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ORIGINAL REPORT

Cardiovascular Mortality After Androgen Deprivation Therapy for Locally Advanced Prostate Cancer: RTOG 85-31

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ABSTRACT

Purpose
Gonadotropin-releasing hormone (GnRH) agonists are associated with greater risk of coronary heart disease and myocardial infarction in men with prostate cancer, but little is known about potential impact on cardiovascular mortality. We assessed the relationship between GnRH agonists and cardiovascular mortality in a large randomized phase III trial of men treated with or without adjuvant goserelin after radiation therapy (RT) for locally advanced prostate cancer.

Patients and Methods
Between 1987 and 1992, 945 men with locally advanced prostate cancer were randomly assigned to RT and adjuvant goserelin or RT alone. Fine and Gray's regression was used to evaluate treatment effect on cardiovascular mortality. Covariates included age, prevalent cardiovascular disease (CVD), hypertension, diabetes mellitus (DM), body mass index, race, Gleason score, stage, acid phosphatase level, prostatectomy history, and nodal involvement.

Results
After a median follow-up of 8.1 years, there were 117 cardiovascular-related deaths but no treatment-related increase in cardiovascular mortality. At 9 years, cardiovascular mortality for men receiving adjuvant goserelin was 8.4% *v* 11.4% for men treated without adjuvant goserelin (Gray's $P = .17$). In multiple regression analyses, treatment arm was not significantly associated with increased risk of cardiovascular mortality (adjusted hazard ratio [HR] = 0.73; 95% CI, 0.47 to 1.15; $P = .16$; when censoring at time of salvage goserelin therapy, HR = 0.99; 95% CI, 0.58 to 1.69; $P = .97$). Traditional cardiac risk factors, including prevalent CVD and DM, were significantly associated with greater cardiovascular mortality.

Conclusion
GnRH agonists do not seem to increase cardiovascular mortality in men with locally advanced prostate cancer. Further studies are warranted to evaluate adverse effects of GnRH agonists in men with lower cancer-specific mortality.

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INTRODUCTION

Several randomized trials demonstrated that adjuvant androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) agonists decreases cancer-specific and, in some cases, all-cause mortality for men with locally advanced or high-grade localized prostate cancer.[1-6] On the basis of, in part, this evidence of improved survival, GnRH agonist therapy increased markedly in prostate cancer patients,[7-9] including men with lower stage disease and older men with significant competing causes of mortality. Routine use of GnRH agonists increases the importance of understanding the unintended adverse effects of treatment.

A recent, large, claims-based analysis using Surveillance, Epidemiology, and End Results-Medicare data for 73,196 men with local or locoregional prostate cancer demonstrated that GnRH agonists are associated with greater risk of incident diabetes mellitus (DM), coronary heart disease, and admission for myocardial infarction (MI).[10] Greater risk of DM and cardiovascular disease (CVD) was observed with short-term treatment and persisted with longer exposure to GnRH agonists. Several mechanisms may account for the association between GnRH agonists and greater risk for DM and CVD. GnRH agonists significantly increase fat mass,[11-14] LDL cholesterol, and triglycerides[11,15] and decrease insulin sensitivity.[16] These adverse effects

of GnRH agonists are suggestive of a metabolic syndrome,[17,18] an independent risk factor for coronary heart disease and cardiovascular mortality.[19,20]

Although GnRH agonists have been associated with greater risk for coronary heart disease, there is limited information about GnRH agonists and cardiovascular mortality. To evaluate the relationship between GnRH agonists and cardiovascular mortality, we analyzed data from Radiation Therapy Oncology Group (RTOG) protocol 85-31, a large randomized trial of men treated with radiation therapy (RT) with or without adjuvant goserelin for locally advanced prostate cancer.

