REVIEW

Association of Androgen Deprivation Therapy With Cardiovascular Death in Patients With Prostate Cancer

A Meta-analysis of Randomized Trials

Paul L. Nguyen, MD
Youjin Je, MS
Fabio A. B. Schutz, MD
Karen E. Hoffman, MD, MPH, MHSc
Jim C. Hu, MD, MPH
Arti Parekh, BA
Joshua A. Beckman, MD, MSc
Toni K. Choueiri, MD

Context Whether androgen deprivation therapy (ADT) causes excess cardiovascular deaths in men with prostate cancer is highly controversial and was the subject of a joint statement by multiple medical societies and a US Food and Drug Administration safety warning.

Objective To perform a systematic review and meta-analysis of randomized trials to determine whether ADT is associated with cardiovascular mortality, prostate cancer–specific mortality (PCSM), and all-cause mortality in men with unfavorable-risk, nonmetastatic prostate cancer.

Data Sources A search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases for relevant randomized controlled trials in English between January 1, 1966, and April 11, 2011.

Study Selection Inclusion required nonmetastatic disease, intervention group with gonadotropin-releasing hormone agonist–based ADT, control group with no immediate ADT, complete information on cardiovascular deaths, and median follow-up of more than 1 year.

Data Extraction Extraction was by 2 independent reviewers. Summary incidence, relative risk (RR), and CIs were calculated using random-effects or fixed-effects models.

Results Among 4141 patients from 8 randomized trials, cardiovascular death in patients receiving ADT vs control was not significantly different (255/2200 vs 252/1941 events; incidence, 11.0%; 95% CI, 8.3%-14.5%; vs 11.2%; 95% CI, 8.3%-15.0%; RR, 0.93; 95% CI, 0.79-1.10; $P=.41$). ADT was not associated with excess cardiovascular death in trials of at least 3 years (long duration) of ADT (11.5%; 95% CI, 8.1%-16.0%; vs 11.5%; 95% CI, 7.5%-17.3%; RR, 0.91; 95% CI, 0.75-1.10; $P=.34$) or in trials of 6 months or less (short duration) of ADT (10.5%; 95% CI, 6.3%-17.0%; vs 10.3%; 95% CI, 8.2%-13.0%; RR, 1.00; 95% CI, 0.73-1.37; $P=.99$). Among 4805 patients from 11 trials with overall death data, ADT was associated with lower PCSM (443/2527 vs 552/2278 events; 13.5%; 95% CI, 8.8%-20.3%; vs 22.1%; 95% CI, 15.1%-31.1%; RR, 0.69; 95% CI, 0.56-0.84; $P<.001$) and lower all-cause mortality (1140/2527 vs 1213/2278 events; 37.7%; 95% CI, 27.3%-49.4%; vs 44.4%; 95% CI, 32.5%-57.0%; RR, 0.86; 95% CI, 0.80-0.93; $P<.001$).

Conclusion In a pooled analysis of randomized trials in unfavorable-risk prostate cancer, ADT use was not associated with an increased risk of cardiovascular death but was associated with a lower risk of PCSM and all-cause mortality.

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ANDROGEN DEPRIVATION therapy (ADT) in the form of a gonadotropin-releasing hormone (GnRH) agonist is a mainstay of prostate cancer treatment, but several studies have suggested that ADT may increase a patient's risk of dying from cardiovascular causes.

In 2006, Keating et al[1] found that GnRH agonist use was associated with a 44% increased risk of incident diabetes, 16% increase in coronary heart disease, 11% increase in myocardial infarction (MI), and 16% increase in sudden cardiac death in the national Surveillance, Epidemiology, and End Results–Medicare database. In 2007, Tsai et al[2] found that ADT was associated with a 2.6-times increase in cardiovascular death among men receiving radical prostatectomy in the CAPSURE database. In addition, D'Amico et al[3] reanalyzed data from 2 randomized trials and found that ADT use was associated with a shorter time to fatal MI in a subgroup of men older than 65 years. On the basis of these and other studies,[4] the American Heart Association, the American Cancer

For editorial comment see p 2382.

Author Affiliations are listed at the end of this article.
Corresponding Author: Paul L. Nguyen, MD, Department of Radiation Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (pnguyen@LROC.harvard.edu).

