Title:

Androgen deprivation therapy and cardiovascular disease

Authors:

C Melloni, MT Roe

Journal:

Urologic Oncology: Seminars and Original Investigations 2019

Urologic Oncology: Seminars and Original Investigations 000 (2019) 1–8

UROLOGIC ONCOLOGY

Seminars article

Androgen deprivation therapy and cardiovascular disease

Chiara Melloni, M.D., M.H.S.*, Matthew T. Roe, M.D., M.H.S.

Duke Clinical Research Institute, Duke University Medical Center, Durham, NC

Abstract

Prostate cancer (PCa) is the most common cancer among men. Advances in early detection and successful treatments have improved cancer-specific survival. With prolonged survival, PCa patients now suffer from the effects of aging and are at increasing risk for the development of cardiovascular (CV) risk factors and CV disease. Androgen deprivation therapy (ADT) is the mainstay treatment of advanced PCa. There is conflicting evidence about whether or not ADT is associated with increased CV morbidity and mortality. Metabolic abnormalities such as increasing body weight, reduced insulin sensitivity, dyslipidemia, and activation of T cells to the Th1 phenotype, resulting in atherosclerotic plaque destabilization, have been proposed as possible mechanisms by which ADT may increase the risk of CV events. Type of ADT and preexisting CV history also seem to play a major role in the risk of subsequent CV events. Ongoing prospective clinical trials will help define whether there is any difference between gonadotropin-releasing hormone agonists and antagonists in terms of CV morbidity and mortality.

Keywords: Androgen deprivation therapy; Cardiovascular comorbidities; Myocardial infarction; Cardiovascular morbidity

Prostate cancer (PCa) is the most common cancer among men (after skin cancer) and affects mainly older men (about 80% of cases are in men >65 years old). For all stages of PCa at diagnosis, the 5-year relative survival rate is 99% and the 15-year relative survival rate is 96% [1]. With aging, men are more likely to develop cardiovascular (CV) risk factors and die of related causes, such as heart disease [2]. Incidence of both PCa and CV disease is highest in older men, and CV disease is the second most common cause of death in men with PCa [3].

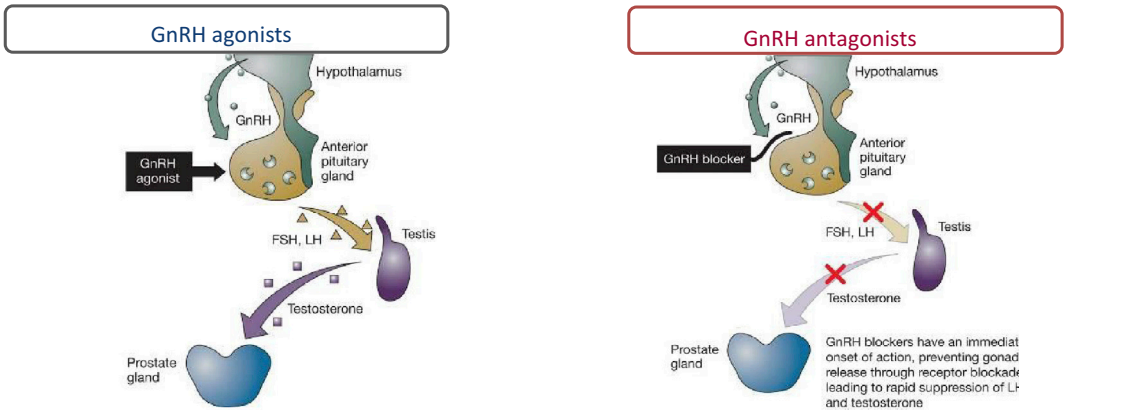
Androgen deprivation therapy (ADT) is the mainstay of systemic therapy for PCa and results in castrate serum levels of testosterone (<50ng/dl). In order to lessen or block cancer progression, ADT needs to reduce serum testosterone (the main androgen hormones) to the recommended level of <50 ng/dl. ADT encompasses surgical castration (bilateral orchiectomy) and chemical castration (gonadotropin-releasing hormone [GnRH] agonists or GnRH antagonists) with or without the addition of antiandrogen therapy. ADT has been shown to improve survival rates, delay cancer progression, and mitigate cancer-related symptoms [4]. The duration of ADT therapy is variable, but is often continued for months to years, if not indefinitely; and therefore, consideration should be given to the most appropriate type of ADT for a given patient [4].

