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## 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***

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Androgen-deprivation therapy (ADT) is a widely used treatment for prostate cancer. Recently, several studies have reported an association between ADT and an increased risk of cardiovascular events, including myocardial infarction and cardiovascular mortality.<sup>1-5</sup> These reports have led to increased interest and discussion regarding the metabolic effects of ADT and its possible association with increased cardiovascular risk. In addition, likely as a result of these reports, internists, endocrinologists, and cardiologists are now being consulted regarding the evaluation and management of patients in whom ADT is being initiated. Most of these physicians are not aware of the possible effects of ADT on cardiovascular risk factors or the issues regarding ADT and cardiovascular disease. Therefore, this multidisciplinary writing group has been commissioned to review and summarize the metabolic effects of ADT, to evaluate the data regarding a possible relation between ADT and cardiovascular events in patients with prostate cancer, and to generate suggestions regarding the evaluation and management of patients, both with and without known cardiac disease, in whom ADT is being initiated (Table 1).

ADT was first used in prostate cancer for patients with overt metastatic disease,<sup>7</sup> and it remains the mainstay of therapy for this group. ADT combined with external-beam radiation therapy is a standard of care in the treatment of men with high-risk prostate cancer, on the basis of evidence that shows a survival benefit in multiple randomized controlled trials.<sup>8-13</sup> However, ADT is also often used for other prostate cancer states (eg, for prostate volume reduction in men planning to undergo definitive local therapy with brachytherapy, or in the case of rising prostate-specific antigen after definitive local treatment),<sup>14,15</sup> and in these cases, its role in prolonging survival is less certain.

### **Adverse Effects of ADT: Potential Mechanisms of Cardiovascular Disease**

Prospective clinical trials have demonstrated that ADT may increase cardiovascular disease risk by increasing body weight, reducing insulin sensitivity, and/or resulting in dyslipidemia (Table 1). ADT significantly decreases lean body mass and increases fat mass.<sup>16-20</sup> In 2 prospective studies of men with nonmetastatic prostate cancer, for example, ADT decreased lean body mass by 2.7% to 3.8% and increased fat mass by 9.4% to 11.0% after 1 year.<sup>18,20</sup> ADT increases subcutaneous rather than visceral fat.<sup>20,21</sup> Alterations in body composition appear to be primarily an early adverse effect, with most of the treatment-related changes in fat and lean body mass apparent within the first few months of therapy.<sup>21,22</sup>

ADT also increases serum cholesterol and triglyceride levels.<sup>18,23</sup> In a prospective 12-month study of 40 men with prostate cancer, ADT increased serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides by 9%, 7%, 11%, and 27%, respectively.<sup>18</sup> Most of the observed long-term alterations in serum lipids are apparent within the first 3 months of treatment.<sup>24</sup>

Insulin resistance is a common metabolic abnormality that underlies type 2 diabetes mellitus and is prevalent in approximately one quarter of nondiabetic men.<sup>25</sup> Hyperinsulinemia in some studies has been reported to be an independent risk factor for cardiovascular disease.<sup>26,27</sup> ADT increases fasting plasma insulin levels, a marker of insulin resistance in men with prostate cancer.<sup>17,28</sup> In a 3-month prospective study of nondiabetic men, ADT significantly increased fasting plasma insulin by 26% and decreased insulin sensitivity by 13%.<sup>24</sup> Little is known about the longer-term effects of ADT on insulin sensitivity.

The metabolic syndrome is a clustering of specific cardiovascular disease risk factors the pathophysiology of which appears to be related to insulin resistance.<sup>29</sup> A cross-sectional study reported a higher prevalence of the metabolic syndrome in 18 men receiving ADT than in age-matched control groups of both untreated men with prostate cancer and men without prostate cancer.<sup>30</sup> Men receiving ADT were more likely to have increased abdominal girth, elevated triglycerides, and elevated fasting plasma glucose, consistent with the results of the prospective studies. In contrast to the metabolic syndrome; however, prospective studies have shown that ADT preferentially increases subcutaneous rather than visceral fat, increases rather than decreases high-density lipoprotein cholesterol, and does not alter blood pressure or waist-hip ratio.<sup>18,21</sup> In addition, the metabolic syndrome is characterized by low levels of adiponectin and elevated markers of inflammation, but ADT significantly increases serum adiponectin levels and does not alter levels of C-reactive protein or other markers of inflammation.<sup>21,31</sup> Taken together, these observations suggest that ADT causes a pattern of metabolic alteration that is distinct from the classically defined metabolic syndrome.

