Androgen Deprivation Therapy Increases Cardiovascular Morbidity in Men With Prostate Cancer

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BACKGROUND. The use of androgen deprivation therapy (ADT) in the treatment of men with prostate cancer has risen sharply. Although cardiovascular disease is the most common reason for death among men with prostate cancer who do not die of the disease itself, data regarding the effect of ADT on cardiovascular morbidity and mortality in men with prostate cancer are limited. In the current study, the authors attempted to measure the risk for subsequent cardiovascular morbidity in men with prostate cancer who received ADT.

METHODS. A cohort of newly diagnosed men in a population-based registry who were diagnosed between 1992 and 1996 were identified retrospectively. A total of 22,816 subjects were identified after exclusion criteria were applied. Using a multivariate model, the authors calculated the risk of subsequent cardiovascular morbidity in men with prostate cancer who were treated with ADT, as defined using Medicare claims.

RESULTS. Newly diagnosed prostate cancer patients who received ADT for at least 1 year were found to have a 20% higher risk of serious cardiovascular morbidity compared with similar men who did not receive ADT. Subjects began incurring this higher risk within 12 months of treatment. However, Hispanic men were found to have a lowered risk for cardiovascular morbidity.

CONCLUSIONS. ADT is associated with significantly increased cardiovascular morbidity in men with prostate cancer and may lower overall survival in men with low-risk disease. These data have particular relevance to decisions regarding the use of ADT in men with prostate cancer in settings in which the benefit has not been clearly established. For men with metastatic disease, focused efforts to reduce cardiac risk factors through diet, exercise, or the use of lipid-lowering agents may mitigate some of the risks of ADT. ***Cancer*** **2007;110:1493–500.**

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The use of androgen deprivation therapy (ADT) in the treatment of men with prostate cancer has risen sharply in the last decade, partially based on evidence supporting specific indications for its use in men with high-risk features who are undergoing radiotherapy. This dramatic rise in the use of ADT in men with prostate cancer is documented in data reported by Cooperberg et al. from a national prostate cancer registry.[1] In that cohort, the proportion of prostate cancer patients treated with external beam radiotherapy who also received ADT rose from 10% in 1989 to 75% in 2001. During the same period, the proportion of men receiving ADT in conjunction with brachytherapy rose from 7% to 25%. In 2001, 8% of men undergoing radical prostatectomy received ADT, although evidence does not support its use in that context. Although not curative, ADT

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was the primary treatment strategy in nearly half of the men diagnosed with high-risk localized disease in 2001.[1] ADT is the mainstay of therapy for men with metastatic prostate cancer. As survival has improved for these men,[2] the skeletal effects of lifelong hormonal deprivation have been widely recognized.[3,4] Although data suggest that cardiovascular disease is the most common reason for death among men with prostate cancer who do not die of the disease itself,[5] the effect of ADT on cardiovascular morbidity and mortality in men with prostate cancer remains poorly described.

Although male sex is a risk factor for coronary artery disease, evidence is accumulating that testosterone may actually have a cardioprotective influence in men with prostate cancer (and in men in general). Studies of men undergoing ADT have documented an increase in adiposity; 1 study demonstrated an increase in body fat of 9.4% after 1 year of ADT.[6] Androgen deprivation has also been associated with significant increases in total serum cholesterol and triglyceride levels in men with prostate cancer.[7] Obesity and hyperlipidemia are risk factors for coronary artery disease.[8] Accordingly, these effects of medically induced hypogonadism could provide a mechanism by which ADT would increase the risk for cardiac morbidity and mortality.

Given the increasing use of ADT in men with prostate cancer, we sought to measure the risk of subsequent cardiac morbidity in this group of men. We hypothesized that a direct correlation exists between ADT use and cardiovascular morbidity. To investigate this hypothesis, we examined cardiovascular outcomes in men receiving ADT for prostate cancer who were registered in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database linkage.

