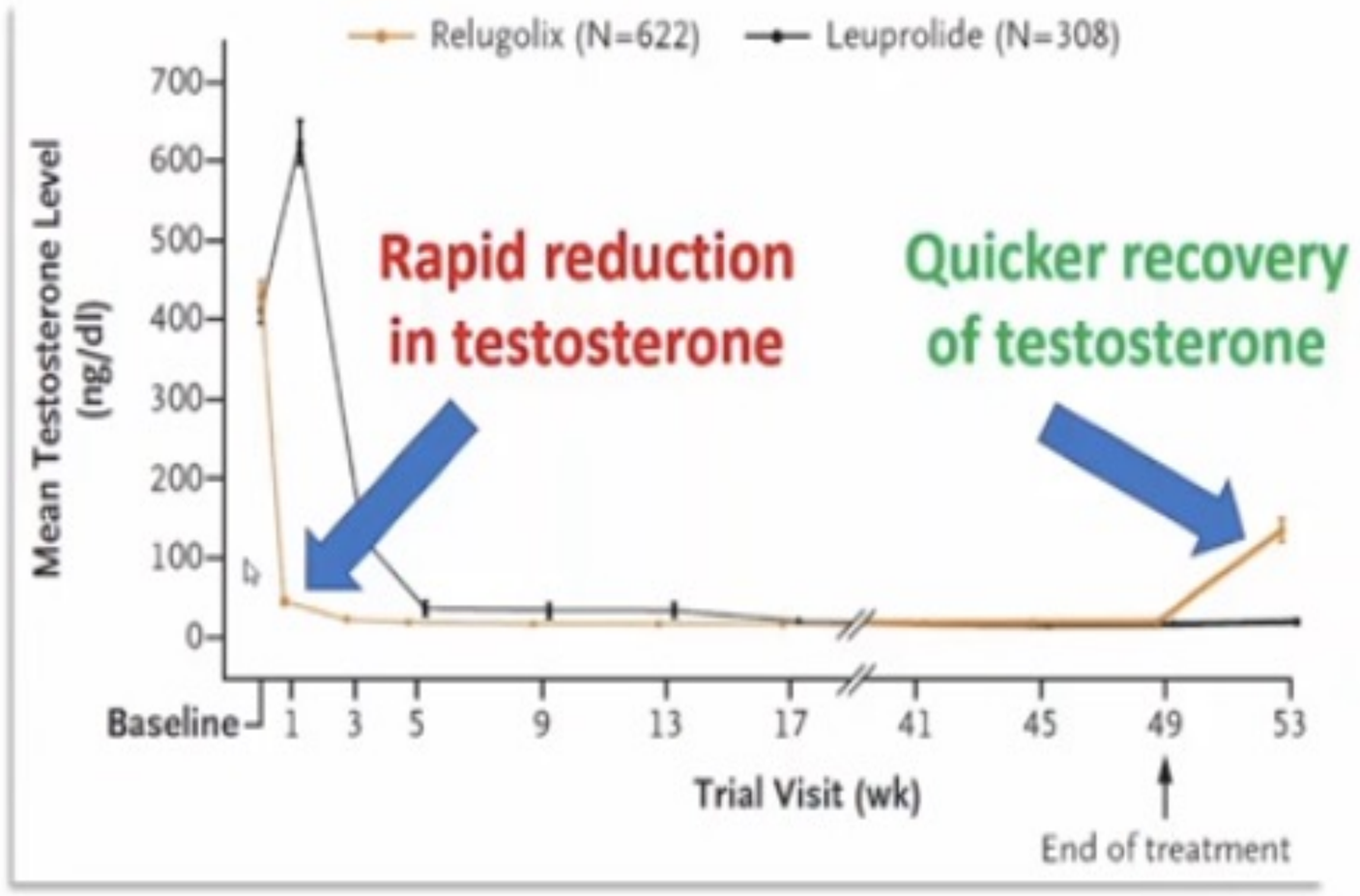
Relugolix ↓ major adverse cardiac events than leuprolide

