

## Single-Therapy Androgen Suppression in Men with Advanced Prostate Cancer: A Systematic Review and Meta-Analysis

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**Purpose:** To compare luteinizing hormone–releasing hormone (LHRH) agonists with orchiectomy or diethylstilbestrol, and to compare antiandrogens with any of these three alternatives.

**Data Sources:** A search of the MEDLINE, Cancerlit, EMBASE, and Cochrane Library databases from 1966 to March 1998 and Current Contents to 24 August 1998 for articles comparing the outcomes of the specified treatments. The search was limited to studies on prostatic neoplasms in humans. Total yield was 1477 studies.

**Study Selection:** Reports of efficacy outcomes were limited to randomized, controlled trials. Twenty-four trials involving more than 6600 patients, phase II studies that reported on withdrawals from therapy (the most reliable indicator of adverse effects), and all studies reporting on quality of life were abstracted.

**Data Extraction:** Two independent reviewers abstracted each article by following a prospectively designed protocol. The meta-analysis combined data on 2-year overall survival by using a random-effects model and reported results as a hazard ratio relative to orchiectomy.

**Data Synthesis:** Ten trials of LHRH agonists involving 1908 patients reported no significant difference in overall survival. The hazard ratio showed LHRH agonists to be essentially equivalent to orchiectomy (hazard ratio, 1.262 [95% CI, 0.915 to 1.386]). There was no evidence of difference in overall survival among the LHRH agonists, although CIs were wider for leuprolide (hazard ratio, 1.0994 [CI, 0.207 to 5.835]) and buserelin (hazard ratio, 1.1315 [CI, 0.533 to 2.404]) than for goserelin (hazard ratio, 1.1172 [CI, 0.898 to 1.390]). Evidence from 8 trials involving 2717 patients suggests that nonsteroidal antiandrogens were associated with lower overall survival. The CI for the hazard ratio approached statistical significance (hazard ratio, 1.2158 [CI, 0.988 to 1.496]). Treatment withdrawals were less frequent with LHRH agonists (0% to 4%) than with nonsteroidal antiandrogens (4% to 10%).

**Conclusions:** Survival after therapy with an LHRH agonist was equivalent to that after orchiectomy. No evidence shows a difference in effectiveness among the LHRH agonists. Survival rates may be somewhat lower if a nonsteroidal antiandrogen is used as monotherapy.

Androgen ablation delays clinical progression and palliates symptoms of metastatic disease in men with advanced prostate cancer (1–4). The earliest method was orchiectomy, and diethylstilbestrol (DES) subsequently became the first reversible method (5–7). Newer alternatives include luteinizing hormone–releasing hormone (LHRH) agonists, such as leuprolide, goserelin, and buserelin (8–10), and nonsteroidal antiandrogens, such as flutamide, nilutamide, and bicalutamide (11–13). Cyproterone acetate is the only steroidal antiandrogen still used for primary hormonal therapy (14–16).

Many randomized, controlled trials have compared two or more of these options for monotherapy in men with advanced prostate cancer. Additional trials have tested the efficacy of antiandrogens combined with orchiectomy or LHRH agonists, an approach that is often called combined or maximal androgen blockade. Previous meta-analyses have compared monotherapy with combined androgen blockade (17–19). To date, no systematic review or meta-analysis has evaluated the evidence on effectiveness of monotherapies.

Systematic reviews offer structured analysis of results of primary investigations by using strategies to limit bias and random error. They efficiently integrate otherwise unmanageable amounts of information to support clinical decision making. When it is feasible, quantitative meta-analysis can increase power and precision and enhance estimates of treatment effects and exposure risks. Meta-analysis also allows evaluation of consistency of findings or exploration of differences in outcomes, according to predefined subpopulations or factors regarding study quality.

As part of a comprehensive review of the evidence on the relative effectiveness and cost-effectiveness of methods of androgen suppression as primary treatment for advanced prostate cancer (20), we conducted a systematic review and meta-analysis

*Ann Intern Med.* 2000;132:566-577.

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See editorial comment on pp 584-585.

**Table 1. Distribution of Trials and Patients by Agent\***

Agent	Systematic Review				Meta-Analysis	
	Control			Trials	Patients	
		Trials	Patients			
		←————— n —————→				
DES	Orchiectomy	3	1302	8	993	
LHRH agonists						
Leuprolide	DES	1	199	1	94	
Goserelin	Orchiectomy or DES	5	1188	7	1137	
Buserelin	Orchiectomy or DES	4	521	4	308	
All LHRH agonists		10	1908	12	1539	
Antiandrogens						
Nonsteroidal						
Flutamide	Orchiectomy or DES	3	236	1	44	
Bicalutamide	Orchiectomy or DES	5	2481	5	1452	
All nonsteroidal agents		8	2717	6	1496	
Steroidal						
Cyproterone	Orchiectomy or DES or LHRH agonist	5	1123	2	93	
All antiandrogens	—	13	3840	—	—	

\* Numbers of trials and patients in the systematic review and meta-analysis differ. The systematic review includes numbers from both control and treatment arms only when a particular agent was used in the treatment arm. The meta-analysis reflects the number of patients who received a particular agent, whether in the control or treatment arm. The meta-analysis excludes studies from the systematic review that did not report overall survival data. DES = diethylstilbestrol; LHRH = luteinizing hormone-releasing hormone.

of randomized, controlled trials that compared different monotherapies.