MATERIALS AND METHODS

Data Source

We identified subjects with newly diagnosed prostate cancer using a linked database combining the SEER national cancer registry and Medicare claims for 1992 through 2000.[9] The SEER registry identifies patients at the time of a new prostate cancer diagnosis; data currently available are from 11 urban and rural regions representative of the general U.S. population. The SEER registry includes the metropolitan areas of Atlanta, Detroit, Los Angeles, San Francisco/Oakland, San Jose/Monterey, and Seattle/Puget Sound, and the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah.

Medicare claims data analyzed included the Medicare Provider Analysis and Review (MEDPAR) file, Outpatient file, and the National Claims History (NCH) records. The MEDPAR file includes all Medicare Part A short-stay and long-stay claims with International Classification of Diseases (9th revision [ICD-9]) diagnosis and procedure codes for each admission. The NCH records detail physician and provider claims with Current Procedural Terminology coding system (4th edition [CPT-4]) codes and corresponding ICD-9 codes. Linkage of the SEER registry with Medicare data allows the integration of detailed cancer information, such as stage and grade, with claims information pertaining to procedural codes, comorbidities, and dates of treatment.

Inclusion and Exclusion Criteria

Study subjects were identified on the basis of primary malignancy codes indicating prostate cancer in the SEER dataset with a diagnosis made between 1992 and 1996 (to allow for adequate follow-up). Subjects must have survived at least 12 months after the initial diagnosis. Patients with all stages of disease at the time of diagnosis were eligible for study inclusion except for those with in situ carcinoma. Subjects were excluded if they were members of health maintenance organizations or if they did not have part A and part B coverage for 12 months before and after diagnosis, due to concerns regarding incomplete claims data. Subjects diagnosed at autopsy were excluded. Subjects were excluded if they underwent bilateral orchiectomy at any time as evidenced by CPT-4 or ICD-9 procedure codes. Subjects were excluded if they had a cardiovascular event within 12 months of diagnosis because these events may have represented manifestation of pre-existing cardiac disease unrelated to ADT. The duration of ADT use was calculated in terms of 1-month equivalent doses using fields found in NCH files (carrier/miles/time/units/service count) or Outpatient files (revenue center unit count).

Cohort Definition

The cohort of subjects receiving ADT was created by identifying subjects with a first hormonal treatment (defined by Medicare claim codes [all coding algorithms are available from the authors by request]) between 3 months prior to diagnosis and 6 months after diagnosis. The control cohort was comprised of men with prostate cancer who at no time received ADT. Both groups were followed for 5 years after diagnosis. The main outcome of interest was cardiac morbidity, as defined using the ICD-9 codes.

Demographic data abstracted included age, sex, race/ethnicity, and marital status. We consolidated race/ethnicity into 4 categories: white, African American, Hispanic, and other. Information regarding individual subject socioeconomic variables is not available through the linked SEER-Medicare files; therefore, values were ascribed to individuals based on ZIP code data from the U.S. Census Bureau. We present annual income as the median income in a subject's ZIP code of residence. Education level is presented as the percentage of residents in a subject's ZIP code with a college-level education.

Calculation of the Comorbidity Index

Patient comorbidity was assessed using the Charlson index, in which a higher score indicates greater comorbidity, abstracted from Medicare claims according to established techniques.[10] The Charlson score was calculated using both physician and hospital claims containing ICD-9 codes indicating a comorbidity of interest. Claims were examined in the year preceding the prostate cancer diagnosis, excluding claims occurring within the same month of diagnosis. We excluded claims for solid tumors, leukemia, and lymphoma because we were measuring comorbidity in a cancer population, as suggested by others.[10] ICD-9 diagnosis codes that only appeared once on a physician claim were excluded, as were claims with a specific ICD-9 diagnosis code that only appeared during a 30-day window. In addition, we ascertained the prevalence of hypertension (not included in the Charlson index) as defined by ICD-9 codes 401-5 and 437.2.