PATIENTS AND METHODS

RTOG 85-31 is a phase III trial designed to compare adjuvant ADT with goserelin, a GnRH agonist, plus external-beam RT versus RT alone in men with locally advanced prostate cancer.[2,21]

Patient Eligibility

All patients had histologically confirmed prostatic adenocarcinoma with either grossly palpable tumor beyond the prostate (clinical stage T3) or documented evidence of regional lymphatic involvement. Patients who underwent radical prostatectomy were eligible if there was penetration through the prostatic capsule to the resection margin and/or seminal vesicles. Karnofsky performance status had to be more than 60%. All institutional state and federal guidelines were followed. All patients provided written informed consent before enrollment.

Pretreatment Evaluation

Pretreatment evaluation included history and physical examination. Laboratory studies included serum acid phosphatase, CBC, serum testosterone, and, after July 1990, prostate-specific antigen measurement. Prostate-specific antigen determination was not mandatory at study inception because it was not widely available. Radiographic evaluation included chest x-ray and bone scan. Lymph node assessment was mandatory by lymphangiography, computed tomography, or lymphadenectomy.

Study Design

Patients were entered onto the study by telephone call to RTOG headquarters within the first week of RT. After confirmation of eligibility, patients were stratified by histologic differentiation determined by institutional pathologists (well differentiated or Gleason score of 2 to 5; moderately differentiated or Gleason score of 6 to 7; and poorly differentiated or Gleason score of 8 to 10), nodal involvement (none *v* below common iliacs *v* common iliac *v* para-aortic), acid phosphatase status (not elevated *v* elevated), and prior radical prostatectomy (no *v* yes). The random assignment scheme described by Zelen[22] was used to achieve balance in treatment assignment among institutions using the stratification variables. Patients were randomly assigned either to RT and adjuvant goserelin (arm 1) or to RT alone followed by observation and goserelin only at relapse (arm 2).

Treatment

RT. Details of RT technique, doses, and fields have been described previously.[2,21] Of note, only a small percentage of patients received para-aortic irradiation (superior field border encompassing T11), and there was no significant difference between the treatment arms (8% in arm 1 *v* 9% in arm 2).

Drug therapy. Patients assigned to arm 1 were treated with adjuvant goserelin acetate (Zoladex; AstraZeneca, Wilmington, DE; 3.6 mg subcutaneously in the anterior abdominal wall monthly), which was started during the last week of RT. Patients in arm 2 were treated with goserelin only for documented local and/or distant disease recurrence. In both arms, goserelin was continued indefinitely or until sign of disease progression.

In arm 1, the median duration of goserelin therapy was 4.2 years (range, 0.0 to 14.1 years). In arm 2, 298 (64%) of 468 patients received salvage GnRH agonist therapy at a median time interval of 3.0 years (range, 0.04 to 13.0 years) from the end of RT.

Table 1. Pretreatment Characteristics

Characteristic	Arm 1 (n = 477) No. of Patients	Arm 1 (n = 477) %	Arm 2 (n = 468) No. of Patients	Arm 2 (n = 468) %	*P*
Age, years					
< 70	230	48	223	48	.86
≥ 70	247	52	245	52	
Prevalent CVD					
No	342	72	345	74	.45*
Yes	133	28	120	26	
Unknown	2	< 1	3	1	
Prevalent HTN					
No	323	68	309	66	.58*
Yes	152	32	157	34	
Unknown	2	< 1	2	< 1	
Prevalent DM					
No	392	82	373	80	.24*
Yes	36	8	45	10	
Unknown	49	10	50	11	
BMI					
Missing	74	16	83	18	
Available	403	84	385	82	
BMI category, kg/m^2					
< 25	132	33	109	28	.40
≥ 25 to < 30	200	50	202	52	
≥ 30	71	18	74	19	
Race					
White	429	90	422	90	.71†
Black	43	9	39	8	
Other	5	1	7	2	
Prostatectomy					
No	406	85	400	85	.88
Yes	71	15	68	15	
Nodal involvement					
No	337	71	345	74	.29
Yes	140	29	123	26	
Acid phosphatase					
Not elevated	318	67	316	68	.78
Elevated	159	33	152	32	
Gleason score (central)					
Missing	41	9	42	9	
Available	436	91	426	91	
2-6	125	29	129	30	.82
7	172	39	160	38	
8-10	139	32	137	32	
Clinical stage					
A/B	141	30	127	27	.41
C	336	70	341	73	

Abbreviations: CVD, cardiovascular disease; HTN, hypertension; DM, diabetes mellitus; BMI, body mass index.
*Comparison of no *v* yes.
†Comparison of white/other *v* black.