Approximately a decade ago, initial reports of a link between ADT and risk of CV events, including myocardial infarction (MI) and CV mortality, were published [5,6]. Although conflicting evidence exists on a definite and quantifiable link between ADT and CV effects, a joint scientific statement from the American Heart Association, American Cancer Society, and American Urological Association was published in 2010 suggesting a possible association between ADT and risk of CV events [7]. The statement had the goal of increasing awareness of the possible connection between ADT and CV risk, emphasizing the importance of a CV risk assessment at baseline before starting ADT, and ensuring appropriate follow-up of patients with preexisting CV risk factors [7]. Shortly after this publication, the Food and Drug Administration and Health Canada revised the GnRH agonist label warning of the possible risks of CV disease and diabetes [8]. The European Medicines Agency required

Disclosures:
Dr. Melloni's disclosure can be viewed at https://www.dcri.org/wp-content/uploads/2017/10/2017-COI-Chiara-Melloni.pdf
Dr. Roe's disclosure can be viewed at https://www.dcri.org/wp-content/uploads/2018/02/M-Roe-DCRI-COI-Form-February-2018.pdf

*Corresponding author.
E-mail address: Chiara.melloni@duke.edu (C. Melloni).

https://doi.org/10.1016/j.urolonc.2019.02.010
1078-1439/



- **Surge in FSH, LH and testosterone before suppression**
- **Microsurges in LH and testosterone on repeat injection**
- **FSH suppression, but not maintained long term**

- **Immediate suppression of FSH, LH and testosterone**
- **No microsurges**
- **Prolonged suppression of FSH, LH and testosterone**

Fig. 1. Mechanism of action of GnRH agonist and antagonist.

a similar warning for both GnRH agonists and antagonists. Since then, there has been a growing body of literature evaluating the effect of ADT on CV risk, exploring potential mechanisms underlying the risk, and understanding clinical implications of 1 type of ADT treatment vs. another; yet optimal management of these patients and clear understanding of the benefit-risk ratio remains uncertain.

GnRH agonists and antagonists reduce testosterone levels through 2 different pathways, and their distinctive mechanisms of action could potentially explain the differing impacts on CV risk. GnRH agonists (such as leuprolide, goserelin, and triptorelin) bind to GnRH receptors on the pituitary gland, causing an initial release of luteinizing hormone (LH) and follicle stimulating hormone (initial "flare" response), but with continuous administration, they desensitize the gland, determining a down regulation of LH secretion and subsequent fall in androgens levels (mainly testosterone). On the other hand, GnRH antagonists (such as degarelix) bind in a competitive way to GnRH receptors in the pituitary gland, blocking the release of follicle stimulating hormone and LH and leading to a rapid suppression of testosterone release from the testes (Fig. 1).

Potential mechanisms of CV disease

Some hypotheses have been generated on the possible mechanism by which ADT increases risk of CV events, but a clear understanding of this relationship is still lacking. Loss of the cardio-protective effect of testosterone has been cited as a possible reason, and metabolic abnormalities such as increasing body weight, reduced insulin sensitivity, and dyslipidemia have been described in the first few months after start of ADT.

Two prospective studies have demonstrated changes in lean body mass and composition, with a decline in lean body mass by 2.5% to 3.8% and an increase in fat mass by 9.4% to 11%, over the course of the first year of ADT treatment [9,10]. The effect of ADT on fat mass was also noted to be primarily an increase in subcutaneous rather than visceral fat [11]. During the first 3 months of ADT, significant changes in patients' lipid profiles have also been described in a few studies [12,13]. Smith et al. have shown that after 48 weeks of treatments, total cholesterol, HDL cholesterol, and LDL cholesterol increased by 9.0% ($P < 0.001$), 11.3% ($P = 0.001$), and 7.3% ($P = 0.05$), respectively, in 40 men with locally advanced PCa [14]. A single prospective study has reported a decrease in the insulin sensitivity index of 12.9% and a rise in fasting plasma insulin levels of 25.9% in a group of patients receiving ADT for 12 weeks [14]. Another cross-sectional study exploring the effect of longer ADT treatment (>12 weeks) on glucose and insulin resistance showed that glucose levels were 131 mg/dl in the ADT group compared with 103 mg/dl in the non-ADT group and 99 mg/dl in the age-matched control group; similarly, insulin levels were higher in the ADT group (45.0 uU/ml vs. 24.0 uU/ml vs. 19.0 uU/ml, respectively). While these changes seem to mimic the typical metabolic syndrome, it is worth noticing that no alterations in blood pressure have been observed in these studies, no change in inflammatory markers such as C-reactive protein has been described, and an increase in subcutaneous fat rather than visceral fat has been noted. More recently, an interesting pathway has been explored. T cells express GnRH receptors, and they are present in atherosclerotic plaque; activation of these receptors by GnRH agonists can stimulate T cell expansion and differentiation in the Th1 phenotype,

potentially promoting fibrotic cap disruption and plaque destabilization [15].