Statistical Analysis

Descriptive statistics are presented for demographic and clinical data. We compared these data among subjects stratified by receipt of ADT using chi-square analysis. To determine the independent association of subject demographic and clinical variables (such as receipt or duration of ADT) with cardiovascular morbidity, we ran a multivariate logistic regression. We incorporated variables thought to influence cardiovascular morbidity, including demographic, socioeconomic, and clinical variables. To ensure that the model adequately fit the data, we also explored possible interaction terms. The interaction between black race and the location of Detroit was persistently found to be significant and was retained in the model. We also created a version of this model that examined the impact of the duration of ADT on subsequent cardiovascular risk. ADT duration was defined as either $\leq$12 months or $>$12 months. One-month equivalent doses were totaled up to the time of first cardiovascular event or death. All statistical analyses were performed using SAS software (version 9.1; SAS Institute Inc., Cary, NC).

RESULTS

We identified 22,816 subjects who were newly diagnosed with prostate cancer between 1992 and 1996 who did not experience a cardiovascular event during the first 12 months after diagnosis. Of these, 4810 subjects (21%) received ADT, with the control cohort comprised of the remaining 18,006 men. Table 1 presents demographic characteristics of the 2 cohorts. Subjects who began ADT at the time of diagnosis were older, less likely to be white, and more likely to be of "other" race than subjects in whom ADT was not initiated at the time of diagnosis ($P < .0001$). Subjects who began ADT were more likely to have metastatic disease at the time of diagnosis ($P < .001$). The 2 groups did not differ significantly with regard to measures of educational and economic status, with the exception that subjects receiving ADT tended to live in ZIP codes with higher median incomes ($P < .0001$) (Table 2). Subjects who began ADT at the time of diagnosis were more likely to be diagnosed after 1994. Approximately 22% of patients undergoing external beam radiotherapy or brachytherapy received ADT compared with 12% of patients undergoing radical prostatectomy.

On univariate analysis, those patients receiving ADT were more likely to have had a cardiovascular event in the 12 months preceding the diagnosis (19% vs 15%; $P < .001$). They were also significantly more likely to have a cardiovascular event 12 to 60 months after diagnosis (24% vs 18%; $P < .001$). The prevalence of 2 cardiac risk factors, hypertension and diabetes, was found to be higher in the ADT group than in men not receiving ADT (20% vs 17% for hypertension [$P < .001$] and 7% vs 5% for diabetes [$P < .002$]). The mean time on ADT represented as 1-month equivalent doses was 21 months. The mean time on ADT represented as the date from the first claim for ADT to the date of the last claim for ADT was 36 months.

Several clinical and demographic features were found to be associated with cardiovascular morbidity on multivariable analysis (Table 3). Subjects receiving ADT had 1.2 times the risk of cardiovascular morbidity as those not receiving such therapy, after controlling for age, stage, grade, race, comorbidity score, history of pretreatment cardiac disease, treatment type, measures of socioeconomic status, and registry location. A Kaplan-Meier analysis (Fig. 1) demonstrated a sustained difference in cardiovascular

TABLE 1
Demographic Comparison of Cohorts

	No. of subjects not receiving androgen deprivation n = 18,006	No. of subjects receiving androgen deprivation n = 4810
Age, y		
65–69	5505 (30%)	1097 (23%)
70–74	6781 (38%)	1622 (34%)
75–79	3795 (21%)	1164 (24%)
≥80	1925 (11%)	927 (19%)
Race/ethnicity		
African American	1657 (9%)	467 (10%)
Caucasian	14,743 (82%)	3822 (79%)
Hispanic	694 (4%)	196 (4%)
Other	912 (5%)	325 (7%)
SEER registry		
San Francisco	1624 (9%)	419 (9%)
Connecticut	2277 (13%)	798 (17%)
Detroit	2419 (13%)	642 (13%)
Hawaii	472 (3%)	127 (3%)
Iowa	2339 (13%)	655 (14%)
New Mexico	1178 (7%)	125 (3%)
Seattle	2500 (14%)	445 (9%)
Utah	1324 (7%)	219 (5%)
Atlanta	1201 (7%)	354 (7%)
San Jose	732 (4%)	234 (5%)
Los Angeles	1940 (11%)	792 (16%)
SEER grade		
1	3429 (19%)	211 (7%)
2	10,686 (60%)	1342 (45%)
3	2384 (13%)	1071 (36%)
4	64 (0.4%)	38 (1%)
Unknown	1443 (8%)	303 (10%)
SEER stage		
Localized/regional	15,703 (87%)	3473 (72%)
Distant	318 (2%)	482 (10%)
Unstaged	1985 (11%)	855 (18%)