## Summary of Major Studies of ADT Use and Cardiovascular Morbidity and Mortality

Several recently published reports<sup>1-5</sup> have suggested that there may be an association between ADT with GnRH therapy (with or without an antiandrogen) or bilateral orchiectomy and incident cardiovascular disease and cardiovascular mortality. Two population-based studies<sup>1,2</sup> using data from Surveillance Epidemiology and End Results (SEER)-Medicare reported that ADT is significantly associated with a greater incidence of cardiovascular disease. In 1 report, the use of a GnRH agonist in men with prostate cancer was associated with an increased risk of incident coronary heart disease (adjusted hazard ratio [HR], 1.16; 95% confidence interval [CI], 1.10 to 1.21), myocardial infarction (adjusted HR, 1.11; 95% CI, 1.01 to 1.21), and sudden cardiac death or life-threatening ventricular arrhythmia (adjusted HR, 1.16; 95% CI, 1.05 to 1.27).<sup>1</sup> An increased risk of coronary heart disease was evident in those treated with a GnRH agonist for as few as 1 to 4 months. In the second report, the use of hormonal treatment was associated with a 20% higher risk of serious cardiovascular morbidity (HR, 1.20; 95% CI, 1.15 to 1.26) after more than 5 years of follow-up.<sup>2</sup>

Several subsequent studies have evaluated the relation between ADT and cardiovascular mortality. Analysis of data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database<sup>4</sup> revealed a significantly increased risk of cardiovascular death over a median follow-up of 3.8 years in men with localized prostate cancer who were treated with radical prostatectomy and received GnRH agonist and/or an antiandrogen

before surgery compared with those who did not (adjusted HR, 2.6, 95% CI, 1.4 to 4.7). Among patients treated with external-beam radiation therapy, brachytherapy, or cryotherapy, the adjusted HR, with ADT was 1.2 (95% CI, 0.8 to 1.9). In a post hoc pooled-data analysis of 3 randomized controlled trials of radiation therapy with or without hormonal androgen suppression therapy, 6 months of ADT use in men older than 65 years of age was associated with a shorter time to the occurrence of a fatal myocardial infarction (by 2 years) compared with men older than 65 years of age with no ADT use.<sup>3</sup> In studies that have detected an increased risk with ADT, the differences in event rates or incidence of events between those treated with ADT and those not receiving ADT usually have been on the order of 1% to 6% of the study population.

Although the above-discussed studies have detected a relation between ADT and cardiovascular risk, not all published studies have reported such a relation. Four other post hoc analyses of randomized clinical trials<sup>12,32,33,37</sup> reported no association between ADT and cardiovascular mortality (Table 2). In a trial of 206 men with localized but unfavorable-risk prostate cancer randomized to radiation therapy or to radiation therapy plus 6 months of ADT, cardiac death occurred in 13 patients in each treatment group. In those who received ADT, most cardiac deaths occurred among those with moderate to severe comorbidities (11 deaths compared with only 2 among those without significant comorbidity), which led to a loss of the overall survival benefit of ADT use in those with moderate or severe comorbidities. A history of myocardial infarction >6 months before study randomization was the most common factor that contributed to the designation of moderate or severe comorbidities.<sup>11</sup> A recent large matched-cohort study comparing prostate cancer patients treated with at least 6 months of some form or combination of ADT found that although ADT treatment was associated with an increased risk of diabetes mellitus (HR, 1.16), neither use of ADT nor duration of ADT treatment was associated with an increased risk of myocardial infarction or sudden cardiac death.<sup>34</sup> Results of a recently completed European Organization for Research and Treatment of Cancer (EORTC) randomized trial (Protocol 22961) comparing radiotherapy plus a total of 6 months of ADT to radiotherapy plus a total of 3 years of ADT in patients with locally advanced prostate cancer detected no significant difference in the incidence of fatal cardiac events at 5-year follow-up (4.0% vs 3.0%, respectively).<sup>35</sup>

A recent retrospective analysis of 5077 men treated with brachytherapy at a single center compared all-cause mortality in those not treated with adjuvant ADT with those treated with ADT (median treatment duration 4 months); median follow-up was approximately 5 years. Treatment decisions regarding ADT were based on clinical indications at the time. Overall, ADT treatment was not associated with an increased risk of all-cause mortality. In subgroup analysis, ADT treatment was not associated with an increased risk of all-cause mortality in the subgroup of patients without cardiac risk factors or known cardiac disease or in the subgroup of patients with 1 cardiac risk factor. All-cause mortality was greater in the subgroup of patients with coronary artery disease-induced congestive heart failure or myocardial infarction, occurring in 25 of 95 ADT-treated patients (26.3%) and 18 of 161 non-ADT-treated patients (11.2%; adjusted HR, 1.96; 95% CI, 1.04 to 3.71,  $P=.04$ ). No data were given on the specific causes of death.<sup>36</sup>

