

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.¹⁻⁵ 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 relationship 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.

The writing group emphasizes that the purpose of this advisory is strictly informative. This advisory should thus not be construed as dictating clinical practice or superseding the clinical judgment of physicians, and it should not be used for medicolegal purposes.

What Is ADT, and Why Is It Used in Prostate Cancer?

Androgens, produced mainly in the testicles, stimulate prostate cancer cells to grow. Lowering androgen levels can eliminate prostate cancer cells that require androgens to survive.⁶ ADT reduces levels of androgens in circulation, with the goal of improving outcomes in men with prostate cancer. Gonadotropin-releasing hormone (GnRH) agonists (eg, leuprolide, goserelin, and triptorelin) currently are the most common form of ADT and have largely supplanted the use of bilateral orchiectomy. Antiandrogens (eg, flutamide and bicalutamide) are a form of prostate cancer therapy that blocks the binding of androgen to its receptor, and this treatment is often coupled with GnRH agonists.

The American Heart Association, American Cancer Society, and American Urological Association make every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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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.

ADT was first used in prostate cancer for patients with overt metastatic disease,⁷ 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.^{8–13} 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),^{14,15} 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.^{16–20} 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.^{18,20} ADT increases subcutaneous rather than visceral fat.^{20,21} 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.^{21,22}

ADT also increases serum cholesterol and triglyceride levels.^{18,23} 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.¹⁸ Most of the observed long-term alterations in serum lipids are apparent within the first 3 months of treatment.²⁴

Insulin resistance is a common metabolic abnormality that underlies type 2 diabetes mellitus and is prevalent in approximately one quarter of nondiabetic men.²⁵ Hyperinsulinemia in some studies has been reported to be an independent risk factor for cardiovascular disease.^{26,27} ADT increases fasting plasma insulin levels, a marker of insulin resistance in men with prostate cancer.^{17,28} In a 3-month prospective study of nondiabetic men, ADT significantly increased fasting plasma insulin by 26% and decreased insulin sensitivity by 13%.²⁴ 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.²⁹ 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.³⁰ 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.^{18,21} Additionally, 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.^{21,31} 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^{1–5} 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^{1,2} 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).¹ 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) over 5 years of follow-up.²

Several subsequent studies have evaluated the relationship between ADT and cardiovascular mortality. Analysis of data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database⁴ 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 over 65 years of age with no ADT use.³ 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 relationship between ADT and cardiovascular risk, not all published studies have reported such a relationship. Four other post hoc analyses of randomized clinical trials^{12,32,33,37} 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.¹¹ 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.³⁴ 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% versus 3.0%, respectively).³⁵

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 indica-

tions 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, $P=0.04$). No data were given on the specific causes of death.³⁶


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 relationship between ADT and cardiovascular events,^{12,32,33,37} 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.⁵ 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 relationship 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 relationship) 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 relationship 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

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), <i>P</i>	Time to Cardiovascular Death: AHR or Point Estimates (95% CI), <i>P</i>
Observational studies				
SEER/Medicare ¹	73 196 Men >65 y old with local/regional prostate cancer	3917 MIs; 15 116 incident cases of coronary heart disease; 3301 sudden cardiac deaths	MI (ADT vs no ADT) AHR=1.11 (1.01–1.21), <i>P</i> =0.03 Coronary heart disease (ADT vs no ADT) AHR=1.16 (1.10–1.21), <i>P</i> <0.001	Sudden cardiac death or life-threatening ventricular arrhythmia (ADT vs no ADT) AHR=1.16 (1.05–1.27), <i>P</i> =0.004
SEER/Medicare ²	22 816 Men >65 y old with prostate cancer, all stages	≈4321 Cardiovascular events (definition of cardiovascular event not provided)	Cardiovascular event (ADT vs no ADT) AHR=1.20 (1.15–1.26), <i>P</i> <0.05	-
CaPSURE ⁴	4,892 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) AHR=2.6 (1.4–4.7), <i>P</i> =0.002 Radiation group (ADT vs no ADT) AHR=1.2 (0.8–1.9); <i>P</i> =0.40
Nanda et al ³⁶	5077 With localized or locally advanced prostate cancer. Patients treated or not treated with adjuvant ADT based on clinical indications	419 All-cause deaths. In the subgroup of patients with "CAD-induced CHF or MI": 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%; AHR=1.08 (0.88–1.33)) Greater mortality in the subgroup of patients with CAD treated with ADT (vs no ADT) AHR=1.96 (1.04–3.71)
Alibhai et al ³⁴	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) AHR=1.16 (1.11–1.21) MI (ADT vs no ADT) AHR=0.91 (0.84–1.00) Sudden cardiac death (ADT vs no ADT) AHR=0.96 (0.83–1.10)	
Postrandomization analyses				
Pooled analysis of RCTs ³	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, 3 vs 8, 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 (<i>P</i> =0.017). Effect seen only in men age ≥65 y old
RTOG 8610 ¹²	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: ADT: 12.5% (8–17%); no ADT 9.1% (5.3–13%); <i>P</i> =0.32
RTOG 9202 ³²	1,554 Men with locally advanced prostate cancer all treated with radiation and 4 mo of ADT who were then randomized to no additional ADT or 24 additional mo of ADT	765 Total deaths; 185 cardiovascular deaths	...	Cardiovascular mortality (28 total mo of ADT vs 4 mo of ADT) AHR=1.09 (0.81–1.47), <i>P</i> =0.58
EORTC 30891 ³⁷	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)