Data Collection and Analysis

Central review of RT delivered, calibration of machines, and review of materials on which diagnosis was based were performed for each patient as per RTOG/National Cancer Institute requirements.[2]

CVD Risk Factors

Information on CVD risk factors, including age, prevalent CVD, hypertension, DM, and body mass index (BMI) at baseline, was collected. BMI was

Table 2. Univariate Analyses of Cardiovascular Mortality

Factor	No. of Patients	No. of Treatment Failures	Cumulative Incidence			Fine and Gray's Models		
			9-Year Failure Rate (%)	95% CI	*P**	Unadjusted HR	95% CI	*P*†
Treatment arm								
Arm 2	468	65	11.4	8.4 to 14.3				
Arm 1	477	52	8.4	5.8 to 11.0	.17	0.77	0.53 to 1.11	.16
Age, years								
< 70	453	38	6.0	3.7 to 8.2				
≥ 70	492	79	13.6	10.5 to 16.8	.0001	2.08	1.41 to 3.06	.0002
Prevalent CVD								
No	687	54	6.5	4.5 to 8.4				
Yes	253	62	18.8	13.9 to 23.6	< .0001	3.24	2.25 to 4.66	< .0001
Prevalent HTN								
No	632	69	8.4	6.1 to 10.6				
Yes	309	47	12.8	9.1 to 16.6	.09	1.36	0.94 to 1.97	.10
Prevalent DM								
No	765	85	8.8	6.7 to 10.9				
Yes	81	21	22.4	13.2 to 31.6	.0003	2.40	1.49 to 3.86	.0003
BMI, kg/m^2								
< 25	241	30	10.0	6.0 to 13.9				
≥ 25 to < 30	402	53	11.0	7.8 to 14.1		1.05	0.67 to 1.65	.82
≥ 30	145	20	9.5	4.6 to 14.5	.94	1.10	0.63 to 1.93	.73
Race								
Black	82	12	10.0	3.4 to 16.7				
Other	863	105	9.8	7.8 to 11.9	.61	0.86	0.48 to 1.55	.62
Prostatectomy								
No	806	109	10.8	8.6 to 13.0				
Yes	139	8	4.5	1.0 to 8.1	.017	0.42	0.21 to 0.87	.019
Nodal involvement								
No	682	92	10.7	8.3 to 13.1				
Yes	263	25	7.7	4.5 to 11.0	.048	0.66	0.42 to 1.02	.06
Acid phosphatase								
Not elevated	634	78	9.4	7.1 to 11.8				
Elevated	311	39	10.8	7.2 to 14.3	.83	1.03	0.70 to 1.51	.89
Gleason score								
2-6	254	37	10.5	6.7 to 14.3				
7	332	41	8.2	5.2 to 11.3		0.87	0.56 to 1.36	.54
8-10	276	29	10.4	6.8 to 14.1	.52	0.74	0.45 to 1.20	.22
Clinical stage								
A/B	268	19	5.7	2.9 to 8.6				
C	677	98	11.6	9.1 to 14.1	.001	2.20	1.34 to 3.60	.002

Abbreviations: HR, hazard ratio; CVD, cardiovascular disease; HTN, hypertension; DM, diabetes mellitus; BMI, body mass index.
*P value determined using Gray's test statistic.
†P value determined using χ^2 test.

categorized according to National Institutes of Health classifications, with a BMI less than 25 kg/m^2 considered normal, a BMI of 25 to 29.9 kg/m^2 considered overweight, and a BMI ≥ 30 kg/m^2 considered obese.[23]

Follow-Up

Patients in both arms were evaluated every 3 months during the first year, every 4 months during the second and third years, every 6 months to year 5, and then annually for the remainder of their life.