Clinical data

In the past decade, data from retrospective and prospective clinical studies have yielded conflicting results on the effect of ADT on clinical CV events. Two observational studies using data from the Surveillance Epidemiology and End Results-Medicare Program were among the first to report an increased incidence in CV events in patients treated with ADT [5,16]. Keating et al. reported data from a population-based cohort of >70,000 men diagnosed with locoregional PCa, a third of whom received a GnRH agonist. During the follow-up period (≥2 years), compared with patients not receiving treatment, those receiving GnRH agonists were at increased risk of incident diabetes (adjusted hazard ratio [aHR] 1.44, 95% confidence interval [CI] 1.34−1.55), incident coronary heart disease (aHR 1.16, 95% CI 1.10−1.21), MI (aHR 1.11, 95% CI 1.01 −1.21), and sudden death (aHR 1.16, 95% CI 1.05−1.27). Orchiectomy was associated with increased risk of incident diabetes but none of the CV events. Similarly, the second study showed that patients newly diagnosed with PCa receiving a LH-releasing hormone agonist experienced a 20% higher risk of CV morbidity (HR 1.2, 95% CI 1.15 −1.26) over a 5-year follow-up period [16]. O'Farrell et al. in another large observational study found a consistent increase in risk of CV disease in men with PCa treated with a GnRH agonist when compared with a matched PCa-free group [17]. They showed that the risk peaked sharply during the first 6 months of treatment, yet it lasted over the first year of treatment. A meta-analysis of 3 randomized clinical trials (RCTs) in men randomized to receive radiation therapy vs. ADT (different durations) showed that men >65 years old who received 6 months of ADT experienced shorter times to fatal MIs compared with those who did not receive ADT. No difference in time to MI was observed when a shorter duration of ADT (3 months) was compared with longer treatment. The increased risk was not observed among those aged <65 years [18]. Two recent meta-analyses including observational studies consistently showed an increased risk of CV events in patients treated with ADT compared with patients receiving a non-ADT treatment. The meta-analysis of 6 observational studies ($n = 295,407$) led by Zhao et al. [19] found ADT was linked to increased risk of CV disease (HR 1.10, 95% CI 1.00−1.21) and CV mortality (HR 1.17, 95% CI 1.04−1.32) (Fig. 2). Subgroup