Society, the American Urological Association, and the American Society for Radiation Oncology issued a joint scientific report to raise awareness of the potential linkage between ADT and cardiovascular events and stated "at this point, it is reasonable, on the basis of the above data, to state that there may be a relation between ADT and cardiovascular events and death."[5] Similarly, the US Food and Drug Administration issued a safety warning on October 20, 2010, requiring labeling on GnRH agonists warning about an "increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer."[6]

However, other studies have not confirmed these findings[7-9] and, due to the significant controversy and clinical concern over this issue, we performed an up-to-date meta-analysis of randomized controlled trials to determine whether ADT is associated with cardiovascular mortality, prostate cancer–specific mortality (PCSM), and all-cause mortality in men with unfavorable-risk, nonmetastatic prostate cancer.

METHODS

Selection of Studies

We reviewed MEDLINE and EMBASE citations between January 1, 1966, and April 11, 2011, and the Cochrane Central Register of Controlled Trials database through April 11, 2011. The search terms used were *prostate cancer* and (*androgen deprivation* or *androgen suppression* or *hormone* or *gonadotropin*), with the results limited to randomized controlled trials in the English language. We included only trials focused on patients with nonmetastatic and non–hormone-refractory disease and that had an intervention group with immediate ADT and a control group of patients receiving no immediate ADT. For inclusion in our study, the trial had to predominantly use a GnRH agonist, have adequate information on cardiovascular deaths, and have a median follow-up of at least 1 year. We required a GnRH agonist because the large observational study by Keating et al[1] found an excess risk of coronary heart disease, MI, and sudden cardiac death among men who received GnRH agonists but not those who received orchiectomy, and because orchiectomy is much less commonly used in modern practice. When more than 1 publication was identified from the same clinical trial, we used the most recent or complete report of that trial. Quality of the trials was assessed using the Jadad/Oxford quality scoring system.[10] For analysis of PCSM and all-cause mortality, we required trials to report those 2 end points but did not require that they report cardiovascular mortality.

Data Extraction and Clinical End Points

Data abstraction was conducted independently by 2 investigators (P.L.N. and A.P.) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement[11] and any discrepancies between reviewers were resolved by consensus. For each study, we extracted the following information: first author's name, year of publication, median age of patients, number of enrolled patients, inclusion criteria, treatment groups, type of ADT, duration of ADT, number of cardiovascular deaths in ADT and control groups, definition of cardiovascular death, median follow-up, number of PCSM deaths, and number of overall deaths. The definition of cardiovascular death was accepted as defined by the study authors. If it was not specifically defined in the study, then we included events broadly related to cardiac disease and vascular disease. Definitions of cardiovascular disease for each included study are shown in the TABLE, alongside the study information.[3,8,9,12-19]

Statistical Analysis

For the calculation of incidence, the number of patients with cardiovascular death and the number of patients who were treated with ADT or placebo were extracted from the individual selected clinical trials. The proportion of patients with those adverse outcomes and 95% CIs were derived from each trial. We also calculated relative risks (RRs) and 95% CIs of cardiovascular death in patients assigned to ADT vs controls in the same trial. To calculate 95% CIs, the variance of a log-transformed study-specific RR was derived using the δ method. For studies reporting zero events in a treatment or control group, we applied a classic half-integer continuity correction to calculate RR and variance. We then repeated this for the end points of PCSM and all-cause mortality.

Statistical heterogeneity among trials included in the meta-analysis was assessed by using the Cochran Q statistic, and inconsistency was quantified with the I^2 statistic [$100\% \times (Q - df)/Q$], which estimates the percentage of total variation across studies due to heterogeneity rather than chance.[20] The assumption of homogeneity was considered invalid for $P < .10$. Summary incidence and RRs were calculated using random-effects or fixed-effects models depending on the heterogeneity of included studies. When substantial heterogeneity was not observed, the summary estimate calculated on the basis of the fixed-effects model was reported by using the inverse variance method. When substantial heterogeneity was observed, the summary estimate calculated on the basis of the random-effects model was reported by using the DerSimonian and Laird method that considers both within-study and between-study variations.[21] For studies with separate treatment groups evaluating varying durations of ADT, we combined the 2 ADT groups for the overall analysis.

To determine the RR of cardiovascular death due to ADT within particular groups, we performed subgroup analyses on trials of short course (ADT for ≤6 months) or long course (ADT for ≥3 years), trials with median age of younger than 70 years or 70 years or older, and trials in which radiation was used. To further test for variation in the RR of cardiovascular death due to ADT

by duration of ADT or median age of patients, we conducted a meta-regression analysis by modeling a log-transformed study-specific RR as a dependent variable and duration of ADT (≤6 months or ≥3 years) or median age (<70 or ≥70 years) as an independent variable. In addition, publication bias was evaluated through funnel plots (ie, plots of study results against precision) and with the Begg and Egger tests. Two-tailed $P<.05$ was considered statistically significant. All statistical analyses were performed by using Stata/SE version 12.0 software (Stata Corp).