Survival End Point

Cause of death was investigator defined and reported in follow-up case report forms by each institution. Protocol did not mandate a death certificate or autopsy report. Cardiovascular mortality was defined as death from coronary artery disease (CAD), CVD, congestive heart failure, cardiac arrest, cardiomyopathy, cardiovascular arrhythmia, MI, or sudden death. To exclude the possibility that our results would be sensitive to the definition of cardiovascular mortality, we performed additional analyses using alternative definitions by restricting the outcome to death from CAD, CVD, or cardiac arrest, and MI; and from MI only. We also considered a broader definition of death as a result of cardiovascular and cerebral events, including cerebrovascular accident, cerebral hemorrhage, cerebral infarction, stroke, and thrombotic occlusion. The end point of cardiovascular mortality was measured from date of random assignment to date of death or most recent follow-up through July 2003.

Statistical Methods

The χ^2 test was used to compare pretreatment characteristics of patients at study entry. The cumulative incidence method[24] was used to estimate time to cardiovascular mortality because it specifically adjusts for other competing causes of mortality. Gray's test[25] was used for comparing cumulative incidence rates over time between treatment arms. Fine and Gray's regression analyses[26] using χ^2 test were performed to evaluate the solitary effect of each variable on cardiovascular mortality. To analyze whether treatment arm was independently associated with cardiovascular mortality while adjusting for other factors, multiple regression analyses were performed using Fine and Gray's

regression model[26] with the following categoric covariates: age (< 70 [reference level {RL}] *v* ≥ 70 years), race (black [RL] *v* white/other), CVD at registration (no [RL] *v* yes), hypertension (no [RL] *v* yes), DM (no [RL] *v* yes), baseline BMI (< 25 [RL] *v* ≥ 25 to 30 *v* ≥ 30 kg/m^2), centrally reviewed Gleason score (2 to 6 [RL] *v* 7 *v* 8 to 10), clinical stage (A/B [RL] *v* C), acid phosphatase (not elevated [RL] *v* elevated), nodal involvement (no [RL] *v* yes), prostatectomy (no [RL] *v* yes), and treatment (arm 2 [RL] *v* arm 1). For the categoric variables, the cut points selected were made before data were examined and were based on established strata.[2,23] Goodness of fit by scaled Schoenfeld-type residual plots indicated that the model adequately fits the data. Unadjusted and adjusted hazard ratios (HRs) were calculated for all covariates using Fine and Gray's regression model with associated 95% CIs and *P* values. All statistical comparisons were two-sided, and a $P < .05$ was considered significant. To eliminate any potential impact of salvage GnRH agonist therapy on the outcome, additional analyses were performed that censored patients at time of initiation of such salvage therapy. Further analyses were performed using a data set with imputed missing values for 304 patients using the multiple imputation method (10 imputations) with Markov chain Monte Carlo estimation.[27,28] Missing at random assumptions were made. The Markov chain Monte Carlo sampler retained 5,000 samples after the first 1,000 samples burned-in. Jeffrey's prior was assigned for prior distributions. There was no autocorrelation between samples, and the posterior distributions were converged. SAS software (SAS Institute, Cary, NC) and software R (http://www.r-project.org/) were used for all analyses.

RESULTS

Pretreatment Characteristics

Between February 1987 and April 1992, a total of 945 eligible patients were enrolled. Four hundred seventy-seven patients were assigned to adjuvant goserelin (arm 1), and 468 patients were assigned to no adjuvant goserelin (arm 2). Median age was 70 years. Pretreatment characteristics, including CVD risk factors, were similar between treatment arms (Table 1).

Cardiovascular Mortality

Median follow-up time was 8.1 years (range, 0.2 to 15.1 years) for all eligible patients and 11.1 years (range, 0.4 to 15.0 years) for surviving patients. There was a total of 574 deaths; 117 (20.4%) were categorized as cardiovascular deaths.