We establish that DES is equivalent to orchiectomy as a comparator for treatments of advanced prostate cancer and summarize our findings on four questions: 1) How effective is an LHRH agonist compared with orchiectomy or DES? 2) How effective is an antiandrogen compared with orchiectomy, DES, or an LHRH agonist? 3) Do the LHRH agonists differ in effectiveness? and 4) Do the antiandrogens differ in effectiveness? Although we sought to compare the adverse effects and quality-of-life effects of these treatments, scant evidence was available.

## Methods

Our review was prospectively designed to define study objectives, search strategy, study selection criteria and methods for determining study eligibility, data elements to be abstracted and methods for abstraction, and methods for assessment of study quality. Two independent reviewers completed each step in this protocol and resolved disagreements by consensus. Disagreements were infrequent and were usually resolved by reconciliation of an oversight. When survival rates were estimated from figures in publications, disagreements were always less than 5% of the measured value, and the consensus estimate was the midpoint.

All efficacy studies were randomized, controlled trials. Reviewers assessed the study quality dimensions that have been shown to be sources of bias (21): adequacy of randomization method, use of blinding and adequacy of concealment of allocation, and documentation of withdrawals and whether

results were analyzed in an intention-to-treat fashion. Except for blinding and intention-to-treat analysis, published reports usually provided insufficient information to permit valid assessments of these quality dimensions. Therefore, studies that blinded patients and investigators to group assignment and used an intention-to-treat analysis of overall survival or progression-related outcomes were classified as higher-quality studies for sensitivity analysis. Blinding was considered not applicable when orchiectomy was one of the study arms.

## Literature Search and Study Selection

We searched the MEDLINE, Cancerlit, EMBASE, and Cochrane Library databases from 1966 to March 1998 and Current Contents through 24 August 1998 for all articles that included at least one of the following terms in their titles, abstracts, or keyword lists: leuprolide (Lupron, TAP Pharmaceuticals Inc., Deerfield, Illinois), goserelin (Zoladex, Zeneca Pharmaceuticals, Wilmington, Delaware), buserelin (Suprefact, Hoechst Marion Roussel, Kansas City, Missouri), flutamide (Eulexin, Schering Corp., Kenilworth, New Jersey), nilutamide (Anandron, Roussel-Uclaf Laboratory, Romainville, France, and Nilandron, Hoechst Marion Roussel), bicalutamide (Casodex, Zeneca Pharmaceuticals, Wilmington, Delaware), cyproterone acetate (Androcur, Schering Corp.), diethylstilbestrol (DES), and orchiectomy (castration or orchidectomy).

Search results were limited to studies on humans indexed under the Medical Subject Heading *prostatic neoplasms*. Randomized, controlled trials were identified by using the search strategy of the United Kingdom Cochrane Center (22). A total of 1477 references were retrieved and checked against the Cochrane Controlled Trials Register, the Cochrane

**Table 2. Overall Survival\***

Study (Reference)	Year	Intervention	Control Group		
			Patients at Risk at Study Entry	Median Overall Survival	Patients Alive at 2 Years
			<i>n</i>	<i>mo</i>	%
Robinson et al. [EORTC Protocol 30805] (45)	1995	Orchiectomy	110	22.9	48
Blackard et al. [Veterans Administration Co-operative Urology Group (VACURG) Trial] (stage III) (5, 37)	1967, 1973	Orchiectomy plus placebo	266	67.0	77
Blackard et al. [VACURG Trial] (stage IV) (5, 37)	1967, 1973	Orchiectomy plus placebo	203	30.0	57
Kaisary et al. [British Prostate Study Group] (50)	1991	Orchiectomy	144	23.9	51
Vogelzang et al., Soloway et al. [Zoladex Prostate Study Group] (53, 54)	1995, 1991	Orchiectomy	145	31.3	63
de Voogt et al., Klijn et al. [EORTC Protocol 30843] (43, 55)	1990, 1993	Orchiectomy	118	25.0	53
Bruun et al. [Danish Buserelin Study Group] (49)	1996	Orchiectomy	46	–	34
Koutsilieris and Tolis [McGill Trial] (34)	1985	Orchiectomy	6	–	50
Seely, Leuprolide Study Group, Garnick (51, 56, 57)	1984, 1986, 1987	DES, 3 mg	99	33.8	64
Waymont et al. [West Midlands Zoladex vs DES Trial] (44)	1992	DES, 3 mg	126	27.7	57
Citrin et al. [American Multicenter Trial] (55)	1991	DES, 3 mg	19	–	68
Huben and Murphy, Klioze et al. [National Prostate Cancer Project Protocol 1700/1700B] (41, 58)	1988	Orchiectomy or DES, 3 mg	55	–	78
Boccon-Gibod et al. [French multicenter trial] (40)	1997	Orchiectomy	50	–	–
Iversen et al., Bales and Chodak [Scandinavian Casodex Cooperative Group Study 0301] (47, 59)	1996	Orchiectomy	190	26.8	57
Ostri et al. [Copenhagen Cyproterone Trial] (39)	1991	Orchiectomy	19	15.0	34
Lund and Rasmussen [Copenhagen Flutamide Trial] (33)	1988	DES, 3 mg	20	–	–
Chang et al. [Eastern Cooperative Oncology Group Trial] (35)	1996	DES, 3 mg	48	43.2	81
Pavone-Macaluso et al., de Voogt [EORTC Protocol 30761] (38, 48)	1986, 1990	DES, 3 mg	63 33 (stage D2)	40.0 35.0	64 58
Kaisary et al., Bales and Chodak [Casodex Study Group Trial 0302] (46, 59)	1995, 1996	Orchiectomy or goserelin, 3.6 mg for 28 days	154	24.3	54
Iversen, Tyrrell et al. [International Casodex Studies 0306/0307] (stage M1) (36, 60)	1994, 1998	Orchiectomy or goserelin, 3.6 mg for 28 days	268	25.6	59
Chodak et al., Bales and Chodak [Casodex Study 0303] (United States and Canada) (42, 59)	1995, 1996	Orchiectomy or goserelin, 3.6 mg for 28 days	257	–	15
Iversen et al. [International Casodex Studies 0306/0307] (stage M0) (29)	1998	Orchiectomy or goserelin, 3.6 mg for 28 days	160	–	81