RESULTS

Selection of Trials

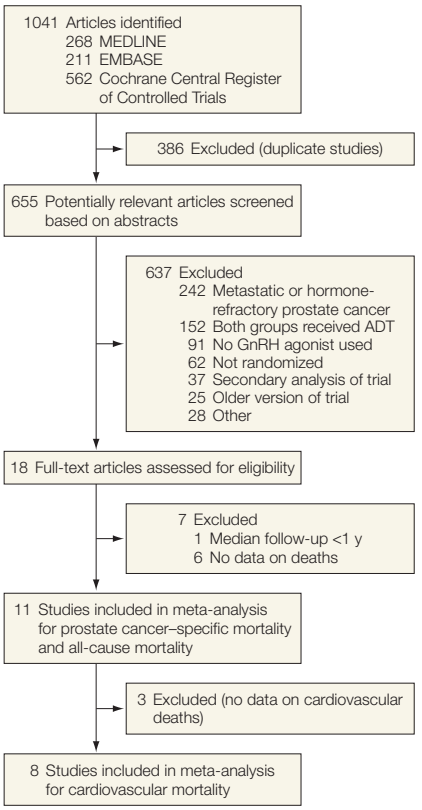
Our initial search yielded 1041 studies (268 from MEDLINE, 211 from EMBASE, and 562 from the Cochrane Central Register of Controlled Trials). After removing 386 duplicate studies, we evaluated the abstracts of 655 stud-

Table. Baseline Characteristics and Number of CV Deaths for the Selected Trials of ADT in Nonmetastatic Prostate Cancer

Source	Median Age, y	Definition of CV Death From Article	Stage	ADT		Median Follow-up, y	Treatment Groups	No. of Patients	No. of Deaths	No. of PCSM Deaths	No. of CV Deaths
				Type	Length						
D'Amico et al,[3] 2008 (DFCI 95-096)	73 (range, 49-82)	Fatal MI	T1b-T2b, N0	Leuprolide + flutamide	6 mo	7.6 (range, 0.5-11.0)	70Gy + ADT	102	30	4	13
							70Gy	104	44	14	13
Messing et al,[12] 2006 (ECOG/EST 3886)	66 (range, 45-78)	Two by vascular disease (1 ischemic bowel, 1 peripheral and CV); 1 by pulmonary embolism; 1 by cerebrovascular disease	pN+	Goserelin or orchiectomy	Lifelong	11.9 (range, 9.7-14.5)	RP+ADT	47	17	7	3
							RP	51	28	25	1
Bolla et al,[13] 2010 (EORTC 22863)	71 (IQR, 67-75) 70 (IQR, 65-75)	CV death	T1-T4, N0-1	Goserelin	3 y	9.1 (IQR, 5.1-12.6)	70Gy + ADT	207	80	26	22
							70Gy	208	112	57	17
Schröder et al,[14] 2009 (EORTC 30846)	67 (range, 52-77) 64 (range, 46-79)	CV and other causes (excluded other cancers, infection, unknown causes, and prostate cancer deaths)	T0-T4, pN1-3	Zoladex + cyproterone acetate or orchiectomy	Lifelong[a]	13	Immediate ADT	119	96	69	10
							Delayed ADT	115	97	70	10
Studer et al,[15] 2006 (EORTC 30891)	73 (range, 52-81)	Death due to CV diseases	T1-T4, N0-1	Buserelin + cyproterone acetate or orchiectomy	Lifelong	7.8	Immediate ADT	492	257	94	88
							Deferred ADT	493	284	99	97
Efstathiou et al,[8] 2009 (RTOG 85-31)	70	Death from coronary artery disease, CV disease, CHF, cardiac arrest, cardiomyopathy, CV arrhythmia, MI, or sudden death	T3 or pN+	Goserelin	Lifelong[b]	8.1 (range, 0.2-15.1)	70Gy+ADT	477	269	82	52
							70Gy	468	306	113	65
Roach et al,[9] 2008 (RTOG 86-10)	70 (range, 50-88) 71 (range, 49-84)	Death from MI, CHF, cardiac arrest, cardiac, arteriosclerotic CV disease, or cardiopulmonary arrest	T2-T4, N0-1	Goserelin + flutamide	4 mo	11.9	70Gy + ADT	224	164	65	31
						13.2	70Gy	232	184	96	26
Denham et al,[16] 2011 (TROG 96.01)	68 (range, 41-87) 67 (range, 51-80)	Cardiac death	T2c-T4, N0	Goserelin + flutamide	3-6 mo	10.6 (IQR, 6.9-11.6)	66Gy + ADT	532	198	89	36
							66Gy	270	136	70	23
Aus et al,[17] 2002 (Aus)	67 (range, 50-77) 66 (range, 54-77)	NA	T1b-T3aNX, M0	Triptorelin + cyproterone acetate	3 mo	6.8 (range, 0.67-8.7)	ADT + RP	63	11	3	NA
							RP alone	63	9	3	NA
Schulman et al,[18] 2000 (ESGNTPC)	NA	NA	T2-T3, NxM0	Goserelin + flutamide	3 mo	NA	ADT + RP	192	8	3	NA
							RP alone	210	8	5	NA
Yee et al,[19] 2010 (MSKCC)	61 (IQR, 57-66) 61 (IQR, 57-65)	NA	T1-T2, N0Mx	Goserelin + flutamide	3 mo	8.0 (range, 0.1-15.3)	ADT + RP	72	10	1	NA
							RP alone	64	5	0	NA