Several potential explanations for the discordant observations regarding the association between ADT and cardiovascular mortality may include factors such as differences in patient populations studied, study design, selection bias in men offered ADT, and the limited number of cardiovascular events in some studies. A competing-risks issue has also been suggested to explain the findings in the studies that have not detected a relation between ADT and cardiovascular events,<sup>12,32,33,37</sup> which emphasizes that the ability to measure an increase in the risk of cardiovascular mortality decreases as the risk of prostate cancer-

specific mortality increases.<sup>5</sup> It may also be that any increased risk occurs primarily in those with existing, overt coronary artery disease. Finally, another important potential explanation for the discordant findings is that there is no actual causal relation between ADT and cardiovascular mortality and that positive studies are the result of uncontrollable confounding factors or the result of post hoc analyses.

Not surprisingly, given all of these considerations, whether an association (or an actual cause-and-effect relation) between ADT use and cardiovascular events and mortality exists remains controversial and continues to be studied. The writing group believes that at this point, it is reasonable, on the basis of the above data, to state that there may be a relation between ADT and cardiovascular events and death. At present, there are no good data on the issue of ADT and stent thrombosis.

## Evaluation and Management of Patients in Whom ADT Is Being Initiated

Given the metabolic effects of ADT, it is advisable that patients in whom ADT is initiated be referred to their primary care physician for periodic follow-up evaluation. This evaluation should include assessment of blood pressure, lipid profile, and glucose level. Given that some of the effects of ADT occur within the first 3 months of treatment, it may be reasonable for an initial follow-up evaluation to occur within 3 to 6 months after initiation of therapy. There are no data to guide at what intervals periodic further follow-up should occur, and this is left to the discretion of the physician initiating ADT and to the patient's primary care physician. It does seem reasonable, however, that for men being treated with long-term ADT, blood glucose and lipids should be checked at least yearly. Primary care providers should be specifically provided information by the referring physician on the potential side effects of ADT, including glucose intolerance, dyslipidemia, and obesity (this information could include reference to the present advisory).

It is the consensus of this writing group that patients in whom ADT is believed to be beneficial do not need to be referred to internists, endocrinologists, or cardiologists for evaluation before initiation of ADT. The decision as to whether or not to initiate ADT in patients with cardiac disease, for whom the benefits of therapy should be weighed against the potential risks, is most appropriately made by the physician treating the patient for prostate cancer. For all patients, and particularly those with cardiovascular disease, prescribing physicians should weigh the benefits of ADT for treating that patient's prostate cancer against the potential risks. In particular, when weighing the risks and benefits of ADT in patients with known coronary artery disease, it is reasonable to consider carefully whether there is a well established likely benefit of ADT in the specific clinical setting.

As noted above, it is the consensus of the writing group that ADT may be associated with an increased incidence of cardiovascular events. Even if a causative relation were established definitively, however, there are no data to indicate that any specific intervention would decrease cardiovascular risk in this setting. Therefore, if a patient who is being considered for ADT is referred for cardiac evaluation, we recommend that the cardiologist not feel compelled to perform any specific testing or coronary intervention before ADT is initiated. There are at present no data to suggest that stress testing can risk stratify any potential future cardiac risks of ADT, and there are no data to suggest that revascularization before ADT would decrease future cardiovascular risk. (One study of the impact of revascularization on the risk of cardiac death in men treated with ADT was under way at the time of this writing.) Prudence and good medical care dictate that patients with cardiac disease receive appropriate secondary preventive measures as recommended by the American Heart Association and other expert organizations. This should generally include statin therapy to lower low-density lipoprotein cholesterol levels to <70 to 100 mg/dL (based on

cardiovascular history and risk), antihypertensive therapies to lower blood pressure to <130-140/80-90 mm Hg (depending on the presence of certain comorbid diseases), and glucose-lowering therapies to reduce glucose and glycosylated hemoglobin levels to recommended levels in patients with diabetes mellitus.<sup>38-42</sup> All patients with cardiovascular disease should be taking aspirin (generally 81 mg/d) unless there is a strong contraindication.<sup>38</sup> Those who continue to smoke should be strongly counseled to stop and should be referred, when amenable, to smoking cessation programs.<sup>38,43</sup>