SEER indicates Surveillance, Epidemiology, and End Results program.

TABLE 2
Educational and Economic Measures by Cohort

	No. of subjects not receiving androgen deprivation n = 18,006	No. of subjects receiving androgen deprivation n = 4810
Education (% high school graduates)		
<7%	2448 (14%)	603 (13%)
7–12.5%	3472 (19%)	971 (20%)
12.6–20%	4707 (26%)	1278 (27%)
>20%	6996 (39%)	1848 (38%)
Unknown	383 (2%)	110 (2%)
Median ZIP code income		
<$38,500	10,909 (60%)	2722 (57%)
$38,500–$48,499	3546 (20%)	1033 (21%)
$48,500–$62,000	1763 (10%)	559 (12%)
>$62,000	1788 (10%)	496 (10%)
% of people living in poverty in ZIP code		
Unknown	383 (2%)	110 (2%)
<20% poverty level	15,435 (86%)	4174 (87%)
>20% poverty level	2188 (12%)	526 (11%)

events over time in men receiving ADT. Older age at diagnosis was found to be associated with a slightly higher risk of cardiovascular morbidity. Hispanic men had a lower risk of cardiovascular morbidity compared with white men, as did men of "other" race. Overall, cardiovascular risk was found to be higher for men treated in Detroit. However, in Detroit, where the plurality of African Americans in the sample were located, African-American men were found to have a cardiovascular risk that was comparable to Hispanics and significantly lower than that of white men.

Subjects from several SEER registry sites, including Detroit, Los Angeles, Atlanta, Connecticut, and Iowa had a higher risk of cardiac morbidity compared with those in Utah. Subjects treated with external beam radiotherapy were found to have a higher risk of cardiovascular morbidity compared with those who received no treatment, whereas those treated with radical prostatectomy had a lower risk. This effect persisted after adding interaction terms between the receipt of radiotherapy and ADT, and pretreatment cardiac disease and radiotherapy (data not shown). Subjects with preexisting cardiac disease (prior to the diagnosis of prostate cancer) had more than twice the risk of cardiovascular morbidity as those who did not have preexisting cardiac disease. Subjects with a Charlson comorbidity index score >0 had 1.6 times the cardiovascular morbidity risk of those with a score of 0. Because subjects undergoing radiotherapy may have had more comorbidities than those undergoing radical prostatectomy, and patients undergoing radical prostatectomy were less likely to receive ADT, the model was run excluding subjects undergoing radical prostatectomy. No significant changes were found (data not shown).

The risk of cardiovascular morbidity was found to be associated with the duration of ADT; those receiving treatment for a total of ≤12 months had a significantly higher risk than those who received ADT for >12 months (hazards ratio of 1.37; 95% confidence interval, 1.29–1.46).