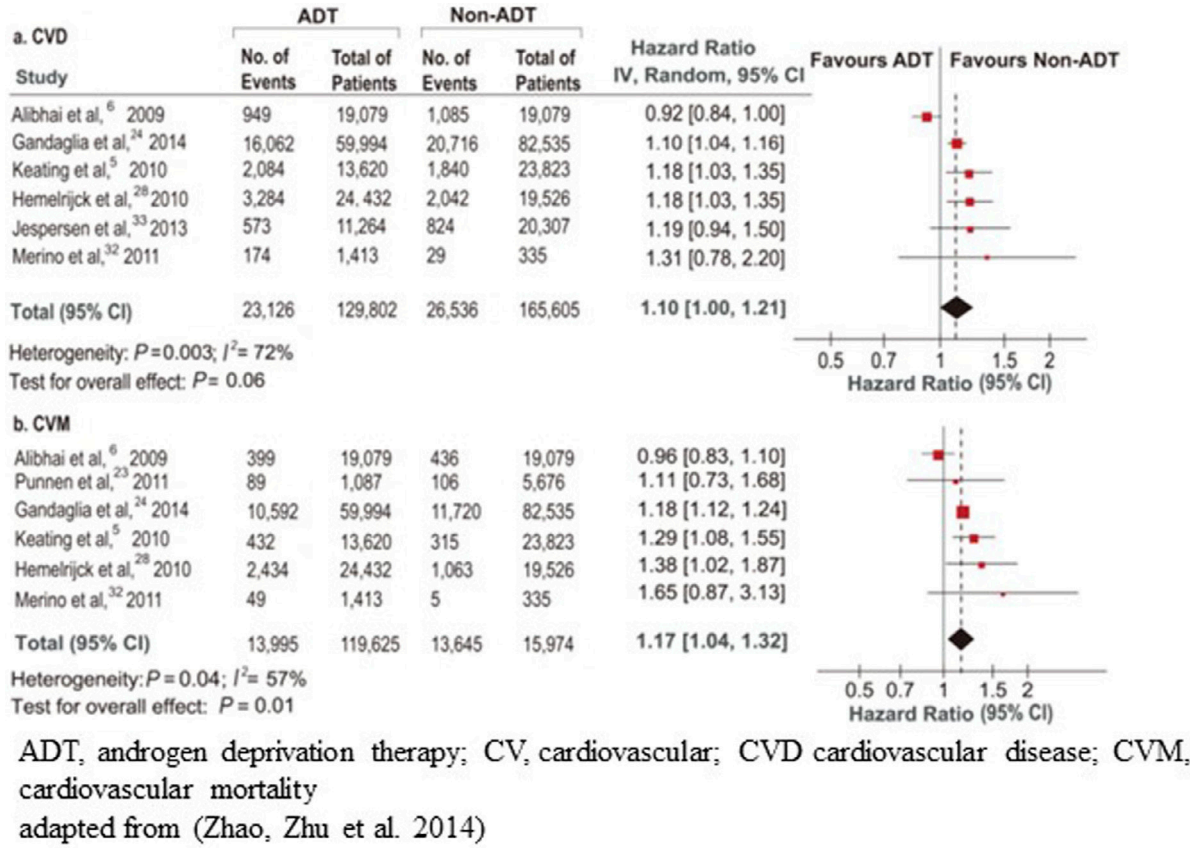


Fig. 2. Androgen deprivation therapy (ADT) is associated with cardiovascular (CV) morbidity and mortality.

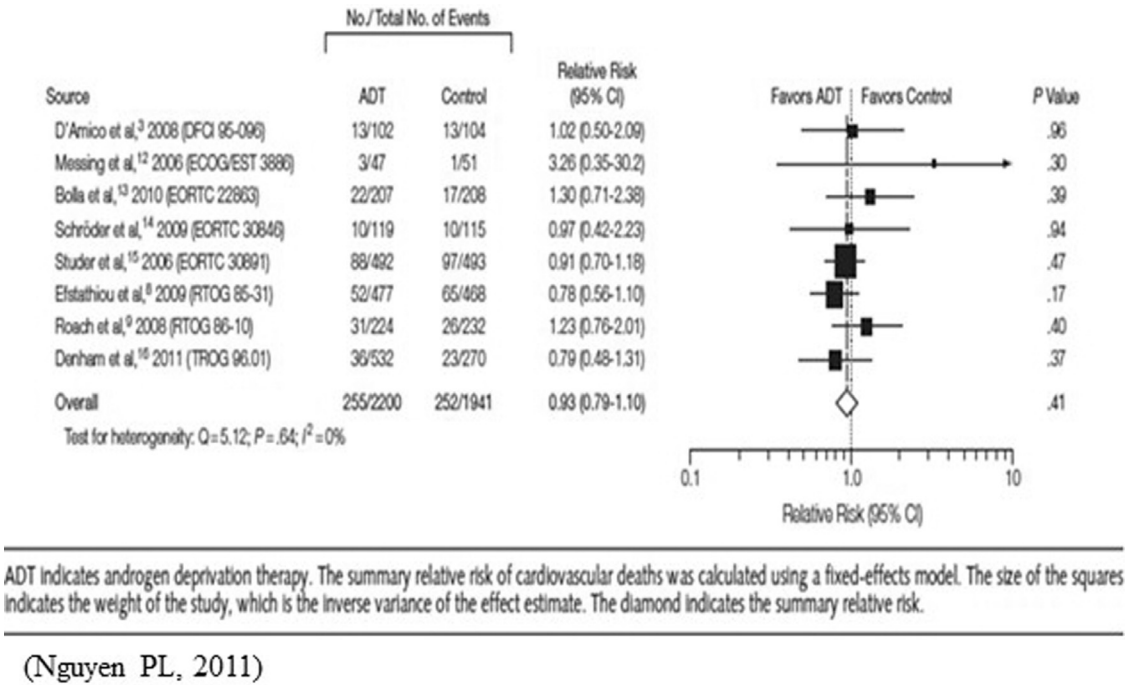


Fig. 3. Relative risk of cardiovascular (CV) death associated with androgen deprivation therapy (ADT) in men with prostate cancer (PCa) (adapted from Nguyen [22]).