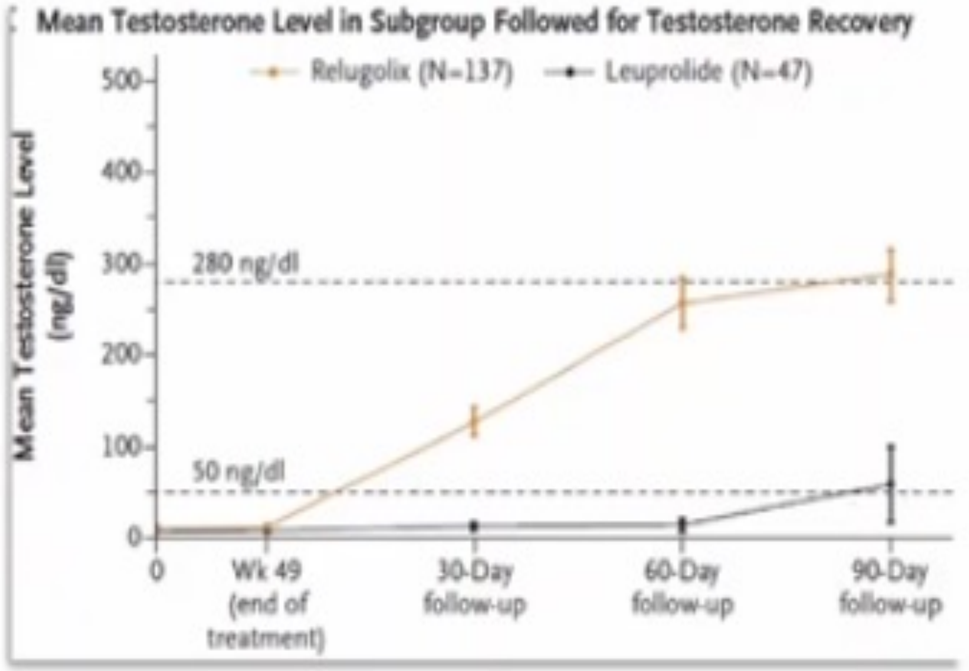


MACE = non-fatal MI + stroke + ACM

Shore, et al. NEJM 2020

Alternatives to LHRHa → HERO trial





Shore, et al. NEJM 2020

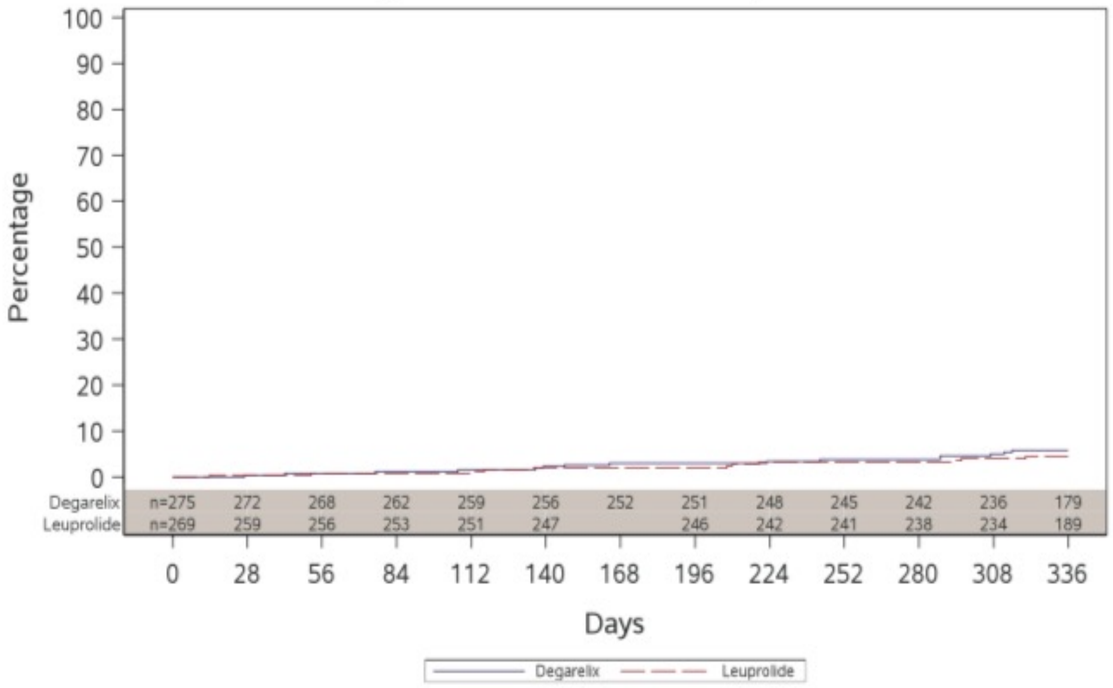
ORIGINAL RESEARCH ARTICLE

Cardiovascular Safety of [illegible]lix Versus Leuprolide in Patients With Prost[illegible]ncer