\* DES = diethylstilbestrol; EORTC = European Organization for Research and Treatment of Cancer.  
† Included only if reported in the referenced article.

Collaboration CENTRAL register, and trials cited in two recent meta-analyses. No additional trials were identified.

Our study selection criteria limited reports of efficacy outcomes to randomized, controlled trials that compared 1) monotherapy with an LHRH agonist and monotherapy with orchiectomy or DES or 2) monotherapy with an antiandrogen and monotherapy with orchiectomy, DES, or an LHRH agonist. To facilitate comparison of results across trials that used different controls, studies that directly compared orchiectomy with DES were also included. Randomized, controlled trials that compared only different doses of the same agent were excluded. For adverse events, phase II studies that reported withdrawals from therapy were included. All studies reporting on quality of life were included.

The patient population of interest was men with advanced prostate cancer, including regional or disseminated metastases (stage D1 or D2 disease [any T, N1 to N3, M0 or any T, any N, M1]) and minimally advanced disease (stage C disease [T3 or

T4, N0 or NX, M0]). We also looked for outcomes that were analyzed by such patient prognostic factors as tumor grade, extent of disease, and performance status. Outcomes of interest were overall cancer-specific and progression-free survival, time to treatment failure, adverse effects, and quality of life. Where available, data on patient preferences were included.

### Adverse Events

We encountered well-described difficulties (23, 24) in capturing infrequent events from small trials and inconsistencies among trials in measuring and reporting adverse events. Summarized here is the most reliable index of serious adverse events: the rate of withdrawal from therapy. A summary of adverse events by category (for example, cardiovascular, endocrine) is included in the full evidence report (20).

### Meta-Analysis

We used the general approach to meta-analysis of trials in prostate cancer described by Caubet and

**Table 2—Continued**

Intervention	Treatment Group			Hazard Ratio (95% CI)	Reported Hazard Ratio (95% CI)†	Reported P Value†
	Patients at Risk at Study Entry	Median Overall Survival	Patients Alive at 2 Years			
	<i>n</i>	<i>mo</i>	%			
DES, 1 mg	107	25.1	55	0.815 (0.552–1.205)	–	0.751
DES, 5 mg	265	60.0	73	1.204 (0.855–1.696)	–	
DES, 5 mg	211	33.0	59	0.889 (0.658–1.202)	–	0.33
Goserelin, 0.25 mg/d, 3.6 mg every 28 days	148	26.4	55	0.888 (0.632–1.248)	–	
Goserelin, 3.6 mg every 28 days	138	27.4	59	1.142 (0.783–1.665)	1.12 (0.85–1.49)	0.42
Buserelin plus short-term cyproterone, 150 mg	113	25.0	53	1.030 (0.703–1.509)	–	0.4
Buserelin, 1.5 mg subcutaneously for 7 days, then 1.2 mg intranasally	72	–	27	1.207 (0.752–1.938)	–	
Buserelin, 0.05 mg subcutaneously, 1.5 mg subcutaneously, 1.0 mg intranasally	13	–	46	–	–	0.58
Leuprolide, 1 mg subcutaneously	94	31.3	61	1.108 (0.696–1.763)	–	
Goserelin, 3.6 mg every 28 days	124	27.4	57	1.000 (0.634–1.462)	–	0.88
Goserelin, 3.6 mg every 28 days	48	–	63	1.198 (0.474–3.028)	1.27 (0.47–3.43)	0.6
Buserelin, 1.5 mg for 7 days, then 0.2 mg subcutaneously and 1.2 mg intranasally	110	–	73	1.339 (0.685–2.619)	–	0.0007
Flutamide, 750 mg	54	–	–	–	–	
Bicalutamide, 50 mg	186	18.5	43	1.505 (1.121–2.021)	1.76 (1.27–2.44)	
Cyproterone, 100 mg	18	9.0	17	1.643 (0.725–3.722)	–	0.009
Flutamide, 750 mg	20	–	–	–	–	
Flutamide, 750 mg	44	28.5	66	1.972 (0.863–4.506)	–	
Cyproterone, 250 mg	75	38.0	65	0.965 (0.548–1.701)	–	0.52
	44	23.0	48	1.347 (0.684–2.655)	–	0.47
	(stage D2)					
Bicalutamide, 50 mg	150	24.6	52	1.061 (0.760–1.482)	1.34 (0.94–1.95)	
Bicalutamide, 150 mg	537	24.2	53	1.203 (1.004–1.442)	1.30 (1.04–1.64)	0.02
Bicalutamide, 50 mg	259		17	0.923 (0.744–1.145)	1.29 (0.96–1.72)	0.09
Bicalutamide, 150 mg	320	53.4	88	0.607 (0.376–0.977)	0.93 (0.66–1.31)	0.67