## Summary

There is a substantial amount of data demonstrating that ADT adversely affects traditional cardiovascular risk factors, including serum lipoproteins, insulin sensitivity, and obesity. Recent studies have reported a relation in patients with prostate cancer between ADT and an increased risk of cardiovascular disease, although different studies both have and have not reported an increased risk of cardiovascular death. Whether the explanation for this discrepancy is related to issues regarding study design and study limitations, competing risk issues, or risk primarily confined to those with established coronary artery disease, or because there is no actual causal relation between ADT and cardiovascular events, cannot be determined definitively at this point. However, it is plausible that ADT could increase cardiovascular risk on the basis of its adverse impact on risk factors for cardiovascular disease. The writing group thus believes at this time that it is appropriate to state that there may be a relation between ADT and cardiovascular risk. Future clinical trials of ADT should prospectively assess cardiovascular risk factors before and after ADT is begun and should prospectively monitor patients for adverse cardiovascular events and mortality.

Despite the metabolic effects of ADT and the possible increased cardiovascular risk, it is the consensus of the writing group that there is no clear indication for patients for whom ADT is believed to be beneficial to be referred to internists, endocrinologists, or cardiologists for evaluation before initiation of ADT. There is no reason at present to believe that there is a role for specific cardiac testing or coronary intervention in patients with cardiovascular disease before initiation of ADT. The decision as to whether or not to initiate ADT in patients with cardiac disease, in whom the benefits of therapy would be weighed against any possible risks, is most appropriately made by the physician treating the patient for prostate cancer. Given the metabolic effects of ADT, it is advisable that patients in whom ADT is initiated be referred to their primary care physician for periodic follow-up evaluation. Prudence and good medical care dictate that patients with cardiac disease receive appropriate secondary preventive measures as recommended by the American Heart Association and other expert organizations, including, when appropriate, lipid-lowering therapy, antihypertensive therapy, glucose-lowering therapy, and antiplatelet therapy.

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**TABLE 1**

## Prospective Studies of the Effects of ADT on Cardiac Risk Factors

OUTCOME	REFERENCE(S)	OBSERVATIONS	COMMENT
Obesity	16-20	Increased fat mass	Fat accumulation is primarily subcutaneous fat
Serum lipids	18, 23	Increased LDL cholesterol and triglycerides	HDL cholesterol is also increased
Insulin sensitivity	17, 24, 28	Increased fasting plasma insulin and decreased insulin sensitivity	Small increase in glycosylated hemoglobin
Blood pressure	21	No significant change	
Waist-hip ratio	21	No significant change	
C-reactive protein	31	No significant change in C-reactive protein or other biomarkers of inflammation	

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

TABLE 2

Summary of Exploratory Studies Evaluating for the Presence of an Association Between ADT Use in the Treatment of Prostate Cancer and Cardiovascular Morbidity and Mortality

DATA SOURCE	STUDY POPULATION	EVENTS	TIME TO CARDIOVASCULAR MORBIDITY: AHR (95% CI), P	TIME TO CARDIOVASCULAR DEATH: AHR OR POINT ESTIMATES (95% CI), P
Observational studies				
SEER/Medicare <sup>1</sup>	73,196 Men aged >65 y with local/regional prostate cancer	3917 MIs; 15,116 incident cases of coronary heart disease; 3301 sudden cardiac deaths	MI (ADT vs no ADT) 1.11 (1.01-1.21), .03; coronary heart disease (ADT vs no ADT) 1.16 (1.10-1.21), .001	Sudden cardiac death or life-threatening ventricular arrhythmia (ADT vs no ADT) 1.16 (1.05-1.27), .004
SEER/Medicare <sup>2</sup>	22,816 Men aged >65 y with prostate cancer, all stages	≈4321 Cardiovascular events (definition of cardiovascular event not provided)	Cardiovascular event (ADT vs no ADT) 1.20 (1.15-1.26), <.05	—
CaPSURE <sup>4</sup>	4892 Men with localized prostate cancer, all ages, including 3262 patients who had radical prostatectomy and 1630 men who had radiation	131 Total cardiovascular deaths; 61 deaths in radical prostatectomy group, 70 in radiation group	—	Radical prostatectomy group (ADT vs no ADT) 2.6 (1.4-4.7), .002; Radiation group (ADT vs no ADT) 1.2 (0.8-1.9), .40
Nanda et al <sup>36</sup>	5077 With localized or locally advanced prostate cancer. Patients treated or not treated with adjuvant ADT on the basis of clinical indications	419 All-cause deaths; Subgroup of patients with CAD-induced CHF or MI had 25/95 deaths in ADT-treated patients; 18/161 deaths in non-ADT-treated patients	—	No difference in all-cause mortality in entire cohort, 11.1% vs 7.0% 1.08 (0.88-1.33); Greater mortality in the subgroup of patients with CAD treated with ADT (vs no ADT) 1.96 (1.04-3.71)
Alibhai et al <sup>34</sup>	Matched-cohort study of 19,079 prostate cancer patients treated with at least 6 mo of ADT	949 MIs in ADT users, 1085 MIs in nonusers; 399 sudden cardiac deaths in ADT users, 436 in nonusers	Diabetes (ADT vs no ADT) 1.16 (1.11-1.21); MI (ADT vs no ADT) 0.91 (0.84-1.00); Sudden cardiac death (ADT vs no ADT) 0.96 (0.83-1.10)	—
Postrandomization analyses				
Pooled analysis of RCTs <sup>3</sup>	1372 Men of all ages with localized prostate cancer treated with radiation who enrolled in 1 of 3 ADT trials in which patients received 0 vs 3 vs 6 mo, 3 vs 8 mo, or 0 vs 6 mo of ADT	51 Cardiovascular deaths (due to MI)	—	Shorter time to fatal MI in those ≥65 y treated with 6 mo of ADT compared with those not treated with ADT (P=.017). Effect seen only in men aged ≥65 y.
RTOG 8610 <sup>12</sup>	456 Men of all ages with locally advanced prostate cancer treated with radiation	348 Total deaths; 57 cardiovascular deaths	—	Estimates of fatal MI at 10 y with ADT 12.5 (8-17) Estimates of fatal MI at 10 y with no ADT 9.1 (5.3-13), .32
RTOG 9202 <sup>32</sup>	1554 Men with locally advanced prostate cancer all treated with radiation and 4 mo of ADT who were then	765 Total deaths; 185 cardiovascular deaths	—	Cardiovascular mortality (28 total mo of ADT vs 4 mo of ADT) 1.09 (0.81-1.47), .58