DISCUSSION

In this population-based study, we found that men who were newly diagnosed with prostate cancer who

TABLE 3
Multivariate Model Predicting Risk of Cardiovascular Morbidity

Variable	HR	95% HR confidence limits
Age at diagnosis	1.036	1.032–1.040
Year	0.916	0.837–1.002
Year squared	1.007	0.996–1.019
Receipt of ADT	1.20	1.146–1.257
Charlson comorbidity index score	1.637	1.485–1.806
Pathologic grade		
Pathologic grade 2	0.951	0.902–1.002
Pathologic grade 3	0.953	0.891–1.019
Pathologic grade 4	0.817	0.618–1.08
Pathologic grade unknown	1.017	0.939–1.102
Cancer stage		
Cancer stage D	1.059	1.00–1.119
SEER registry site		
San Francisco	1.094	0.983–1.218
Connecticut	1.158	1.047–1.282
Detroit	1.85	1.676–2.043
Hawaii	1.019	0.866–1.2
Iowa	1.138	1.035–1.251
New Mexico	1.02	0.907–1.148
Seattle	0.953	0.865–1.051
Los Angeles	1.424	1.289–1.573
Atlanta	1.157	1.034–1.294
San Jose	1.094	0.962–1.245
Pre-existing cardiac disease	2.01	1.93–2.093
Hypertension	1.144	1.092–1.199
Treatment type		
Brachytherapy	1.027	0.938–1.125
External beam radiotherapy	1.123	1.077–1.171
Radical prostatectomy	0.929	0.879–0.982
Race		
African American	0.914	0.832–1.005
Hispanic	0.805	0.719–0.900
Other	0.890	0.807–0.981
Marital status		
Married	1.006	0.965–1.05
ZIP code median income	0.999	0.997–1.001
Census tract % nonhigh school graduates	1.000	0.998–1.002
African American/Detroit interaction term	0.793	0.693–0.907

HR indicates hazards ratio; ADT, androgen deprivation therapy.

received ADT had a 20% higher risk of serious cardiovascular morbidity than similar men who did not receive ADT. These data may temper physician enthusiasm for ADT in situations in which the clinical benefit has not been established, such as primary treatment for men with localized prostate cancer. Given the contribution of cardiovascular disease to mortality in men with low-risk or intermediate-risk disease, those patients who undergo adjuvant or neoadjuvant ADT for even a short duration may actually experience decreased overall survival as a result of this intervention. For men being treated with ADT for metastatic disease, physicians should focus on interventions that may mitigate cardiovascular risks. Counseling on the importance of a low-fat diet, the promotion of aerobic exercise, and medical therapy to improve lipid profiles may have special benefits in these patients. Our finding that the risk of cardiovascular morbidity was observed during the first 12 months of treatment should encourage physicians to begin these counseling interventions at the time of the initiation of therapy to achieve maximum benefit. We found a nonsignificant risk for longer durations of ADT, perhaps because subjects were at higher risk from the time of the initiation of therapy. As time progressed, fewer men were eligible to incur this outcome, limiting our power to detect a difference.

Prior investigation of the correlation between androgens and cardiovascular health support our findings in men with prostate cancer. Studies of animal models of atherosclerosis have demonstrated that after castration, aortic atherosclerosis was increased, an effect inhibited by testosterone.[11,12] One population-based study of 1032 men and women in the Netherlands found that men within the highest tertile for bioavailable testosterone had a relative risk of 0.2 for severe atherosclerosis, compared with men within the lowest tertile.[13] Several cross-sectional observational studies in humans have also noted lower testosterone levels in men with coronary artery disease compared with controls, although other studies have found similar levels in cases and controls.[14] Interventional data from prospective randomized controlled trials have provided evidence that testosterone supplementation may function as a coronary vasodilator in men with coronary artery disease. Testosterone supplementation has been found to reduce exercise-induced ischemia (as measured by ST segment depression) during treadmill testing.[15,16] Although they did not report data concerning variations in risk by ethnicity or treatment type, data from the study by Keating et al.[17] support our findings regarding the overall risk of cardiac disease in men with prostate cancer who receive ADT. The Early Prostate Cancer trials examined the effect of the antiandrogen bicalutimide versus usual care on overall and progression-free survival. These trials did not find an effect on overall survival in men who were being treated with the agent.[18] However, a trend toward reduced survival was noted in men with localized disease being observed with watchful waiting who began therapy with bicalutimide. The reason for this trend was not clear. Although myocardial infarction rates were similar in both treatment arms in the overall sample, congestive heart failure rates were found to be higher in the bicalutamide group.