Abbreviations: ADT, androgen deprivation therapy; CHF, congestive heart failure; CV, cardiovascular; IQR, interquartile range; MI, myocardial infarction; NA, not applicable; PCSM, prostate cancer–specific mortality; RP, radical prostatectomy.
[a] Median duration of ADT in the EORTC 30846 trial was 5.1 (95% CI, 3.9-6.5) years for immediate ADT.
[b] Median duration of ADT in the RTOG 85-31 trial was 4.2 years.

Figure 1. Article Selection



ADT indicates androgen deprivation therapy; GnRH, gonadotropin-releasing hormone.

ies. After evaluating the abstract of each study, 637 studies were excluded because they did not meet inclusion criteria. Subsequently, we carefully read the full text of each of the remaining 18 trials and excluded 1 trial for having a follow-up of less than 1 year (n=167 patients)[22] and 6 trials (n=1105 patients)[22-28] for no mention of mortality outcomes, which resulted in 11 trials with 4805 patients for PCSM and all-cause mortality end points.[3,8,9,12-19] Three of these trials (n=664 patients)[17-19] had no information on cardiovascular deaths; therefore, the remaining 8 trials (n=4141 patients) were ultimately selected for inclusion in the cardiovascular death meta-analysis.[3,8,9,12-16] Median follow-up in these 8 included trials ranged between 7.6 and 13.2 years. A detailed selection process is shown in FIGURE 1.

The baseline characteristics of each trial are shown in the Table. All selected trials included patients with nonmetastatic disease who were treated with immediate predominantly GnRH-agonist–based ADT vs no immediate ADT. Local therapy consisted of external beam radiation (5 trials), surgery (4 trials), or no local therapy (2 trials). Three trials included a substantial proportion of patients with lymph node involvement. The duration of ADT varied from 3 months to lifelong.

Quality of the Studies and Publication Bias

All trials included in the meta-analysis were randomized, multicenter, phase 3 trials. All of the trials were open label and have all been published in full manuscript form. The Jadad/Oxford quality scales require a double-blinded placebo for 2 of the 5 points. Because this would have required sham injections, none of the 11 trials included a double-blinded placebo; therefore, their maximum score was 3 out of 5 points (7 trials), and 4 trials scored 2 out of 5 points.[10] No evidence of publication bias was detected for RR of cardiovascular death by either Begg test ($P=.54$) or Egger test ($P=.11$), or for the RR of PCSM (Begg test, $P=.53$; Egger test, $P=.24$), or for the RR of all-cause mortality (Begg test, $P=.76$; Egger test, $P=.72$).

Incidence and RR of Cardiovascular Death

Among the 2200 patients who were treated with ADT, there were 255 cardiovascular deaths. The overall incidence of cardiovascular death was 11.0% (95% CI, 8.3%-14.5%) in the ADT group (heterogeneity test: Q=33.58; $P<.001$; $I^2=79.2\%$). For the control group, there were 1941 patients and 252 cardiovascular deaths, for an overall incidence of 11.2% (95% CI, 8.3%-15.0%; heterogeneity test: Q=33.81; $P<.001$; $I^2=79.3\%$). The corresponding RR of cardiovascular death for ADT vs control was not significant (RR, 0.93; 95% CI, 0.79-1.10; $P=.41$). No significant heterogeneity was observed in the RR analysis of cardiovascular death (heterogeneity test: Q=5.12; $P=.64$; $I^2=0\%$). Results of individual trials are shown in FIGURE 2.