analysis by type of ADT showed that increased risk of CV disease was associated with GnRH agonists alone (HR 1.19, 95% CI 1.04−1.36) and GnRH agonists plus antiandrogen (AA) (HR1.46, 95% CI 1.03−2.08) but not with AA alone or orchietomy (HR 0.94, 95% CI 0.85−1.03; and HR 1.15, 95% CI 0.92−1.43, respectively). A similar association was found in the subgroup analysis by ADT type and CV mortality (GnRH alone: HR 1.36, 95% CI 1.10−1.68; GnRH plus AA: HR 1.44, 95% CI 1.33−1.57; AA alone: HR 0.95, 95% CI 0.70−1.27). Similarly, Bosco et al. showed an increased risk of non-fatal CV events (MI and stroke) among patients treated with ADT, specifically GnRH agonists, compared with those not receiving ADT (relative risk [RR] 1.38, 95% CI 1.29−1.48) [20]. When they looked at the associations between GnRH agonists and nonfatal and fatal MI and stroke, they appeared to be even stronger (RR 1.57, 95% CI, 1.26−1.94; and RR 1.51, 95% CI, 1.24−1.84, respectively) [20].

Conversely, during the same time frame, secondary analyses from RCTs reported no association between ADT and CV risk. An RCT comparing radiotherapy plus ADT for 6 months vs. radiotherapy plus ADT for 3 years in patients with locally advanced PCa showed no difference in the rate of fatal cardiac events at 5 years [21]. Another RCT randomizing 206 men with localized but high-risk PCa to radiation therapy alone vs. radiation therapy plus ADT showed no difference in cardiac deaths between the 2 groups. Yet, a higher number of cardiac deaths were observed in men with moderate to severe comorbidities [18].

A meta-analysis of 8 RCTs comparing immediate ADT treatment (all modalities and different durations) with non-immediate ADT in 4,141 men with high-risk, non-metastatic PCa did not find an association between ADT and increased risk of CV death, both when long-term (at least 3 years) or short-term (6 months or less) ADT treatment duration was taken into account (RR 0.91, 95% CI 0.75−1.10; and RR 1.00, 95% CI 0.73−1.37; $P = 0.99$) [22] (Fig. 3).

Many factors have been called into play to try to explain these differences in study results, such as study-specific characteristics, treatment-specific factors, or patient factors. For example, heterogeneity in study population, in study design (including different follow-up periods/methods), and intrinsic selection bias in men receiving a type of ADT observed in observational studies make generalizability of results difficult. Treatment-specific factors such as lack of data on type of ADT, extensive variability in duration of ADT, and comparison to age-matched groups rather than to patients with PCa not treated with ADT, also make comparison difficult. Furthermore, since the GnRH antagonist degarelix was approved only in 2008, it is important to keep in mind that the majority of patients enrolled in the above studies were most likely treated with agonists and not antagonists. Finally, all these studies included mixed cohorts of both patients with and without existing CV disease, and CV events were not systematically collected or adjudicated.

Table 1
Androgen deprivation therapy and incidence of cardiovascular disease.

	Adjusted HR (95% CI)			
Treatment	Incident CHD	Myocardial infarction	Sudden cardiac death	Stroke
No ADT	Ref	Ref	Ref	Ref
GnRH agonist	1.19 (1.10−1.28)	1.28 (1.08−1.52)	1.35 (1.18−1.54)	1.21 (1.05−1.40)
Orchiectomy	1.40 (1.04−1.87)	2.11 (1.27−3.50)	1.29 (0.76−2.18)	1.49 (0.92−2.43)
Combined androgen blockade	1.27 (1.05−1.53)	1.03 (0.62−1.71)	1.22 (0.85−1.73)	0.93 (0.61−1.42)
Antiandrogen	1.10 (0.80−1.53)	1.05 (0.47−2.35)	1.06 (0.57−1.99)	0.86 (0.43−1.73)

ADT = androgen deprivation therapy; CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio. (Keating, O'Malley, et al. 2010).

Due to increased awareness of these differences, some studies have subsequently looked specifically at the effect of ADT on CV risk in patients with preexisting CV comorbidities and have accounted for type and length of ADT received.