(Continued)

Table 2. Continued

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>
RTOG 85-31 ³³	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> =0.17). Arm 2 vs Arm 1 AHR=0.73 (0.47–1.15), <i>P</i> =0.16 No significant treatment-related effect found after censoring for salvage ADT
D'Amico et al ¹¹	206 Men with localized but unfavorable-risk prostate cancer randomized to radiation therapy alone or radiation therapy plus 6 mo of ADT	74 Total deaths (44 in the RT-alone group and 30 in the RT+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 a loss of the survival benefit in this subgroup
Randomized study analysis				
EORTC 22961 ³⁵	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)

MI indicates myocardial infarction; AHR, adjusted hazard ratio; CI, confidence interval; SEER, Surveillance Epidemiology and End Results; MI, myocardial infarction; CAD, coronary artery disease; CHF, congestive heart failure; CaPSURE, longitudinal, observational registry of men with biopsy proven prostate cancer; RTOG, Radiation Therapy Oncology Group; RT, radiation therapy; RCT, randomized controlled trial; EBRT, external-beam radiation therapy; and Rx, treatment.

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 relationship 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 (1 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.^{38–42} All patients with cardiovascular disease should be taking aspirin (generally 81 mg/d) unless there is a strong contraindication.³⁸ Those who continue to smoke should be strongly counseled to stop and should be referred, when amenable, to smoking cessation programs.^{38,43}

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 relationship 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 relationship 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 relationship 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.

Disclosures

Writing Group Disclosure Table

Writing Group Member	Employment	Research Grant	Other Research		Speakers'		Consultant/Advisory		Other
			Support		Bureau/Honoraria	Expert Witness	Ownership Interest	Board	
Glenn N. Levine	Baylor College of Medicine and Michael E. DeBakey Medical Center	None	None	None	None	None	None	None	None
Peter Berger	Geisinger Health System	None	None	None	None	None	Accumetrics*; Eli Lilly & Co/Daiichi Sankyo*; PlaCor*; The Medicines Company*	None	None
Peter E. Clark	Vanderbilt University Medical Center	None	None	None	None	None	None	None	None
Anthony V. D'Amico	Brigham and Women's Hospital	None	None	None	None	None	None	None	None
Robert H. Eckel	University of Colorado at Denver	Sanofi-Aventis†	None	INNOVIA* (Sanofi-Aventis-sponsored event)	None	None	None	Sanofi-Aventis*	None
Nancy L. Keating	Harvard Medical School	None	None	None	None	None	None	None	None
Richard V. Milani	Ochsner Health System	None	None	None	None	None	None	None	None
Arthur I. Sagalowsky	UT Southwestern Medical Center	None	None	None	None	None	Bioniche/Parexel*	Data Monitoring Committee for bladder cancer trial by Bioniche*	None
Matthew R. Smith	Massachusetts General Hospital	Lance Armstrong Foundation†; Prostate Cancer Foundation†	None	None	None	None	GTX Inc†	None	None
Neil Zakai	University of Vermont	None	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosure Table

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Eric Bates	University of Michigan	None	None	None	None	None	None	None
Ann F. Bolger	University of California, San Francisco	None	None	None	None	None	None	None
Graham Foley Greene	Arkansas Cancer Research Center	None	None	None	None	None	None	None
Andrew K. Lee	MD Anderson Cancer Center	None	None	None	None	None	None	None
W. Robert Lee	Duke University	None	None	None	None	None	None	None
Robert E. Safford	Mayo Clinic	None	None	None	None	None	None	None
Christopher Saigal	University of California Los Angeles	None	None	None	None	None	None	None
Paul F. Schellhammer	Urology of Virginia/Sentara Medical Group	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