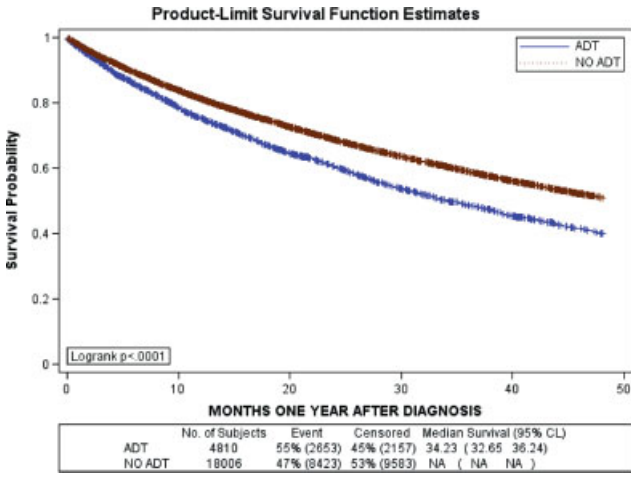

FIGURE 1. Kaplan-Meier estimate of probability of cardiovascular events over time. ADT indicates androgen deprivation therapy; NA, not applicable; 95% CL, 95% confidence limits.

Several mechanisms may explain the increase in risk for cardiovascular morbidity in men rendered hypogonadal as a result of ADT. Aside from testosterone's potential direct dilatory effects on vascular walls,[19] low serum testosterone has been associated with several modifiable risk factors for cardiac disease. A meta-analysis of the effects of testosterone supplementation in hypogonadal men documented a significant decrease in total cholesterol and low-density lipoprotein, although it was also was found to be associated with a decrease in serum high-density lipoprotein.[20] Obesity, particularly visceral obesity, is a recognized risk factor for cardiac disease. Androgen receptors present on visceral adipocytes may inhibit triglyceride uptake and thus retard fat accumulation. Higher serum testosterone levels are associated with lower levels of visceral obesity,[21] and replacement therapy in hypogonadal men has clearly been shown to reduce visceral obesity.[22,23] Hypogonadism has been associated with and found to predict hyperinsulinemia; cardiac risk may be elevated through this link to diabetes.[24,25] Lower serum testosterone has been associated with a prothrombotic state, which may predispose men to myocardial infarction.[26] Pugh et al.[27] reported additional evidence of a link between testosterone and the coagulation cascade in a case-control study of men experiencing myocardial infarction. Serum free testosterone fell acutely after myocardial infarction; lower baseline levels of testosterone were associated with increased complications after myocardial infarction.[27] A prothrombotic effect was also associated with diethylstilbestrol (DES) treatment (another hormonal therapy for advanced prostate cancer) in the Veterans' Administration Cooperative Urologic Research trials,[28] perhaps due to an effect on the coagulation cascade.[29]

Hispanic men with prostate cancer in the current study sample were found to have a lower risk for cardiovascular morbidity after controlling for various risk factors, including receipt of ADT. Other research has documented a "Hispanic paradox" of lowered cardiovascular mortality despite an increase in cardiovascular risk factors.[30–32] This may be due to genetic factors or the "healthy immigrant" hypothesis, which holds that included in the Hispanic male group are a selected subset of individuals healthy enough to meet the challenges of immigration. Lower socioeconomic status as measured in the current study did not predict an increased risk of cardiac morbidity, although lower socioeconomic status has been established as a predictor of cardiac morbidity in many population-based studies.[33,34] Our measures may be too crude to capture this risk; we are limited to using group variables (median ZIP code values) to impute individual socioeconomic status.