colleagues (17), with additional guidance from Whitehead and Whitehead (25). To combine evidence from studies with several different treatment arms, it was necessary to go beyond standard meta-analysis techniques (26). The solution to the problem entails defining variables that describe the possible interventions. The poor survival rates for metastatic prostate cancer have implied a large value for the hazard rate (rate of death across time). We made the same assumption that is used in standard meta-analysis—that is, we assumed that the effect measure (hazard ratio in this case) remains constant across studies. Because several different treatments are now available, we assumed that all of the hazard ratios among the various treatments remain constant. The model is a generalization of the random-effects model described by DerSimonian and Laird (27). It is essentially the same model used by EGRET (28), except that it is applied to continuous outcomes instead of dichotomous outcomes. The model is a generalization that includes both fixed-effects and random-effects terms.

The fixed-effects terms are the individual study intercepts. The random-effects terms are the slopes for the treatment effects. Estimates of all variables, including the extra variation, are obtained by maximum likelihood.

On the basis of the preceding assumptions, our objective was to estimate the hazard rate for each arm of each study or to estimate the proportional hazards term and its standard error. We obtained estimates from other statistics for studies that did not provide this information directly. Caubet and colleagues (17) suggested a technique for estimating the log-hazard ratio  $\beta$  from the chi-square value of the log-rank test. Where Kaplan–Meier curves were given, it was usually possible to estimate individual hazards, as described in the comprehensive evidence review (20). To use this meta-analysis method, we constructed a table of hazard rates for each arm of each study. The meta-analysis was done with software developed at the Duke Clinical Research Institute, Durham, North Carolina.

Sensitivity analyses were used to test for hetero-

generality of methods (including the effect of including studies of lower methodologic quality), participants, and interventions. An initial analysis determined whether the results of orchiectomy and DES were comparable and whether it was valid to pool studies in which the control groups used either of these monotherapies. Separate analyses also compared the available monotherapies and categories of monotherapies. All meta-analysis results were reported as hazard ratios relative to orchiectomy.

## Data Synthesis

### Overview of the Evidence Base

The literature search identified 24 controlled trials that, collectively, randomly assigned more than 6600 patients to treatment with different monotherapies for advanced prostate cancer. **Table 1** shows the numbers of patients in trials of each monotherapy agent used in the treatment arm. Thirteen trials were considered higher quality for sensitivity analysis. The earliest trial (5–7), the Veterans Administration Co-operative Urology Research Group (VACURG) study, began in 1960, and the most recent trial (29) began in 1992. During the intervening period, new diagnostic techniques were developed, new staging and grading systems were implemented, and methods of monitoring patients for progression and relapse were improved.

Three trials directly compared DES with orchiectomy in 1302 randomly assigned patients (**Table 1**); all trials used 3 mg of DES per day. These trials were analyzed to establish that DES is equivalent to orchiectomy when used as a comparator in trials of LHRH agonists or antiandrogens; this analysis maximized the evidence base for our review.

Ten randomized trials involving 1908 patients compared an LHRH agonist with orchiectomy, DES, or the choice of orchiectomy or DES. Previous studies comparing doses or dosage forms showed that all regimens used in these trials reduced serum testosterone concentrations to castration levels 1 to 3 weeks after treatment began and maintained those levels during treatment. No studies directly compared two LHRH agonists.

Thirteen randomized trials involving 3840 patients compared an antiandrogen to orchiectomy, DES, an LHRH agonist, or the choice of orchiectomy or an LHRH agonist. Eight of these trials involving 2717 patients investigated a nonsteroidal antiandrogen; 5 trials involving 1123 patients investigated the steroidal antiandrogen cyproterone.

Two studies, each with three monotherapy arms, were counted more than once in the mentioned overview (30–32). However, neither trial reported over-

all survival. In addition, the VACURG trial, which compared orchiectomy with DES, reported most outcomes separately for patients who received a diagnosis of stage III or stage IV disease. To accommodate this, **Table 2** lists the VACURG trial twice.