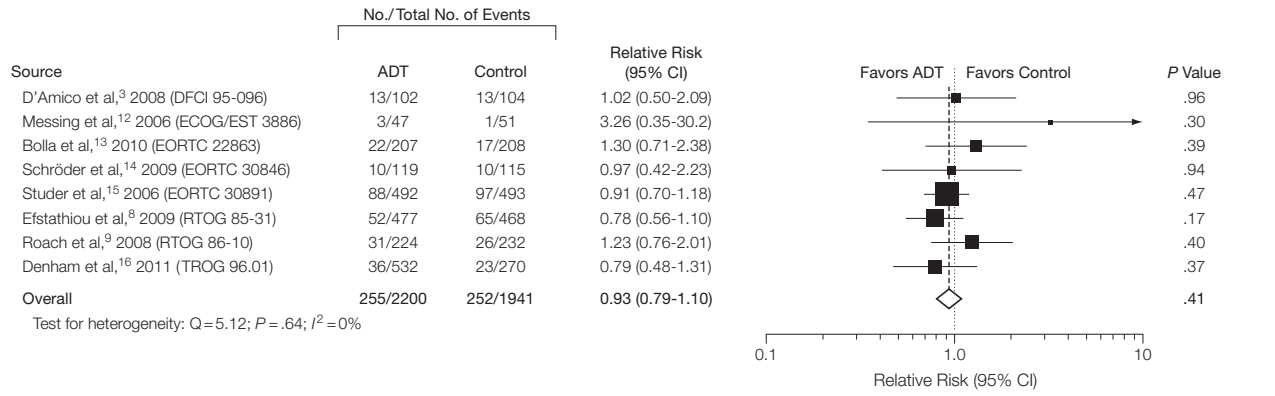
Variation of Association by Duration of ADT

Three trials (DFCI 95-096,[3] TROG 96.01,[16] and RTOG 86-10[9]) with 1464 patients used ADT for 6 months or less (range, 3-6 months), and 5 trials (EORTC 22863,[13] RTOG 85-31,[8] EORTC 30891,[15] EORTC 30846,[14] and ECOG/EST 3886[12]) with 2667 patients used ADT for at least 3 years (range, 3 years to lifelong). Among patients in short-course ADT trials, the incidence of fatal cardiovascular events for ADT vs control was 10.5% (95% CI, 6.3%-17.0%) vs 10.3% (95% CI, 8.2%-13.0%), respectively, and the RR of cardiovascular death was 1.00 (95% CI, 0.73-1.37; $P=.99$). Among patients in long-course ADT trials, the incidence of fatal cardiovascular events for ADT vs control was 11.5% (95% CI, 8.1%-16.0%) vs 11.5% (95% CI, 7.5%-17.3%), respectively, and the RR of cardiovascular death was 0.91 (95% CI, 0.75-1.10; $P=.34$). When comparing the RRs of cardiovascular death due to ADT among long-course trials with short-course trials, we did not observe a statistically significant difference ($P=.63$).

Variation of Association by Median Age in Study

Among the 5 trials with a median age of 70 years or older (DFCI 95-096,[3] RTOG 85-31,[8] RTOG 86-10,[9] EORTC 22863,[13] and EORTC 30891[15]), there was no association between ADT and cardiovascular death (13.3%; 95% CI, 10.4%-16.7%; vs 13.1%; 95% CI, 9.6%-17.6%; RR for ADT vs no ADT, 0.95; 95% CI, 0.79-1.13; $P=.53$; test for heterogeneity: Q=3.49; $P=.48$; $I^2=0\%$). Among the 3 trials with a median age of younger than 70 years (TROG 96.01,[16] ECOG/EST 3886,[12] and EORTC 30846[14]), there was also no evidence of an association between ADT

Figure 2. Relative Risk of Cardiovascular Deaths Associated With ADT Among Patients With Prostate Cancer



ADT indicates androgen deprivation therapy. The summary relative risk of cardiovascular deaths was calculated using a fixed-effects model. The size of the squares indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond indicates the summary relative risk.

and cardiovascular death (7.1%; 95% CI, 5.4%-9.2%; vs 8.2%; 95% CI, 5.9%-11.3%; RR, 0.88; 95% CI, 0.58-1.34; $P=.55$; test for heterogeneity: Q=1.53; $P=.46$; $I^2=0\%$). When comparing the RRs of cardiovascular death due to ADT among trials with median age of younger than 70 years vs 70 years or older, we did not observe a statistically significant difference ($P=.77$).