Univariate Analyses

In univariate analyses, there was no treatment-related increase in cardiovascular mortality (Table 2). At 9 years, cardiovascular mortality rate for men treated with adjuvant goserelin on arm 1 was 8.4% *v* 11.4% for men treated without adjuvant goserelin on arm 2 (Gray's $P = .17$). The corresponding unadjusted HR was 0.77 (95% CI, 0.53 to 1.11; $P = .16$). Figure 1 graphically displays time to cardiovascular mortality by treatment arm. Similar results were observed in additional analyses that censored patients at time of initiation of salvage goserelin therapy (data not shown). Established CVD risk factors, including age, prevalent CVD, and DM, were significantly associated with greater cardiovascular mortality. In addition, prostatectomy and advanced clinical stage were significantly associated with increased cardiovascular mortality.

Multiple Regression Analyses

In multiple regression analyses, prevalent CVD and DM were significantly associated with greater cardiovascular mortality (Table 3). Adjuvant goserelin treatment was not associated with cardiovascular mortality (adjusted HR = 0.73; 95% CI, 0.47 to 1.15; $P = .16$). Notably, there were no interaction effects between treatment arm and other covariates (data not shown). Similar results were observed in additional analyses that censored patients at time of initiation of salvage goserelin therapy (Table 3). In censored analyses, traditional cardiovascular risk factors, including prevalent CVD and DM, were associated with greater cardiovascular mortality, whereas adjuvant goserelin treatment was not (adjusted HR = 0.99; 95% CI, 0.58 to 1.69; $P = .97$).

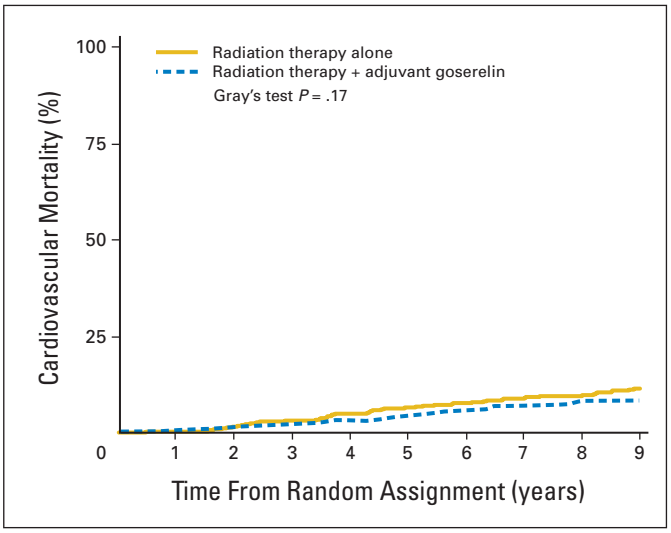

Fig 1. Time to cardiovascular mortality by treatment arm for all eligible patients.

Our primary analysis was based on 641 patients with complete multivariable data. To address the possibility that our results may have been affected by the exclusion of patients with missing data, additional analyses were performed using imputed missing values (Table 4). Consistent with the primary analyses, adjuvant goserelin was not significantly associated with time to cardiovascular mortality, whereas prevalent CVD and DM were significant in both uncensored and censored analyses.

We also considered the possibility that our results were sensitive to the definition of cardiovascular mortality. To address this issue, we performed further analyses using alternative definitions based on a more limited composite of causes of cardiovascular death (CAD, CVD, cardiac arrest, and MI) and then further restricted the definition to death as a result of MI only. We also considered a broader definition of death as a result of cardiovascular and cerebral events, including cerebrovascular accident, cerebral hemorrhage, cerebral infarction, stroke, and thrombotic occlusion (an additional 28 events). Similar results were observed in both univariate and multiple regression analyses irrespective of the definition used (data not shown). Specifically, treatment arm was not significantly associated with cardiovascular mortality, whereas traditional cardiac risk factors, including prevalent CVD and DM, were consistently associated with cardiovascular mortality.

