

Overview: Key Points

- American Heart Association and observational studies link androgen deprivation therapy (ADT) to increased risk of cardiovascular events
 - ~50% of patients with locally advanced and metastatic prostate cancer receive ADT
- ABCDE algorithm- awareness, aspirin, blood pressure, cholesterol, cigarette cessation, diabetes, diet, exercise- may reduce cardiovascular disease (CVD) risks
- Study recommends initial CVD screening and quarterly monitoring appointments during the first year of therapy
- Preliminary trials show CVD event risk with GnRH antagonist treatment (degarelix) is 50% lower than with GnRH agonist treatment (leuprolide, goserelin, triptorelin, histrelin)

Levine et al. *Circulation*. 2010;121. Nguyen et al. *Eur Urol*. 2015; 67. Conteduca et al *Crit Rev Oncol Hematol*. 2013; 86. Bhatia et al. *Circulation*. 2016; 133. Albertsen et al. *Eur Urol*. 2014; 65

- Testosterone binds to androgen receptor, creates androgen response which stimulates prostate cancer growth
- ADT goal: Reduce serum testosterone to levels <50 ng/dL by
 - Pharmacological castration, bilateral orchiectomies
 - GnRH agonist- LH surge, eventual receptor downregulation decreases LH
 - GnRH antagonist- inhibits LH release
 - Gonadotropin-releasing hormone (GnRH) receptors stimulate LH production in anterior pituitary
 - Luteinizing hormone (LH) stimulates testosterone production in testes
 - Antiandrogens directly block androgen receptor at prostate cancer cell

GnRH Agonists

Leuprolide - Lupron

Goserelin - Zoladex

Triptorelin - Trelstar

Histrelin - Supprelin

GnRH Antagonists

Degarelix - Firmagon

Antiandrogens

Flutamide - Eulexin

Bicalutamide - Casodex

Nilutamide - Nilandron

Enzalutamide - Xtandi

- Most data, primarily derived from GnRH agonists, demonstrate:
 - Decreased glucose tolerance, lean body mass
 - Increased metabolic syndrome, low-density lipoprotein, high-density lipoprotein, triglyceride levels, insulin resistance, body fat

ADT may promote atherosclerosis and risk of coronary artery disease

- Decreased vasodilation, high-density lipoprotein
- Increased visceral fat deposits
- Increased thrombotic state
 - Risk of deep vein thrombosis, pulmonary embolism, arterial thrombosis, stroke

How ADT affects Cardiovascular System: Unknown

- No clear relationship between ADT and blood pressure
- *ADT improves vascular endothelial function*
 - Would typically protect against atherosclerosis, so atherogenesis mechanism is unclear
- ADT may increase risk of arrhythmia (prolonged QT interval)

GnRH Antagonists vs Agonists

- GnRH antagonists (degarelix) decrease both follicle -stimulating hormone and LH, but GnRH agonists primarily decrease LH
 - Drug classes may affect endothelial function, lipid metabolism, and fat accumulation differently
- 2014 collection of 6 randomized, controlled trials: patients with history of CVD twice as likely to have cardiac event when treated with GnRH agonist compared to GnRH antagonist treatments
 - Prospective studies needed

- No single prospective study has established the effect androgen deprivation therapy has on cardiovascular disease or CVD mortality
- Patients who have experienced heart attack or congestive heart failure are at highest risk of cardiovascular events with ADT, particularly in first 6 months of treatment
- Use ABCDE approach to promote cardiovascular health

A: Awareness, Aspirin

- Increase patients' awareness of CVD signs and symptoms
 - Screen for undiagnosed CVD and metabolic risks
 - Refer to cardio-oncologist to establish baseline electrocardiogram and monitor QTc (corrected QT interval)
 - Echocardiogram if history or evidence of congestive heart failure or structural heart disease
- Aspirin for primary and secondary prevention of CVD- 81 mg daily
 - Studies show aspirin may lower prostate cancer-specific mortality in diagnosed patients (hazard ratio 0.6; 95% CI 0.37-0.97)

B: Blood Pressure

- Hypertension is a major risk of cardiovascular disease
 - Goal: <140/90 mmHg
- ACE inhibitors reduce mortality in patients with CVD and diabetes
 - Delayed prostate-specific antigen failure in ACE inhibitor treatment-potentially protective effect in patients with prostate cancer

C: Cholesterol, Cigarette Cessation

- High-intensity statin therapy is the recommended hyperlipidemia treatment, especially for patients with diabetes or CVD
- Cessation support- smoking increases all-cause and prostate cancer-specific mortality in patients with prostate cancer

- ADT can impact glycemic control- monitor blood glucose and adjust therapy accordingly
 - Metformin is first-line treatment for diabetes and has positive effect on metabolic syndrome
- American Society of Clinical Oncology encourages regular physical activity and calorie restriction to maintain healthy weight

- Increase intake of fruits, vegetables, and whole grains
- Consume 600 IU of vitamin D, 1200mg calcium daily
- Decrease saturated fats
- Limit alcohol intake to ≤ 2 servings per day
- Consider counseling referral: psychological stress from cancer diagnosis can affect eating habits and independently increase CVD risk

- Growing evidence shows structured exercise programs decrease ADT side effects
- American College of Sports Medicine recommends 2.5 hours/week moderate exercise or 75 minutes/week vigorous exercise
 - Moderate- brisk walking, light swimming; vigorous- jogging, hard swimming
 - Gradually build to recommended activity levels

Closing Points

- 1) Emphasize patient protection of cardiovascular health using ABCDE approach
- 2) Follow-up at least once each quarter in first year of androgen deprivation therapy