Our finding that radiotherapy was associated with an increased risk of subsequent cardiovascular morbidity, whereas radical prostatectomy was associated with a lower risk, is unexpected. We had no a priori hypothesis regarding such risks and therefore the finding should be viewed with caution. This finding persisted after adding interaction terms with receipt of ADT and preexisting cardiac disease. However, it appears plausible that unmeasurable risk factors (eg, disease severity, smoking status, obesity) for cardiac disease in the patients receiving radiotherapy or those steered away from surgery may explain this finding.

The use of ADT differed in our sample in ways that are consistent with earlier findings. Men receiving ADT had higher-risk prostate cancer than men not receiving ADT, and men undergoing radiotherapy were more likely to receive ADT, a finding that is consistent with data supporting its use in this setting.[35] Differences in the use of ADT by registry location are difficult to explain. They may be related to therapeutic uncertainty regarding the usefulness of ADT in situations in which few data are available for guidance, or they may reflect physician or patient preferences.

The current study has limitations. We were unable to control for the use of nonsteroidal antiandrogens as part of combined androgen blockade; combined androgen blockade may be associated with a higher risk of cardiac morbidity due to the establishment of a more complete hypogonadal state. We were unable to control for 2 cardiac risk factors,

obesity and smoking status, which are not captured in claims data. We were also unable to control for diet, activity level, or the use of medications that modify cardiac risk, such as statins. Because our sample consisted of Medicare beneficiaries, all subjects had access to healthcare. This access may have masked socioeconomic differences in cardiac risk that otherwise would have been apparent. The current study is neither prospective nor randomized and men selected for ADT may have been at higher risk for cardiovascular morbidity. To address this potential limitation, we created a model that adjusted for variables that appeared relevant to this bias, and created interaction terms when indicated. Further prospective study is needed to confirm these findings. Finally, the study is limited by the fact that it employed claims data. Claims data are designed for administrative use, as opposed to clinical studies; practice patterns that create incomplete or incorrect coding may bias results in unpredictable ways.

In this population-based study of men with newly diagnosed prostate cancer, the use of ADT was found to increase the odds of subsequent cardiac morbidity by 20%. Increased risk for cardiac morbidity was observed within the first 12 months of treatment. Hispanic men had a lower risk for cardiac morbidity. These data have particular relevance to decisions regarding the use of ADT in men with prostate cancer in settings in which the benefit has not been clearly established. For men with metastatic disease, focused efforts to reduce cardiac risk factors through diet, exercise, or lipid-lowering agents may mitigate some of the risks of ADT.