Subgroup Analyses

On the basis of the observation that advanced age, prevalent CVD, and DM were associated with cardiovascular mortality, we evaluated the effect of treatment in men ≥ 70 years old and in men

Table 3. Multiple Regression Analyses of Cardiovascular Mortality Without and With Censoring at Time of Salvage GnRH Agonist Therapy (N = 641)

Covariate	Without Censoring			With Censoring		
	HR	95% CI	*P*	HR	95% CI	*P*
Treatment arm: arm 2 *v* arm 1	0.73	0.47 to 1.15	.16	0.99	0.58 to 1.69	.97
Age: < 70 *v* ≥ 70 years	1.57	0.95 to 2.59	.08	1.39	0.79 to 2.45	.26
Prevalent CVD: no *v* yes	2.60	1.65 to 4.11	< .0001	2.92	1.71 to 4.98	< .0001
Prevalent HTN: no *v* yes	1.32	0.85 to 2.04	.22	1.57	0.96 to 2.57	.08
Prevalent DM: no *v* yes	2.54	1.49 to 4.34	.0006	2.92	1.57 to 5.43	.0007
BMI, kg/m^2						
< 25	—	—		—	—	
≥ 25 to < 30	0.94	0.58 to 1.54	.81	0.89	0.49 to 1.61	.70
≥ 30	0.87	0.45 to 1.67	.67	0.92	0.42 to 2.01	.83
Race: black *v* other	1.25	0.60 to 2.59	.55	2.05	0.74 to 5.63	.17
Prostatectomy: no *v* yes	0.45	0.14 to 1.47	.18	0.33	0.09 to 1.28	.11
Nodal involvement: no *v* yes	1.31	0.65 to 2.63	.45	0.84	0.35 to 2.03	.70
Acid phosphatase: not elevated *v* elevated	1.15	0.72 to 1.84	.57	1.26	0.73 to 2.19	.41
Gleason score						
2-6	—	—		—	—	
7	0.81	0.49 to 1.34	.41	0.72	0.40 to 1.30	.28
8-10	0.62	0.35 to 1.10	.10	0.55	0.28 to 1.11	.10
Clinical stage: A/B *v* C	1.13	0.46 to 2.83	.79	0.57	0.20 to 1.61	.29

Abbreviations: GnRH, gonadotropin-releasing hormone; HR, hazard ratio; CVD, cardiovascular disease; HTN, hypertension; DM, diabetes mellitus; BMI, body mass index.

with prevalent CVD or DM. As displayed in Table 5, there was no significant treatment-related effect on cardiovascular mortality in these subgroups of high-risk patients. Results were similar in additional analyses that censored patients at time of salvage goserelin therapy (data not shown).

DISCUSSION

A recent claims-based analysis linked GnRH agonists with a greater risk for incident coronary heart disease and MI.[10] Using data from a large, multicenter, prospective, randomized controlled trial with long follow-up, we found that adjuvant goserelin was not associated with increased cardiovascular mortality in men with locally advanced prostate cancer. Specifically, the 9-year cardiovascular mortality rate for men treated with adjuvant goserelin was 8.4% *v* 11.4% for men treated without adjuvant goserelin. The lack of an apparent treatment-related detrimental effect was similarly seen after censoring patients at time of salvage GnRH agonist therapy and when using alternative definitions of cardiovascular mortality. Our results also confirmed that established cardiovascular risk factors, such as prevalent CVD and

Table 4. Multiple Regression Analyses of Cardiovascular Mortality Without and With Censoring at Time of Salvage GnRH Agonist Therapy (N = 945 using imputed missing values)