Findings in Patients Who Received Radiation Therapy

When analysis was limited to the 5 trials in which definitive radiation was used (DFCI 95-096,[3] TROG 96.01,[16] RTOG 85-31,[8] RTOG 86-10,[9] and EORTC 22863[13]), there was also no evidence of excess cardiovascular death due to ADT (10.5%; 95% CI, 8.1%-13.6%; vs 11.5%; 95% CI, 9.8%-13.3%; RR, 0.94; 95% CI, 0.76-1.17; $P=.57$; test for heterogeneity: Q=3.87; $P=.42$; $I^2=0\%$).

Association of ADT With PCSM

There were 443 PCSM deaths among 2527 patients in the ADT group and 552 PCSM deaths among 2278 patients in the control group. The incidence of PCSM among men receiving ADT vs control was 13.5% (95% CI, 8.8%-20.3%) vs 22.1% (95% CI, 15.1%-31.1%). The RR was 0.69 (95% CI, 0.56-0.84; $P<.001$; heterogeneity test: Q=24.57; $P=.006$; $I^2=59.3\%$), favoring ADT use (FIGURE 3).

Association of ADT With Overall Survival

There were 1140 total deaths among 2527 patients in the ADT group and 1213 total deaths among 2278 patients in the control group. The incidence of all-cause mortality among men receiving ADT vs control was 37.7% (95% CI, 27.3%-49.4%) vs 44.4% (95% CI, 32.5%-57.0%). The RR of death was 0.86 (95% CI, 0.80-0.93; $P<.001$; heterogeneity test: Q=16.86; $P=.08$; $I^2=40.7\%$) (FIGURE 4).

COMMENT

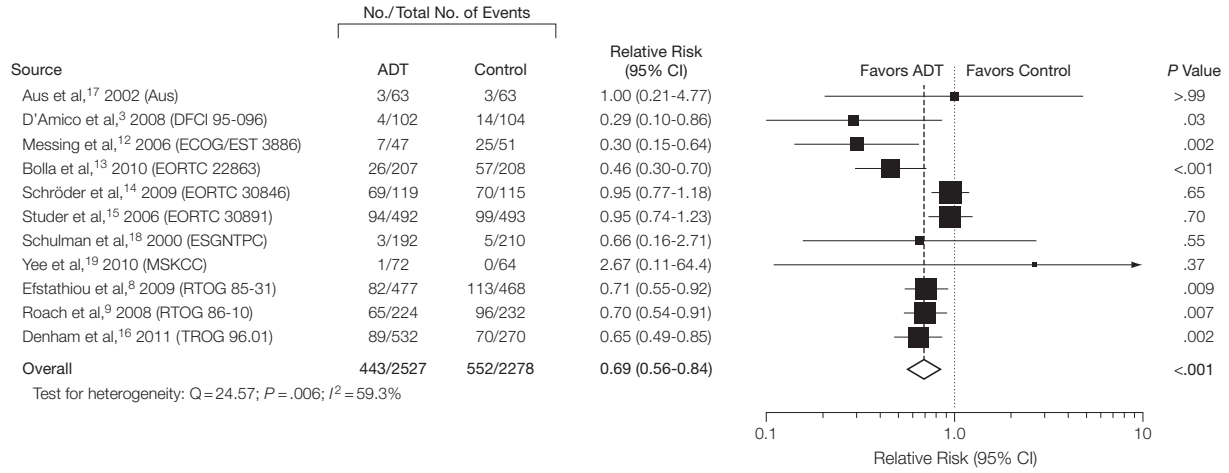
Whether ADT causes excess cardiovascular mortality in men with prostate cancer has been highly controversial for the last 5 years and recently led to a joint statement by the American Heart Association, the American Cancer Society, the American Urological Association, and the American Society for Radiation Oncology that there may be a relationship between ADT and cardiovascular events and death, and a safety warning by the Food and Drug Administration requiring GnRH agonist manufacturers to warn about an increased risk of diabetes, heart attack, sudden cardiac death, and stroke.[5,6] Because most of the data raising concern about the effect of ADT on cardiovascular events and cardiovascular death has been retrospective, we performed a meta-analysis of prospective randomized trials comparing immediate GnRH-agonist–based ADT vs no ADT or deferred ADT for men with nonmetastatic, unfavorable-risk prostate cancer. In our study of 4141 patients in 8 randomized trials with median follow-up of 7.6 to 13.2 years, we could not find any evidence that ADT causes excess cardiovascular mortality. Our study suggests that for the population as a whole, there is either no adverse effect of ADT on cardiovascular mortality or the magnitude of this effect is likely rather small.