The Primary Results of the PRONOUNCE Randomized Trial

First RCT with MACE as primary endpoint

Primary End Point: Inverted Kaplan-Meier Estimates of Cumulative Probability of First Adjudicated MACE - Full Analysis Set



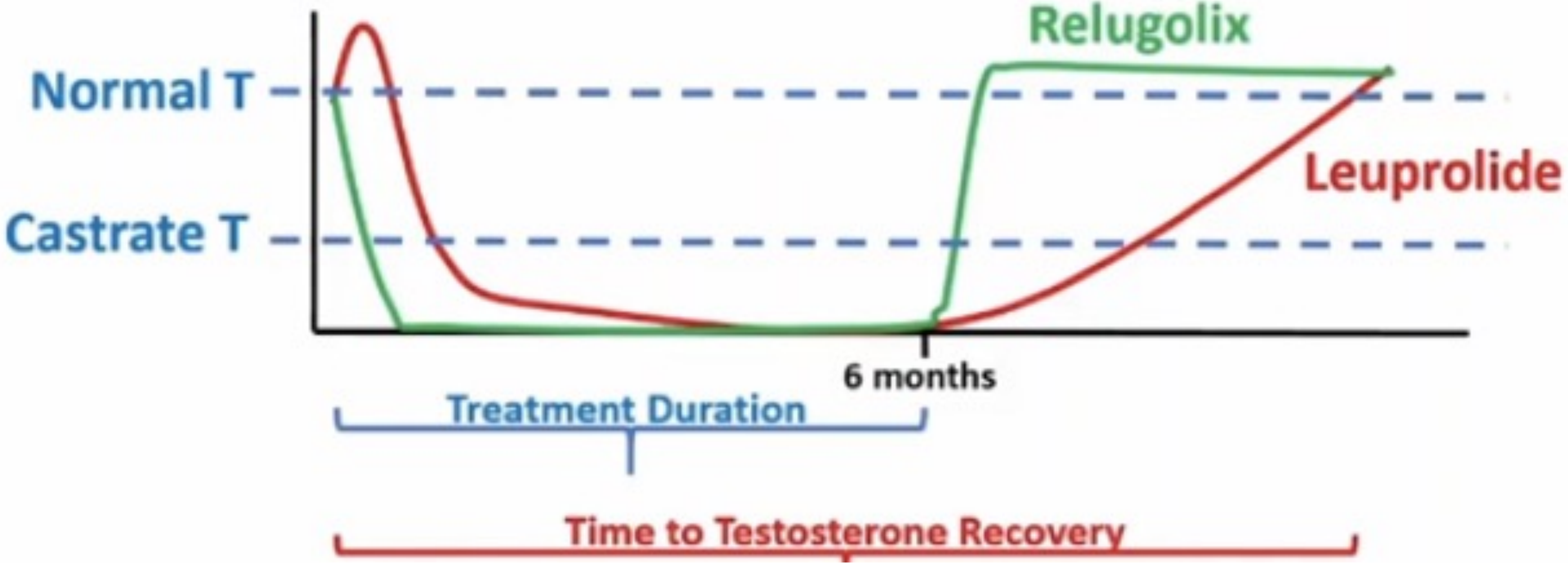
What Are the Clinical Implications?

- The relative cardiovascular safety of GnRH antagonists and agonists remains unresolved.
- Cardiovascular events might be lower in patients with prostate cancer through better awareness and attention to cardiovascular risk factor control.
- In light of improved cancer survivorship and the competing risk of cardiovascular disease, there is an ongoing need for rigorous cardio-oncology clinical trials.
- PRONOUNCE provides a model for interdisciplinary collaboration between urologists, oncologists, and cardiologists with a shared goal of evaluating the impact of cancer therapies on cardiovascular outcomes.

Lopes, et al. Circulation 2021

A better way to report ADT duration ?