The vast majority of patients had metastatic disease that was staged as D2 or M1. Within trials, patient and tumor characteristics at study entry were generally well balanced between arms. The prognostic factors evaluated included age (19 studies), tumor grade (12 studies), presence or absence of bone pain (14 studies), and performance status (13 studies). Three small studies were imbalanced regarding patients with poorly differentiated tumors (33) or bone pain at study entry (34, 35). Only 3 trials reported one or more primary outcomes separately by disease stage (5, 29, 36–38). None reported primary outcomes by other prognostic factors.

### Overall Survival

Twenty-one trials reported data on overall survival (**Table 2**). The number of patients at risk at study entry and the percentage alive after 2 years are listed for each treatment arm. Three trials reported only crude survival without an actuarial (Kaplan–Meier or life-table) analysis (33, 34, 39). A fourth trial reported no statistically significant difference between treatment arms by actuarial analysis but did not include survival curves or data (40). Differences in overall survival among studies probably reflect differences in patient samples (for example, patients with stage III disease [5] or patients with stage M1 or D2 disease [41]).

Fourteen trials reported median survival, ranging from a low of 9 months for 18 patients with symptomatic metastases treated with cyproterone (39) to a high of 67 months for 266 VACURG patients with stage III disease who were treated with orchiectomy (5). Most studies primarily included patients with metastatic disease and reported median survivals of 20 to 40 months. Twenty trials reported 2-year survival rates, which ranged from 15% of 257 patients given a choice of orchiectomy or goserelin (42) to 88% of 320 patients given bicalutamide (29). In most trials, 2-year survival rates were 50% to 75%.

Only six trials reported 5-year survival rates (data not shown), which ranged from 12% of 118 patients with metastatic disease treated with orchiectomy (43) to 53% of 266 VACURG patients with stage III disease treated with orchiectomy (5). Two additional trials reported 4-year survival rates of 31% and 67% (29, 44).

### Diethylstilbestrol Compared with Orchiectomy

The two trials that compared DES with orchiectomy found no statistically significant difference in

median, 2-year, or 5-year survival rates (5, 37, 45). One trial also reported no difference in 10-year survival rates (5, 37).

#### ***Luteinizing Hormone–Releasing Hormone Agonists Compared with Orchiectomy or Diethylstilbestrol***

Of nine trials that compared an LHRH agonist with orchiectomy or DES, none found a statistically significant difference in survival rates.

#### ***Antiandrogens Compared with Orchiectomy, Diethylstilbestrol, or Luteinizing Hormone–Releasing Hormone Agonists***

Eight studies compared nonsteroidal antiandrogen monotherapy with orchiectomy, DES, or the choice of orchiectomy or an LHRH agonist. Three of these studies used flutamide (33–35, 40), and five used bicalutamide (29, 36, 42, 46, 47). In one study on flutamide (35) and two studies on bicalutamide (36, 47), statistically significant longer survival was seen in the control arms. No statistically significant difference was noted in survival between treatment arms in the remaining five trials. Trials that compared cyproterone with orchiectomy or DES found no significant difference in survival between treatment arms (38, 39, 48).

#### **Progression-Free Survival and Time to Progression**

Fifteen of 24 trials reported progression-free survival or time to progression (data not shown). Most trials used the National Prostate Cancer Project criteria for progression, which specify an increase in tumor volume by 25% or more. However, some trials defined progression as an increase by 50% in the size of the lesions or in the prostate volume. Only 1 of the 15 trials used increasing prostate-specific antigen levels to indicate disease progression (40).

Two of the 15 trials reported actuarial analyses of progression-free survival (41, 45); 2 trials reported the crude progression-free rate with no actuarial analysis (33, 49); and 11 trials reported time to disease progression. However, 5 of these 11 trials considered death to indicate progression when death due to prostate cancer was not ruled out; the other 6 trials did not. Therefore, it was not possible to perform a combined analysis of data from the 11 studies that reported time to progression.

With few exceptions, the median time to progression or progression-free survival ranged from approximately 12 to 24 months. In most studies reporting these outcomes, just under 30% to approximately 55% of patients remained free of progression 2 years after study enrollment.

#### ***Luteinizing Hormone–Releasing Hormone Agonists Compared with Orchiectomy or Diethylstilbestrol***

No significant differences in progression-related outcomes were found in four of five trials that compared an LHRH agonist with orchiectomy or DES. One trial (41) favored the control arm ( $P < 0.05$ ).

#### ***Antiandrogens Compared with Orchiectomy, Diethylstilbestrol, or Luteinizing Hormone–Releasing Hormone Agonists***

Trials that compared an antiandrogen with DES, orchiectomy, or an LHRH agonist generally found no difference between treatment arms or found a modest benefit in favor of the control arm. However, two identical trials comparing bicalutamide with surgical or chemical castration had conflicting results (29). One trial significantly favored bicalutamide, and the other significantly favored the control arm.

#### **Time to Treatment Failure**

Eleven trials reported data on time to treatment failure (data not shown). All of the trials had considered death from any cause, withdrawal due to adverse events or patient decision, and disease progression to constitute treatment failure; therefore, definitions of treatment failure were similar. As noted, most trials used the National Prostate Cancer Project definition of disease progression.