Covariate	Without Censoring			With Censoring		
	HR	95% CI	*P*	HR	95% CI	*P*
Treatment arm: arm 2 *v* arm 1	0.76	0.52 to 1.09	.14	0.97	0.63 to 1.48	.88
Age: < 70 *v* ≥ 70 years	1.59	1.04 to 2.42	.032	1.47	0.91 to 2.37	.12
Prevalent CVD: no *v* yes	2.70	1.84 to 3.95	< .0001	2.97	1.91 to 4.60	< .0001
Prevalent HTN: no *v* yes	1.09	0.75 to 1.58	.67	1.15	0.75 to 1.74	.53
Prevalent DM: no *v* yes	1.79	1.10 to 2.89	.018	1.83	1.07 to 3.12	.027
BMI, kg/m^2						
< 25	—	—		—	—	
≥ 25 to < 30	1.10	0.71 to 1.70	.68	1.07	0.64 to 1.79	.81
≥ 30	1.09	0.62 to 1.92	.80	1.21	0.63 to 2.32	.57
Race: black *v* other	0.86	0.47 to 1.55	.60	1.25	0.58 to 2.69	.57
Prostatectomy: no *v* yes	0.77	0.30 to 1.98	.59	0.61	0.20 to 1.86	.38
Nodal involvement: no *v* yes	1.17	0.68 to 2.02	.57	0.88	0.46 to 1.70	.71
Acid phosphatase: not elevated *v* elevated	1.01	0.68 to 1.51	.96	1.10	0.70 to 1.74	.67
Gleason score						
2-6	—	—		—	—	
7	0.94	0.61 to 1.46	.80	0.80	0.48 to 1.31	.37
8-10	0.82	0.50 to 1.35	.43	0.74	0.41 to 1.34	.32
Clinical stage: A/B *v* C	1.67	0.80 to 3.45	.17	1.11	0.49 to 2.54	.80

Abbreviations: GnRH, gonadotropin-releasing hormone; HR, hazard ratio; CVD, cardiovascular disease; HTN, hypertension; DM, diabetes mellitus; BMI, body mass index.

Table 5. Univariate Analyses of Cardiovascular Mortality by Treatment Arm for Subgroups of Patients With Age ≥ 70 Years, Prevalent CVD, or DM

			Cumulative Incidence			Fine and Gray's Models		
Subgroup	No. of Patients	No. of Failures	9-Year Failure Rate (%)	95% CI	*P**	Unadjusted HR	95% CI	*P*†
Age ≥ 70 years								
Arm 2	245	40	14.3	9.7 to 18.9				
Arm 1	247	39	13.0	8.6 to 17.3	.74	0.94	0.60 to 1.45	.77
Prevalent CVD								
Arm 2	120	36	24.3	16.5 to 32.0				
Arm 1	133	26	13.7	7.8 to 19.7	.086	0.63	0.38 to 1.03	.065
Prevalent DM								
Arm 2	45	11	22.2	9.9 to 34.6				
Arm 1	36	10	22.7	8.5 to 36.8	.67	1.18	0.51 to 2.74	.70

Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio.
*P value determined using Gray's test statistic.
†P value determined using χ^2 test.

DM, are associated with increased risk of cardiovascular mortality. Within subgroups of men with highest risk, there remained no apparent treatment-related increase in cardiovascular mortality.

To the best of our knowledge, these are the first analyses using data from a large prospective study to directly address the potential relationship between GnRH agonists and cardiovascular mortality. Our results are consistent with other published reports. In a prospective randomized controlled trial (RTOG 92-02), long-term adjuvant treatment with GnRH agonists was associated with greater noncancer mortality than short-term therapy, although there seemed to be no difference when classified as cardiovascular death.[5,5a] Notably, there was an imbalance between the groups, with the long-term arm having a higher rate of prevalent CVD that the short-term arm (55% *v* 44%, respectively). A retrospective study suggested that neoadjuvant GnRH agonist therapy in men treated for early-stage prostate cancer with prostate brachytherapy was associated with worse overall survival compared with hormone-naïve men, although cancer-specific mortality was similar.[29] In that series, CVD was the single largest cause of death in both groups without any obvious discrepancy between the groups (representing 24% and 22% of overall mortality in patients who did and did not receive GnRH agonist therapy, respectively). In European Organisation for Research and Treatment of Cancer trial 30891,[30] in which 985 men with localized prostate cancer not suitable for local curative treatment were treated with immediate or deferred ADT (orchiectomy or GnRH agonist), overall survival favored the immediate arm seemingly as a result of fewer noncancer deaths. Specifically, death from CVD was 17.9% in the immediate arm compared with 19.7% in the deferred arm. In a recent pooled data analysis[31] of three trials using varying courses of short-term GnRH agonist therapy, it was suggested that a subset of men age 65 years or older who received 6 months of ADT experienced shorter times to fatal MIs compared with men in this age group who did not receive ADT; notably, this study did not show any difference in total number of fatal MIs (18 *v* 16 MIs, respectively). Furthermore, compared with our study, the analysis was limited by a lower number of events (approximately one third), shorter follow-up, short treatment duration, and lack of information on known CVD risk factors.