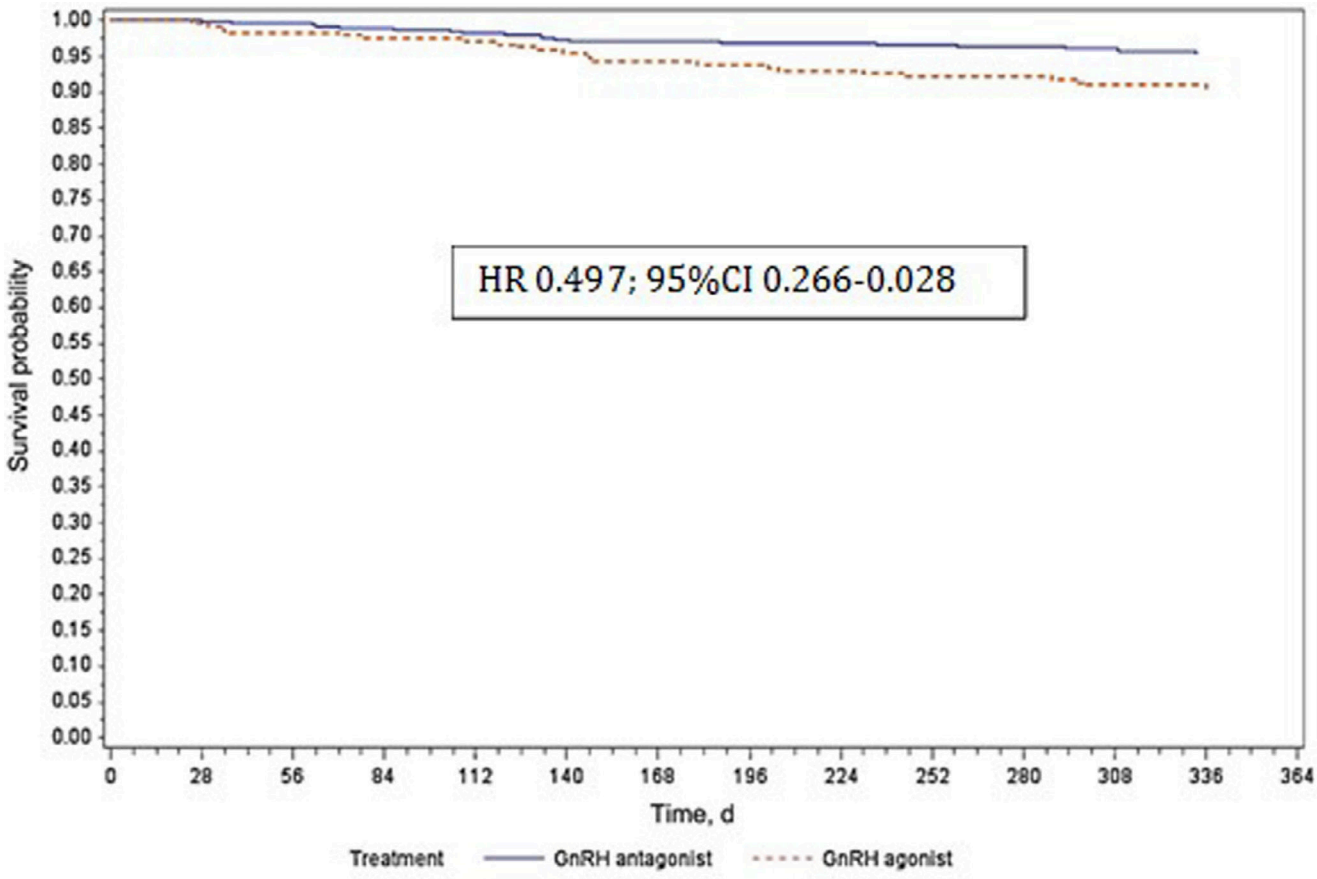
Does preexisting CV history or mode of ADT matter?

A retrospective analysis of 5,077 men with localized or locally advanced PCa treated with or without ADT for 4 months followed by radiotherapy showed that ADT treatment was not associated with an increased risk of all-cause mortality among those without cardiac risk factors/known CV disease (9.6% vs. 6.7%, aHR 0.97, 95% CI 0.72−1.32) or with a single CV risk factor (10.7% vs. 7.0%, aHR 1.04, 95% CI 0.75−1.43). All-cause mortality was higher only among those with CAD (26.3% vs. 11.2%, aHR 1.96, 95% CI 1.04−3.71) [23]. Another study led by Ziehr et al. found that among 5,077 men with non-metastatic PCa treated with brachytherapy with and without ADT, a link between ADT and CV death existed only among those with a history of congestive heart failure and MI (aHR 3.28, 95% CI 1.01−10.64) [24]. Keating et al. specifically investigated each ADT modality and found that each one is associated with a different risk profile [25] (Table 1). A few years later, an analysis from the Surveillance Epidemiology and End Results-Medicare database in 104,474 patients with non-metastatic PCa found that treatment with GnRH agonists and not orchiectomy was associated with increased 10-year rates of coronary artery disease, acute MI, and sudden cardiac death [26]. Pooled data from 6 phase-3 RCTs that randomized 2,328 patients to a GnRH agonist vs. antagonist found that among patients with preexisting CV disease receiving GnRH antagonists, their risk of subsequent CV events within 1 year of initiation of therapy was lower compared with those receiving a GnRH agonist (HR 0.44, 95% CI 0.26−0.74) [15] (Fig. 4). Bosco et al., in their meta-analysis of observational data on ADT and risk of CV disease in men with PCa, performed a secondary analysis to explore the risk profile by type of ADT, showing that the risk was consistently higher among those receiving ADT treatment compared with those not treated, but it differed based on type of treatment (GnRH agonist: RR 1.38, 95% CI 1.29−1.48; orchiectomy: RR 1.448, 95% CI 1.28−1.62; and antiandrogens: RR 1.21, 95% CI 1.07−1.37) [20]. Similar findings were observed in a pooled analysis of 1,704 men from 9 clinical trials [13].