In our analysis, we could not find a subgroup in which ADT was associated with excess cardiovascular mortality. Specifically, we did not see an excess risk of cardiovascular mortality due to ADT among men receiving short-course ADT (≤6 months), men receiving long-course ADT (≥3 years), men receiving radiation, or in trials in which the median age of enrollment was 70 years or older. As shown in some of the individual trials, our meta-analysis found that the use of ADT in men with unfavorable-risk prostate cancer is associated with improved prostate cancer–specific survival and overall survival. Of note, these improved survival findings only apply to men with unfavorable-risk prostate cancer, because the trials analyzed generally did not contain men with low-risk disease, a

group for whom there is no compelling evidence that ADT improves survival.

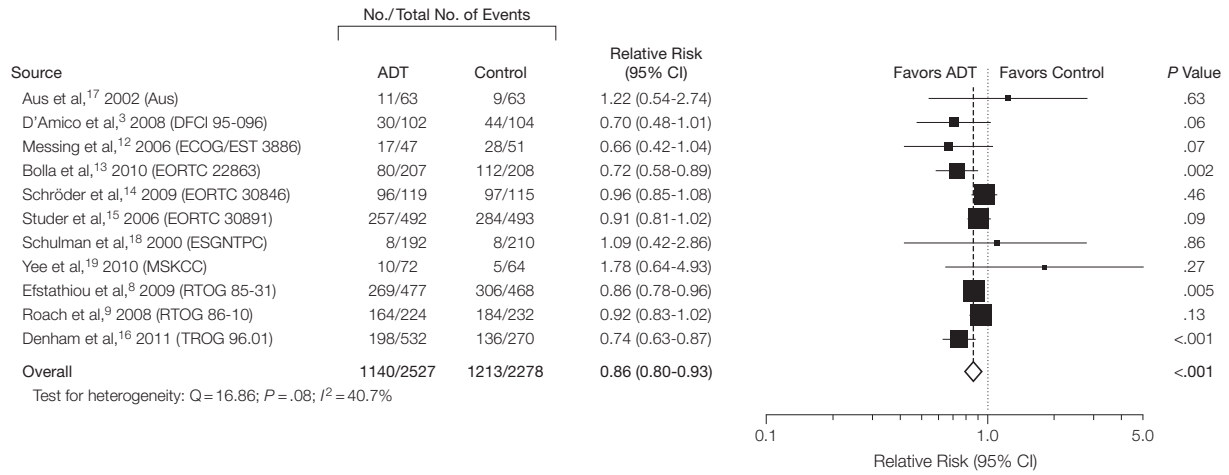
Overall, the results of our study should be generally reassuring to most men with unfavorable-risk prostate cancer considering ADT, because it was associated with improved survival without a measurable excess in cardiovascular mortality, but a few important points need to be raised. First, none of the trials were stratified by preexisting cardiovascular comorbidity; therefore, our study cannot exclude the possibility that a small subgroup of men with underlying cardiac disease (even if controlled) could experience excess cardiovascular mortality due to ADT.[29] For example, a post hoc reanalysis of one of the trials included in our meta-analysis (DFCI 95-096[3]) found that men with moderate to severe comorbidity (mainly cardiac) appeared to have poorer overall survival when treated with ADT and radiation vs radiation alone, although this difference was not statistically significant ($P=.08$).[3] In addition, a retrospective review of a large data set of men who were treated with brachytherapy-based radiation found that although 95% of the men were not harmed by ADT, the 5% of men with a prior history of MI or congestive heart failure (CHF) appeared to have a higher incidence of all-cause

Figure 3. Relative Risk of Prostate Cancer–Specific Mortality Associated With ADT Among Patients With Prostate Cancer



ADT indicates androgen deprivation therapy. The summary relative risk of prostate cancer–specific mortality was calculated using a random-effects model. The size of the squares indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond indicates the summary relative risk.

Figure 4. Relative Risk of All-Cause Mortality Associated With ADT Among Patients With Prostate Cancer



ADT indicates androgen deprivation therapy. The summary relative risk of all-cause mortality was calculated using a random-effects model. The size of the squares indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond indicates the summary relative risk.

mortality when treated with ADT plus radiation compared with radiation alone (25/95 vs 18/161 events; 26.3% vs 11.2% at 5 years; adjusted hazard ratio [HR], 1.96; $P=.04$).