Median time to treatment failure ranged from 6 months in one study (50) to 26 months in another (36). Twenty-four percent of patients (46) to 55% of patients (35) remained free of treatment failure at 2 years.

#### ***Luteinizing Hormone–Releasing Hormone Agonists Compared with Orchiectomy or Diethylstilbestrol***

There were no significant differences in time to treatment failure in trials that compared an LHRH agonist with orchiectomy or DES.

**Table 3. Therapies That Produced Adverse Events Leading to Withdrawal from Therapy**

Treatment	Studies	Patients	Withdrawals
	<i>n</i>	<i>n</i>	<i>n</i> (%)
Diethylstilbestrol, 1 mg/d	1	98	14 (14.3)
Diethylstilbestrol, 3 mg/d	5	284	53 (18.7)
Leuprolide, 1 mg/d	1	268	0 (0.0)
Goserelin, 3.6 mg/mo	11	1679	33 (2.0)
Goserelin, 10.8 mg quarterly	2	77	1 (1.3)
Buserelin, 0.4 mg/d	1	72	3 (4.2)
Flutamide, 750 mg/d	2	92	9 (9.8)
Bicalutamide, 50 mg/d	3	628	25 (4.0)
Nilutamide, 300 mg/d	1	44	3 (6.8)
Cyproterone, 250 mg/d	1	82	1 (1.2)
Cyproterone, 300 mg/d	2	405	17 (4.2)

**Table 4. Data Extraction Elements**

Category	Data Element	
Article identifiers	Article identification number	
	Reference	
	Institution	
	Published language	
	Number of arms	
	Trial name	
Methods	Study group name	
	Related articles	
	Control and treatment interventions, dose, duration	
	Concurrent treatments	
	Randomization method (adequate, inadequate, unclear)	
	Concealment of allocation (adequate, inadequate, unclear)	
	Double-blinding (mentioned, not applicable, unclear)	
	Inclusion/exclusion criteria	
	Power analysis (details)	
	Enrollment period dates	
	Number enrolled	
	Number enrolled but not randomly assigned (reasons)	
	Number randomly assigned but not completed (reasons)	
	Number completed	
	Number analyzed	
	Documentation of withdrawals (full, partial, undocumented)	
	Intention-to-treat analysis (yes, no, unclear)	
Patient characteristics*	Compliance (mentioned, analyzed)	
	Age (mean, median, range, SD, distribution)	
	Duration of disease (mean, median, range, SD, distribution)	
	Ethnic group (distribution)	
	Country of origin (distribution)	
	Stage (distribution)	
	Performance status (distribution)	
	Biopsy method/histologic grading system/grade (distribution)	
	Prostate-specific antigen (mean, median, range, SD, distribution)	
	Symptomatic (distribution)	
	Previous therapy (type, distribution)	
	Treatment for relapse (distribution)	
	Other reported patient characteristics (specified)	
	Survival outcomes*	Duration of follow-up (mean, median, range, SD, distribution)
		Overall survival (actuarial/other, number at risk at different intervals, median, 1-year, 2-year, 5-year, 10-year)
		Cancer-specific survival (actuarial/other, number at risk at different intervals, median, 1-year, 2-year, 5-year, 10-year)
		Progression-free survival (actuarial/other, number at risk at different intervals, median, 1-year, 2-year, 5-year, 10-year)
Hormone-dependent survival (actuarial/other, number at risk at different intervals, median, 1-year, 2-year, 5-year, 10-year)		
Time to treatment failure (actuarial/other, number at risk at different intervals, median, 1-year, 2-year, 5-year, 10-year)		
Adverse events*		Post-treatment performance status
	Nonspecified pain	
	Bone pain	
	Breast pain	
	Other pain	
	Symptom flare	
	Fracture	
	Spinal cord compression	
	Fatigue	
	Nonspecified cardiovascular	
	Deep venous thrombosis	
	Phlebitis	
	Embolic events	
Myocardial infarction		

Continued

**Table 4—Continued**

Category	Data Element
Other data elements	Stroke
	Other cardiovascular
	Hot flashes
	Gynecomastia
	Hair loss
	Vocal change
	Impotence
	Urologic
	Nonspecified pulmonary
	Dyspnea
	Pneumonitis
	Other pulmonary
	Anemia
	Nonspecified gastrointestinal
	Nausea
	Vomiting
	Diarrhea
	Constipation
	Other gastrointestinal
	Nonspecified neurologic
	Vertigo
Other neurologic	
Hepatic (specified)	
Renal (specified)	
Ophthalmologic (specified)	
Psychiatric (specified)	
Other (specified)	
Quality-of-life evaluation method, results	
Satisfaction/preference evaluation method, results	
Cost	
Subgroup analyses	

\* Type of statistical test and test results that were reported for any patient characteristic and outcome were recorded.