References

- Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2006;24:4448–4456.
- Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS; and the Urologic Diseases in America Project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer*. 2007;110:1493–1500.
- D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ, Lamb DS, Joseph D, Tai KH, Malone S, Ludgate C, Steigler A, Kantoff PW. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol*. 2007;25:2420–2425.
- 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;99:1516–1524.
- D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Causes of death in men undergoing androgen suppression therapy for newly diagnosed localized or recurrent prostate cancer. *Cancer*. 2008;113:3290–3297.
- Tammela T. Endocrine treatment of prostate cancer. *J Steroid Biochem Mol Biol*. 2004;92:287–295.
- Paulson DF. Management of metastatic prostatic cancer. *Urology*. 1985;25(suppl):49–52.
- Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Mattelaer J, Lopez Torecilla J, Pfeffer JR, Lino Cutajar C, Zurlo A, Pierart M. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet*. 2002;360:103–106.
- Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, Brereton HD, Venkatesan V, Lawton CA, Rosenthal SA, Sandler HM, Shipley WU. Ten-year follow-up of Radiation Therapy Oncology Group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol*. 2008;26:2497–2504.
- Denham JW, Steigler A, Lamb DS, Joseph D, Mameghan H, Turner S, Matthews J, Franklin I, Atkinson C, North J, Poulsen M, Christie D, Spry NA, Tai KH, Wynne C, Duchesne G, Kovacev O, D'Este C; Trans-Tasman Radiation Oncology Group. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial. *Lancet Oncol*. 2005;6:841–850.
- D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA*. 2008;299:289–295.
- Roach M III, Bae K, Speight J, Wolkov HB, Rubin P, Lee RJ, Lawton C, Valicenti R, Grignon D, Pilepich MV. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol*. 2008;26:585–591.
- Pilepich MV, Winter K, Lawton CA, Krisch RE, Wolkov HB, Movsas B, Hug EB, Asbell SO, Grignon D. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma: long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys*. 2005;61:1285–1290.
- Moul JW, Bañez LL, Freedland SJ. Rising PSA in nonmetastatic prostate cancer. *Oncology (Williston Park)*. 2007;21:1436–1445.
- Wang H, Wallner K, Sutlief S, Blasko J, Russell K, Ellis W. Transperineal brachytherapy in patients with large prostate glands. *Int J Cancer*. 2000;90:199–205.
- Tayek JA, Heber D, Byerley LO, Steiner B, Rajfer J, Swerdloff RS. Nutritional and metabolic effects of gonadotropin-releasing hormone agonist treatment for prostate cancer. *Metabolism*. 1990;39:1314–1319.
- Smith JC, Bennett S, Evans LM, Kynaston HG, Parmar M, Mason MD, Cockcroft JR, Scanlon MF, Davies JS. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. *J Clin Endocrinol Metab*. 2001;86:4261–4267.
- Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, Kantoff PW. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab*. 2002;87:599–603.
- Berruti A, Dogliotti L, Terrone C, Cerutti S, Isaia G, Tarabuzzi R, Reimondo G, Mari M, Ardisson P, De Luca S, Fasolis G, Fontana D, Rossetti SR, Angeli A; Gruppo Onco Urologico Piemontese (G.O.U.P.), Rete Oncologica Piemontese. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol*. 2002;167:2361–2367.
- Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology*. 2004;63:742–745.
- Smith MR, Lee H, McGovern F, Fallon MA, Goode M, Zietman AL, Finkelstein JS. Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer: differences from the classic metabolic syndrome. *Cancer*. 2008;112:2188–2194.
- Lee H, McGovern K, Finkelstein JS, Smith MR. Changes in bone mineral density and body composition during initial and long-term gonadotropin-

- releasing hormone agonist treatment for prostate carcinoma. *Cancer*. 2005;104:1633–1637.
23. 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;154:100–104.
 24. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab*. 2006;91:1305–1308.
 25. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2008;31(suppl):S55–S60.
 26. Després JP, Lamarche B, Mauriège P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med*. 1996;334:952–957.
 27. Pyörälä M, Miettinen H, Laakso M, Pyörälä K. Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Circulation*. 1998;98:398–404.
 28. Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. *Clin Sci (Lond)*. 2003;104:195–201.
 29. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415–1428.
 30. Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, Basaria S. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol*. 2006;24:3979–3983.
 31. Smith MR, Lee H, Fallon MA, Nathan DM. Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer. *Urology*. 2008;71:318–322.
 32. Efsthathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, Smith MR. Cardiovascular mortality and duration of androgen deprivation for locally advanced prostate cancer: analysis of RTOG 92-02. *Eur Urol*. 2008;54:816–823.
 33. Efsthathiou J, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, Smith MR. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. *J Clin Oncol*. 2009;27:92–99.
 34. Alibhai SM, Duong-Hua M, Sutradhar R, Fleshner NE, Warde P, Cheung AM, Paszat LF. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. *J Clin Oncol*. 2009;27:3452–3458.
 35. Bolla M, de Reijke TM, Van Tienhoven G, Van den Bergh AC, Oddens J, Poortmans PM, Gez E, Kil P, Akdas A, Soete G, Kariakine O, van der Steen-Banasik EM, Musat E, Piérart M, Mauer ME, Collette L; 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;360:2516–2527.
 36. Nanda AN, 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;302:866–873.
 37. Studer UE, Whelan P, Albrecht W, Casselman J, de Reijke T, Hauri D, Loidl W, Isorna S, Sundaram SK, Debois M, Collette L. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. *J Clin Oncol*. 2006;24:1868–1876.
 38. Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update [published correction appears in *Circulation*. 2006;113:e847]. *Circulation*. 2006;113:2363–2372.
 39. American Diabetes Association. Standards of medical care in diabetes—2008. *Diabetes Care*. 2008;31(suppl):S12–S54.
 40. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ; for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines [published correction appears in *Circulation*. 2004;110:763]. *Circulation*. 2004;110:227–239.
 41. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.
 42. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [published correction appears in *JAMA*. 2003;290:197]. *JAMA*. 2003;289:2560–2572.
 43. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. *Circulation*. 1997;96:3243–3247.

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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

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