REFERENCES

1. Cooperberg MR, Grossfeld GD, Lubeck DP, Carroll PR. National practice patterns and time trends in androgen ablation for localized prostate cancer. *J Natl Cancer Inst*. 2003;95:981–989.
2. Brenner H, Arndt V. Long–term survival rates of patients with prostate cancer in the prostate–specific antigen screening era: population–based estimates for the year 2000 by period analysis. *J Clin Oncol*. 2005;23:441–447.
3. 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.
4. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med*. 2005;352:154–164.
5. Satariano WA, Ragland KE, Van Den Eeden SK. Cause of death in men diagnosed with prostate carcinoma. *Cancer*. 1998;83:1180–1188.
6. Smith MR, Finkelstein JS, McGovern FJ, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab*. 2002;87:599–603.
7. Tayek JA, Heber D, Byerly 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.
8. Nilsson PM, Nilsson JA, Berglund G. Population–attributable risk of coronary heart disease risk factors during long–term follow–up: the Malmo Preventive Project. *J Intern Med*. 2006;260:134–141.
9. Potosky AL, Riley GF, Lubitz JD, Mentnech RM, Kessler LG. Potential for cancer related health services research using a linked Medicare–tumor registry database. *Med Care*. 1993;31:732–748.
10. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. *J Clin Epidemiol*. 2000;53:1258–1267.
11. Larsen BA, Nordestgaard BG, Stender S, Kjeldsen K. Effect of testosterone on atherogenesis in cholesterol–fed rabbits with similar plasma cholesterol levels. *Atherosclerosis*. 1993;99:79–86.
12. Alexandersen P, Haarbo J, Byrjalsen I, Lawaetz H, Christiansen C. Natural androgens inhibit male atherosclerosis: a study in castrated, cholesterol–fed rabbits. *Circ Res*. 1999;84:813–819.
13. Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. *J Clin Endocrinol Metab*. 2002;87:3632–3639.
14. Alexandersen P, Haarbo J, Christiansen C. The relationship of natural androgens to coronary heart disease in males: a review. *Atherosclerosis*. 1996;125:1–13.
15. Wu SZ, Weng XZ. Therapeutic effects of an androgenic preparation on myocardial ischemia and cardiac function in 62 elderly male coronary heart disease patients. *Chin Med J (Engl)*. 1993;106:415–418.
16. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low–dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double–blind, placebo–controlled study. *Circulation*. 2000;102:1906–1911.
17. 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.
18. Iversen P. The third analysis of the bicalutamide Early Prostate Cancer programme. *BJU Int*. 2006;97:438–439.
19. Jones RD, Pugh PJ, Jones TH, Channer KS. The vasodilatory action of testosterone: a potassium–channel opening or a calcium antagonistic action? *Br J Pharmacol*. 2003;138:733–744.
20. Whitsel EA, Boyko EJ, Matsumoto AM, Anawalt BD, Siscovik DS. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta–analysis. *Am J Med*. 2001;111:261–269.
21. Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. *J Endocrinol Invest*. 1999;22(5 suppl):110–116.
22. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab*. 1999;84:2647–2653.
23. Wang C, Swerdloff RS, Iranmenesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab*. 2000;85:2839–2853.
24. Haffner SM, Karhapaa P, Mykkanen L, Laakso M. Insulin resistance, body fat distribution, and sex hormones in men. *Diabetes*. 1994;43:212–219.

25. Haffner SM, Valdez RA, Mykkanen L, Stern MP, Katz MS. Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men. *Metabolism*. 1994;43:599–603.
26. Caron P, Bennet A, Camare R, Louvet JP, Boneu B, Sie P. Plasminogen activator inhibitor in plasma is related to testosterone in men. *Metabolism*. 1989;38:1010–1015.
27. Pugh PJ, Channer KS, Parry H, Downes T, Jone TH. Bio–available testosterone levels fall acutely following myocardial infarction in men: association with fibrinolytic factors. *Endocr Res*. 2002;28:161–173.
28. Byar DP, Corle DK. Hormone therapy for prostate cancer: results of the Veterans Administration Cooperative Urological Research Group studies. *Natl Cancer Inst Monogr*. 1988; (7):165–170.
29. Owens MR, Cimino CD. Diethylstilbestrol selectively modulates plasma coagulation protein synthesis by the perfused rat liver. *Blood*. 1985;66:402–406.
30. Sorlie PD, Backlund E, Johnson NJ, Rogot E. Mortality by Hispanic status in the United States. *JAMA*. 1993;270:2464–2468.
31. Becker TM, Wiggins C, Key CR, Samet JM. Ischemic heart disease mortality in Hispanics, American Indians, and non–Hispanic whites in New Mexico, 1958–1982. *Circulation*. 1988;78:302–309.
32. Rewers M, Shetterly SM, Hoag S, Baxter J, Marshall J, Hamman RF. Is the risk of coronary heart disease lower in Hispanics than in non–Hispanic whites? The San Luis Valley Diabetes Study. *Ethn Dis*. 1993;3:44–54.
33. Lantz PM, House JS, Lepkowski JM, Williams DR, Mero RP, Chen J. Socioeconomic factors, health behaviors, and mortality: results from a nationally representative prospective study of U.S. adults. *JAMA*. 1998;279:1703–1708.
34. Shishehbor MH, Litaker D, Pothier CE, Lauer MS. Association of socioeconomic status with functional capacity, heart rate recovery, and all–cause mortality. *JAMA*. 2006;295: 784–792.
35. Bolla M, Collette L, Blank L, et al. 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.