DATA SOURCE	STUDY POPULATION	EVENTS	TIME TO CARDIOVASCULAR MORBIDITY: AHR (95% CI), <i>P</i>	TIME TO CARDIOVASCULAR DEATH: AHR OR POINT ESTIMATES (95% CI), <i>P</i>
	randomized to no additional ADT or 24 additional mo of ADT			
EORTC 30891 <sup>37</sup>	985 Men of all ages with locally advanced or node-positive disease not suitable for local curative treatment assigned to immediate vs deferred ADT	541 Total deaths; 185 cardiovascular deaths	—	Cardiovascular mortality after median 7.8-y follow-up: 17.9% in immediate-ADT group vs 19.7% in deferred-ADT group ( <i>P</i> not given, but percentage was lower in the immediate-ADT group.)
RTOG 85-31 <sup>33</sup>	945 Men of all ages with locally advanced or node-positive prostate cancer treated with EBRT and then randomized to either long-term adjuvant ADT (Arm 1) or ADT therapy only for local and/or distant disease recurrence (Arm 2). Arm 1 median ADT Rx 4.2 y. In Arm 2, 64% of patients received salvage ADT a median of 3.0 y after EBRT.	574 Total deaths; 117 cardiovascular deaths	—	Cardiovascular mortality at 9 y: Arm 1 (EBRT with ADT) =8.4%; Arm 2 (“salvage” ADT for recurrence)=11.4% ( <i>P</i> =.17). Arm 2 vs Arm 1 0.73 (0.47-1.15), .16. No significant treatment-related effect found after censoring for salvage ADT
D’Amico et al <sup>11</sup>	206 Men with localized but unfavorable-risk prostate cancer randomized to RT alone or RT plus 6 mo of ADT	74 Total deaths (44 in the RT-alone group and 30 in the RT plus ADT group; 13 cardiac deaths in each treatment group)	—	In patients treated with ADT, there were more cardiac deaths (11 vs 2) in men with moderate to severe comorbidity than in those without such comorbidity, which led to a loss of the survival benefit in this subgroup.
Randomized study analysis				
EORTC 22961 <sup>35</sup>	1113 Men with locally advanced prostate cancer randomized to brachytherapy and a total of 6 mo of ADT or brachytherapy and a total of 3 y of ADT	132 Deaths in short-term group, 98 deaths in long-term group; 31 cardiac deaths in short-term group, 25 in long-term group	—	No significant difference in fatal cardiac events (4.0% in short-term group; 3.0% in long-term group)

AHR indicates adjusted hazard ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results; CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor, a longitudinal, observational registry of men with biopsy-proven prostate cancer; MIs, myocardial infarctions; ADT, androgen-deprivation therapy; CAD, coronary artery disease; CHF, congestive heart failure; RCTs, randomized controlled trials; RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EBRT, external-beam radiation therapy; RT, radiation therapy; Rx, treatment.