Although there is increased awareness of the changes in patients' metabolic profiles, potential risk of CV events in men with PCa receiving ADT, and the fact that at treatment initiation a high percentage of men already present CV risk factors, there are no written guidelines that confirm whether screening or intervention practices for CV disease prevention should mimic those used for the general population. Some centers have proposed and are implementing a screening and treatment algorithm (e.g., ABCDE) to control baseline CV risk factors and prevent subsequent CV events (Fig. 5). Increased patient awareness, counseling on the potential CV effects of ADT treatment, and education on how to address modifiable CV risk factors should be a critical part of the management of these patients.

Three studies are currently underway and will address some of the key questions on the relationship between ADT and risk of CV events. RADICAL-PC combines 2 prospective studies, 1 of which is inserted in the other. The role of ADT in CV disease—a longitudinal PCa study (RADICAL PC1) is a prospective cohort study of men ($n = 1,884$) enrolled within the first year of their initial diagnosis of PCa, or who are within 1 month of initiation of ADT. The main objective of the study is to identify factors associated with the development of CV disease among men with PCa, with a focus on ADT. The second study, the randomized intervention for CV andlLifestyle risk factors in PCa patients (RADICAL PC2) is an RCT embedded in RADICAL PC1 aiming to enroll >4,000 patients. RADICAL PC2 will test a systematic approach to modifying CV and lifestyle risk factors. The intervention group will receive: 1) standardized advice on healthy diet and exercise; 2) a low-dose antiplatelet agent; 3) a low- to moderate-dose statin; and 4) angiotensin-converting enzyme inhibition for baseline systolic blood pressure ≥130 mmHg. The composite primary efficacy endpoint includes CV death, MI, stroke, heart failure, and arterial revascularization (ClinicalTrials.gov #NCT03127631).

The PRONOUNCE study (A trial comparing CV safety of degarelix vs. leuprolide in patients with advanced PCa



(Albertsen PC, 2014)

Fig. 4. Kaplan-Meier plot of time to first cardiovascular event or death among men with preexisting cardiovascular disease.

A	Awareness and Aspirin	• Increased awareness of patients about CV signs and symptoms. • Aspirin 81 mg daily for primary or secondary prevention of CV events.
B	Blood Pressure	Goal blood pressure < 140/90 mmHg
C	Cholesterol and Cigarettes	• High intensity statin therapy for pre-existing CVD or hyperlipidemia. • Smoking cessation counseling, therapy.
D	Diet and Diabetes	• Frequent blood glucose monitoring • Metformin for diabetes if possible. • Diet rich in fruits, vegetables, whole grain and low in saturated fat with 600 IU of vitamin D daily and adequate calcium (1200 mg/day). • Avoidance of excessive alcohol.
E	Exercise	150 minutes per week of moderate intensity physical activity or 75 minutes per week of vigorous exercise.

(Bhatia, Santos et al. 2016)

Fig. 5. ABCDE algorithm for prostate cancer survivors.

and CV disease) is a multi-center, randomized, assessor-blind, controlled trial comparing the occurrence of major adverse CV events in patients with PCa and CV disease receiving a GnRH antagonist or a GnRH agonist, and it is currently enrolling across >30 sites in the United States and Canada. The primary objective is to demonstrate whether treatment with a GnRH antagonist (degarelix) is associated with a lower risk of major adverse CV events (a composite of death due to any cause, non-fatal MI, non-fatal stroke, or non-fatal unstable angina requiring hospitalization) as compared with a GnRH agonist (leuprolide) in patients with PCa and concomitant CV disease (ClinicalTrials.gov #NCT02663908).