### ***Antiandrogens Compared with Orchiectomy, Diethylstilbestrol, or Luteinizing Hormone–Releasing Hormone Agonists***

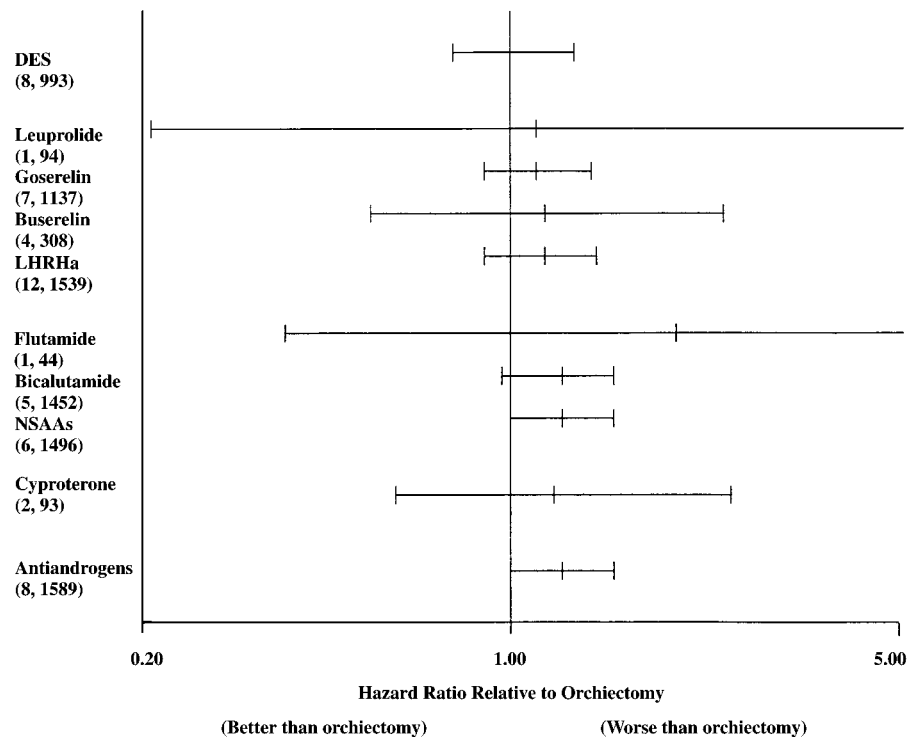
Most trials that compared an antiandrogen with DES or orchiectomy favored the control arm or found no significant difference. As noted, conflicting results were reported from two identical trials comparing bicalutamide with the choice of orchiectomy or buserelin (29).

### **Adverse Events Leading to Withdrawal of Therapy**

Orchiectomy is an irreversible procedure and is not included in our analysis. The data pooled from all available studies are shown in **Table 3**. Withdrawals occurred less often among patients treated with an LHRH agonist (0% to 4%) than among patients treated with nonsteroidal antiandrogens (4% to 10%). Among the antiandrogens, the rate of withdrawal from therapy due to adverse events was highest for flutamide (9.8%), primarily because of gastrointestinal intolerance.

### **Quality of Life**

The validity and reliability of the Health Related Quality of Life Scale was established in patients with advanced prostate cancer (61). Using this scale, two randomized trials comparing patients who re-



**Figure 1. Meta-analysis of survival at 2 years.** Point estimates for hazard ratios (*center marks*) and 95% CIs (*error bars*) relative to orchiectomy for data on survival after 2 years of treatment. Data on each monotherapy are pooled for all studies. DES = diethylstilbestrol; LHRHa = luteinizing hormone–releasing hormone agonist; NSAA = nonsteroidal antiandrogen. Numbers in parentheses are pooled numbers of studies and patients, respectively.

ceived bicalutamide with controls who were offered a choice of surgical or chemical castration (29, 42) reported that patients in the bicalutamide groups showed greater improvements from pretreatment measurements of sexual interest and physical capacity ( $P < 0.01$ ). Other randomized trials used disease symptoms or adverse events as proxies but did not use a quality-of-life instrument.

Among nonrandomized studies comparing types of monotherapy, one used a different instrument, the Functional Living Index: Cancer scale, to measure quality of life in 115 men who chose goserelin therapy and 32 men who chose orchiectomy (62). Scores improved from baseline at 3 and 6 months in the goserelin group ( $P < 0.001$ ) but did not change in the orchiectomy group. Another study of 173 patients found that those who had orchiectomy tended to have better scores on quality-of-life scales than those who received LHRH agonists (63). These data must be interpreted cautiously, however, because the studies were nonrandomized and the factors that influenced choice of therapy may have biased the results.

Although not strictly a measure of quality of life, patients' choice between treatments may provide useful information. Two studies on bicalutamide in which the control group chose orchiectomy or therapy with an LHRH agonist reported the number of patients who chose each option (29, 46). Of 285 patients offered this choice, 87 (31%) chose orchi-

ectomy. However, no direct evidence compared quality of life in patients treated with orchiectomy and those treated with an LHRH agonist. Therefore, it is unknown whether patient perceptions regarding this choice are borne out by the realities of life after treatment.