- Instead of "**treatment duration**" should we report "**# months of castration**"?
- With quicker acting drugs, **time to testosterone recovery** should be monitored & reported in all future ADT trials



Strategies to increase compliance to ADT

1. Do not give ADT to patients for whom there is no oncologic benefit
2. Make sure all patients starting ADT are medically optimized (ABCDE)
    A. for **A**wareness and **A**spirin
    B. for **B**lood pressure **C**ontrol
    C. for **C**holesterol and **C**igarettes
    D. for **D**iabetes mellitus and **D**iet
    E. for **E**xercise
3. Consider referral to cardiologist in case of multiple cardiovascular risk factors or history of cardiovascular events

Strategies to increase compliance to ADT

4. Do not prescribe intermittent ADT in patients with M+ disease

- OS is worse in IAD compared to CAD!
  - –Median OS differences of 8-10 months in CAD vs. IAD

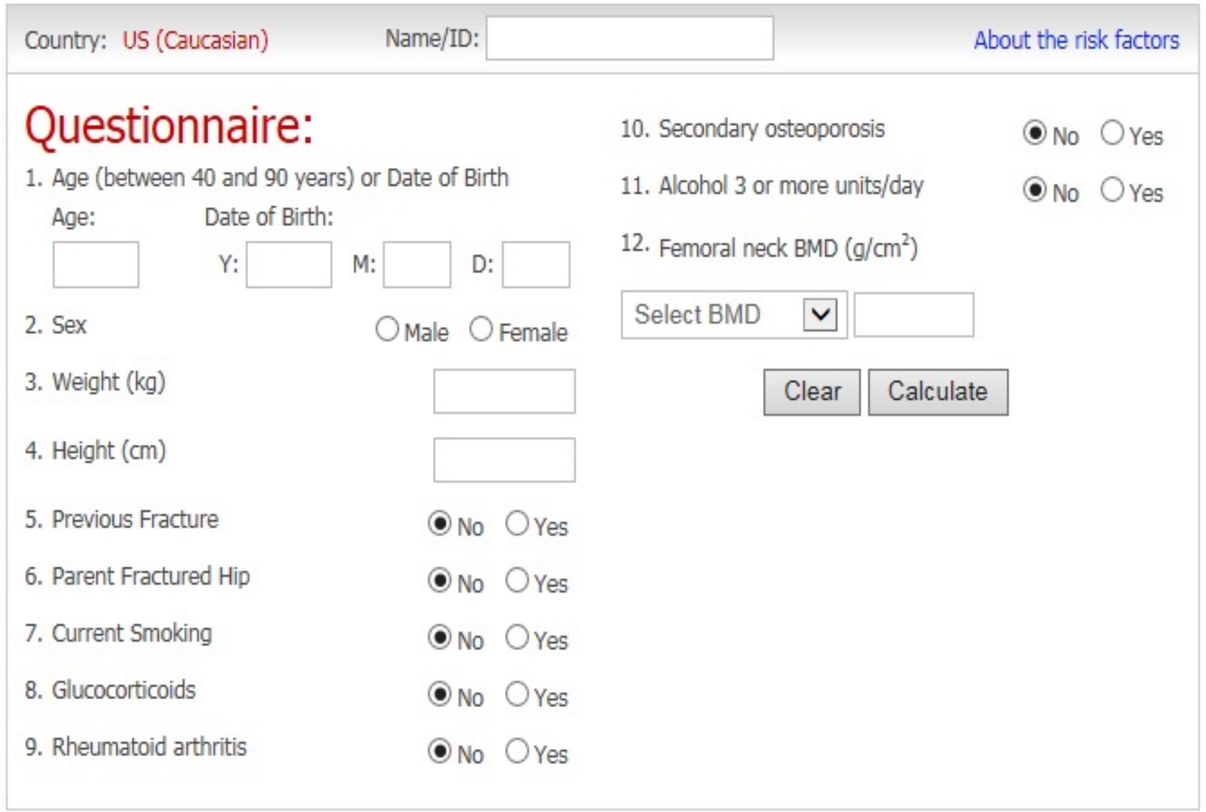
- Combined data from RCTs does not support large or durable effects on QOL

Hussain, et al. J Clin Oncol 2016

Strategies to increase compliance to ADT

5. Assess the risk of fractures with specific tools (FRAX)

- Up to a 21% relative increase in clinical fractures on ADT due to bone loss



NCCN guidelines

- For men with a 10 year risk of hip fracture >3% based on the FRAX algorithm
- 1200 mg calcium, 800-1000 IU vitamin D

AND either

-Denosumab 60mg SQ every 6 months

-Zolendronic acid 5mg IV annually

-Alendronate 70 mg PO weekly


Thank you