Advances in early detection and successful treatments have improved cancer-specific survival. With prolonged survival, PCa patients now suffer from the effects of aging and are at increasing risk for the development of CV risk factors and CV disease. Over the long-term, CV mortality has become more common than cancer mortality for many cancer survivors. ADT appears to be associated with a higher risk of CV events, a risk that peaks as early as the first 6 months of treatment. The underlying mechanism seems to be multifactorial, encompassing both metabolic and immunomodulatory changes, and the risk of subsequent events varies based on existence of concomitant CV comorbidities and type of ADT received. Therefore, due to the frequent coexistence of these 2 diseases, effective communication and collaboration between various providers (oncologists, urologists, and cardiologists) as essential members of a care team is crucial to meet the challenge of balancing cancer and CV outcomes towards optimizing survival. Ongoing prospective clinical trials will help define whether there is any difference between GnRH agonists and antagonists in terms of CV morbidity and mortality.

References

[1] American Cancer Society. Survival rates for prostate cancer. 2017 Available at: https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/survival-rates.htm.

[2] Epstein MM1, Edgren G, Rider JR, Mucci LA, Adami HO. Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst 2012;104:1335–42.

[3] Driver JA, Djoussé L, Logroscino G, Gaziano JM, Kurth T. Incidence of cardiovascular disease and cancer in advanced age: prospective cohort study. BMJ 2008;337:a2467.

[4] Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. JAMA 2005;294:238–44.

[5] Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–56.

[6] Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst 2007;99:1516–24.

[7] Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL. American Heart Association Council on Clinical Cardiology and Council on Epidemiology and Prevention, the American Cancer Society, and the American Urological Association. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. Circulation 2010;121:833–40.

[8] U.S. Food & Drug Administration. FDA drug safety communication: update to ongoing safety review of gnrh agonists and notification to manufacturers of gnrh agonists to add new safety information to labeling regarding increased risk of diabetes and certain cardiovascular diseases. 2010. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm229986.htm.

[9] Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. Urology 2004;63:742–5.

[10] Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 2002;87:599–603.

[11] Smith MR, Lee H, McGovern F, Fallon MA, Goode M, Zietman AL, et al. Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer: differences from the classic metabolic syndrome. Cancer 2008;112:2188–94.

[12] Eri LM, Urdal P, Bechensteen AG. Effects of the luteinizing hormone-releasing hormone agonist leuprolide on lipoproteins, fibrinogen and plasminogen activator inhibitor in patients with benign prostatic hyperplasia. J Urol 1995;154:100–4.

[13] Smith MR, Klotz L, van der Meulen E, Colli E, Tankó LB. Gonadotropin-releasing hormone blockers and cardiovascular disease risk: analysis of prospective clinical trials of degarelix. J Urol 2011;186:1835–42.

[14] Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab 2006;91:1305–8.

[15] Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol 2014;65:565–73.

[16] Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS. Urologic Diseases in America Project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110:1493–500.

[17] O'Farrell S, Garmo H, Holmberg L, Adolfsson J, Stattin P, Van Hemelrijck M. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. J Clin Oncol 2015;33:1243–51.

[18] D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ, Lamb DS, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol 2007;25:2420–5.

[19] Zhao J, Zhu S, Sun L, Meng F, Zhao L, Zhao Y, et al. Androgen deprivation therapy for prostate cancer is associated with cardiovascular morbidity and mortality: a meta-analysis of population-based observational studies. PLoS One 2014;9:e107516.

[20] Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating NL, Van Hemelrijck M. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol 2015;68:386–96.

[21] Bolla M, de Reijke TM, Van Tienhoven G, Van den Bergh AC, Oddens J, Poortmans PM. EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009;360:2516–27.

[22] Nguyen PL, Je Y, Schutz FA, Hoffman KE, Hu JC, Parekh A, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. JAMA 2011;306:2359–66.

[23] Nanda A, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA 2009;302:866–73.

[24] Ziehr DR, Chen MH, Zhang D, Braccioforte MH, Moran BJ, Mahal BA, et al. Association of androgen-deprivation therapy with excess cardiac-specific mortality in men with prostate cancer. BJU Int 2015;116:358–65.

[25] Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst 2010;102:39–46.

[26] Gandaglia G, Sun M, Popa I, Schiffmann J, Abdollah F, Trinh QD, et al. The impact of androgen-deprivation therapy (ADT) on the risk of cardiovascular (CV) events in patients with non-metastatic prostate cancer: a population-based study. BJU Int 2014;114:E82–9.