The absence of an apparent increase in cardiovascular mortality in our study and other trials does not exclude the possibility that GnRH agonists increase noncancer mortality. Men with prostate cancer have higher rates of noncancer death than the general population,[32] and GnRH agonists may contribute to this through multiple mechanisms. In the recent claims-based Surveillance, Epidemiology, and End Results-Medicare analysis that first reported an association between GnRH agonists and incident nonfatal coronary heart disease and MI,[10] the effect was modest (16% and 11% increased risk, respectively) and may not translate into an apparent increase in cardiovascular mortality. Notably, the analyses by Keating et al[10] also showed a greater risk for other adverse events, including incident DM (44% increased risk), which may independently contribute to noncancer, noncardiac mortality. GnRH agonists also decrease bone mineral density[33,34] and increase fracture risk in men with prostate cancer,[35,36] another possible cause of death.[37] In addition, GnRH agonists may lead to declines in hemoglobin,[38] and anemia has been shown to be a prognostic factor for survival in men with hormone-refractory prostate cancer.[39] Other adverse effects such as fatigue and psychological distress[40] impact quality of life and overall frailty. Thus, GnRH agonists have the potential to impact noncancer mortality through several mechanisms.

Additional studies are necessary to assess potential effects of neoadjuvant/adjuvant GnRH agonist therapy on cardiovascular mortality in men with earlier stage prostate cancer and lower rates of cancer-specific mortality. In our population of men with locally advanced disease, there was a significant rate of prostate cancer–specific mortality (35%). Cardiovascular mortality represented approximately 20% of all deaths in our study, whereas it represents closer to 30% of all deaths in the general male population.[41] Especially among men with earlier stage disease and favorable prognosis in whom the role for GnRH agonists has not been clearly defined, treatment decisions need to carefully weigh potential risks and benefits.

Our study has substantial strengths. First, it is one of few prostate cancer trials with a control arm of no hormone therapy. Second, our study was large, with 945 patients, more than 11 years of follow-up for living patients, and 117 cardiovascular deaths. Although it is possible that we could have missed a small adverse treatment effect, the clinical significance of any such small effect may be questionable. Third, although we used investigator-defined cause of death as our study outcome, our ascertainment of cardiovascular mortality seems reliable given the strong association with traditional CVD risk factors, including prevalent CVD and DM, and consistency of results using

alternative definitions of cardiovascular mortality. Data were not collected on each individual investigator, and thus, controlling for each investigator was not feasible. Fourth, we had information on a number of known CVD risk factors, and importantly, rates of prevalent CVD were similar between the treatment arms. We did lack detailed information on other risk factors including hyperlipidemia and certain lifestyle factors, such as smoking, diet, and physical activity, as well as CVD severity and use of cardiac medications. It is unlikely that there would have been any imbalance between the arms with respect to these other factors, however, given the size and randomized nature of our study. Fifth, the study's follow-up requirements for both arms seem to substantially exceed routine follow-up for adult men without cancer; accordingly, the possibility that any incremental difference in intensity of oncology follow-up for administration of a GnRH agonist led to a decrease in cardiovascular mortality in arm 1 seems remote and is unlikely to have affected the outcome. Finally, we observed consistency in our results when applying alternative definitions of cardiovascular mortality, when censoring at the time of salvage GnRH agonist therapy, and when imputing missing data.

In summary, although GnRH agonists are associated with greater risk of incident coronary heart disease and MI, we found no evidence that adjuvant long-term treatment with GnRH agonists increased cardiovascular mortality in men with locally advanced prostate cancer. Additional studies are needed to assess the potential relationship between GnRH agonists and cardiovascular mortality in men with lower cancer-specific mortality.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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