The adverse effect of ADT in men with a history of MI or CHF was confirmed in a second large retrospective study[30] that found that even if such men had high-risk prostate cancer (prostate-specific antigen >20 ng/mL or Gleason score of 8-10 or clinical T3), their risk of all-cause mortality appeared to be higher with ADT than without it (adjusted HR, 2.57; $P=.02$). In that study, the men with a history of MI or CHF constituted only 9% of the total cohort of men being treated with radiation. Because we were not able to stratify our analysis by underlying cardiac comorbidity, it remains possible that the subgroup of men with prostate cancer and a history of CHF or MI could experience excess cardiovascular mortality due to ADT, and for these men it would seem prudent to continue to be mindful of possible metabolic and cardiovascular sequelae when using ADT. It should also be noted that participants in the phase 3 trials may have had fewer comorbidities than the general age-matched population and could have been less susceptible to any adverse effects of ADT. For example, in the RTOG 85-31 trial,[8] the median age was 70 years but only 33% had hypertension and only 9% had diabetes. In contrast, the National Health and Nutrition Examination Survey study[31] has shown that the prevalence of hypertension in average men older than 60 years is 60% to 70% and the Centers for Disease Control and Prevention estimates 27% of US men older than 65 years have diabetes.[31] To answer the question definitively for men with high-risk cardiac features, we recommend that future randomized trials testing the value of ADT stratify by comorbidity/cardiac history. One example of such a trial is the RTOG 08-15 trial, which compares high-dose radiation with or without short-course ADT in men with intermediate-risk disease and stratifies by Adult Comorbidity Evaluation 27 score.

A second issue is that although our study assessed total cardiovascular deaths, it could not exclude the possibility that cardiovascular deaths happen earlier in men receiving ADT. As mentioned, the postrandomization analysis by D'Amico et al combining the DFCI 95-096[3] and TROG 96.01[16] data suggested that for men older than 65 years, the cumulative incidence of fatal MI by year 8 was the same for those receiving ADT vs no ADT, but the time to fatal MI was significantly shorter for those men who received ADT.[3] Also, the retrospective study that established patients with CHF and MI as a vulnerable subgroup found that the excess deaths with ADT seemed to happen in only the first 6 to 24 months after ADT.[32] Because our study is based on trials with approximately a 10-year median follow-up, a theoretical effect in which ADT caused an earlier timing of cardiovascular deaths could have been missed by the time events were totaled at year 10. An additional consideration is that cause of death was generally determined by the treating physician or trial investigator, and only 1 trial (EORTC 30891[15]) required adjudication of cause of death by 2 independent central reviewers, so it is possible that some cardiovascular deaths were underreported or misclassified.

In addition, although we could not detect excess cardiovascular mortality due to ADT, our study does not exonerate ADT from the metabolic sequelae, which it has been demonstrated to cause in men in prospective series. For example, in a prospective study of men without diabetes,[33] ADT significantly increased fasting plasma insulin by 26% and decreased insulin sensitivity by 13% after only 12 weeks of therapy.

Our findings are discordant with the studies of Keating et al[1] and Tsai et al,[2] 2 of the first to raise concern about excess cardiovascular deaths due to ADT. Since those studies were both retrospective, it is possible that subtle imbalances in the underlying health status of men being selected for ADT vs no ADT could have contributed to those findings. Such imbalances would be less likely to occur in randomized trials. An alternative explanation for the discrepancy, as mentioned above, may be that the patients in these phase 3 trials could have been healthier and less susceptible to any adverse cardiovascular effects of ADT than the general population.

In conclusion, our meta-analysis of more than 4000 patients could not find any evidence that ADT increases the risk of cardiovascular death among men with unfavorable-risk, nonmetastatic prostate cancer, but did find a significant association between ADT and improved prostate cancer–specific survival and overall survival. For the majority of men considering ADT for aggressive prostate cancer, these results should be reassuring. It remains unknown whether these results are also applicable to the subgroup of men with a prior history of CHF or MI, and therefore stratification of future randomized trials by cardiovascular comorbidity is needed.

Author Affiliations: Department of Radiation Oncology (Dr Nguyen) and Lank Center for Genitourinary Oncology (Drs Schutz and Choueiri), Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; Harvard School of Public Health, Boston, Massachusetts (Ms Je); Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston (Dr Hoffman); Center for Surgery and Public Health and Divisions of Urology (Dr Hu) and Cardiovascular Medicine (Dr Beckman), Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and Boston University School of Medicine, Boston, Massachusetts (Ms Parekh).

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Study concept and design: Nguyen, Hoffman, Choueiri.
Acquisition of data: Nguyen, Parekh, Choueiri.
Analysis and interpretation of data: Nguyen, Je, Schutz, Hoffman, Hu, Parekh, Beckman, Choueiri.
Drafting of the manuscript: Nguyen.
Critical revision of the manuscript for important intellectual content: Nguyen, Je, Schutz, Hoffman, Hu, Parekh, Beckman, Choueiri.
Statistical analysis: Je.
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