### Meta-Analysis

The meta-analysis included data from 18 of 21 studies (Table 2) that compared overall survival for two or more monotherapies. The number of patients pooled for each monotherapy agent (Table 1) reflects those who received a particular agent regardless of whether they received it in the control or treatment arm. One study (34) was omitted because it did not report an actuarial analysis of survival and included only six patients in the control group. Another trial (33) was omitted because it reported no mortality in one arm of the study and because no hazard ratio could be calculated. A third trial (40) was omitted because no survival data were provided, although it reported no significant difference between arms at a median follow-up of 69 months. Two studies included in the meta-analysis (5, 37, 38) had separate entries for patient subgroups: patients with stage III and stage IV disease in the VACURG study and patients with stage C and stage D disease in the other study.

Figure 1 presents the combined estimates for each monotherapy relative to orchiectomy. Results

are reported separately for each LHRH agonist and antiandrogen. **Figure 1** also provides combined estimates by drug class for all LHRH agonists, nonsteroidal antiandrogens, and all antiandrogens. A hazard ratio of 1.0 indicates that patients treated with the therapy of interest and patients treated with orchiectomy had an equal chance of death from any cause within 2 years of treatment.

These results suggest that no treatment is better than orchiectomy and that some treatments seem to be less effective. The CIs for individual agents tend to be large (**Figure 1**), but estimates for drug classes are much smaller. The results suggest that DES and LHRH agonists as a class are essentially equivalent to orchiectomy and that patients treated with nonsteroidal and steroidal antiandrogens seem to have lower survival rates.

The combined analysis by class of intervention assumed that the various grouped treatments were actually equivalent. To formally test that hypothesis, we calculated the likelihood ratio chi-square value with four degrees of freedom and found it to be 1.268 ( $P > 0.2$ ), indicating that the treatments did not differ.

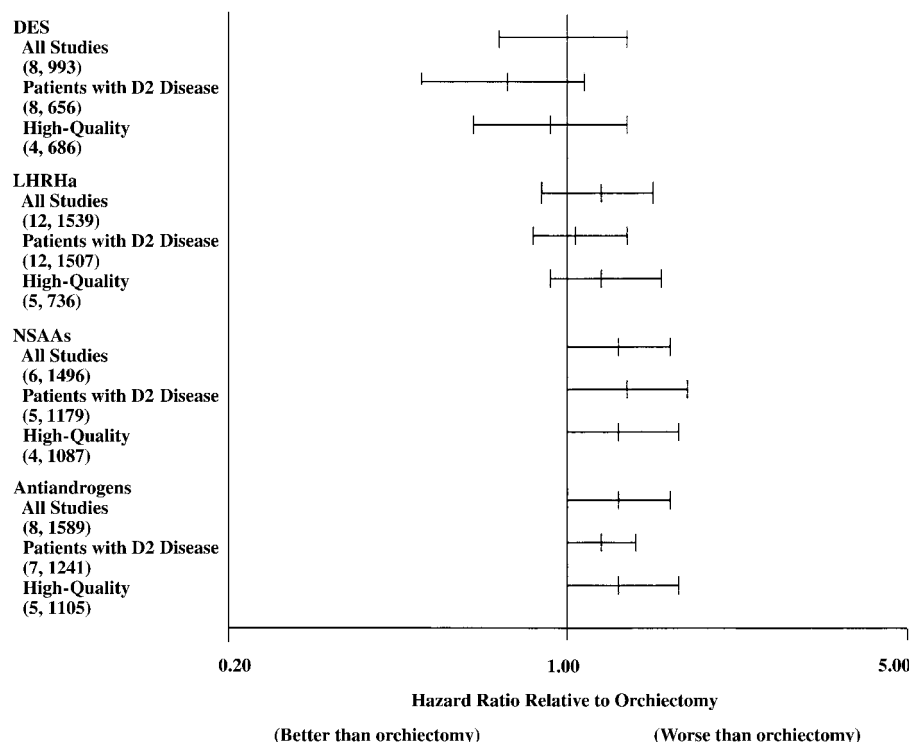
This analysis was repeated for studies that included only patients with stage D2 or M1 disease to test for heterogeneity of study participants. **Figure 2** shows the results of this sensitivity analysis, which

eliminated six comparisons of monotherapies from four studies (5, 29, 37, 38, 44). For one of these studies, only the data for patients with stage C disease were eliminated (38). The results were almost identical to those from analysis of all disease stages, and survival rates were similar among the various treatments except that the confidence bands were slightly wider.

**Figure 2** also shows the results of the sensitivity analysis for studies that were determined to be of higher quality on the basis of whether the trial was double-blinded, except when orchiectomy was an intervention, and whether an intention-to-treat analysis was performed. These criteria eliminated six trials (38, 39, 44, 49, 51, 52). Again, the results are almost identical to those obtained in the analysis of all studies except for slightly wider confidence bands.

## Conclusions

No statistically significant difference in survival was found for patients treated with LHRH agonists compared with patients treated with orchiectomy or DES. Ten trials involving 1908 patients reported overall survival at 2 years, 5 years, or the median. None reported a statistically significant difference between treatments. The meta-analysis found that the 2-year survival hazard ratio with LHRH agonists



**Figure 2. Sensitivity analyses for drug categories.** Point estimates for hazard ratios (*center marks*) and 95% CIs (*error bars*) relative to orchiectomy for data on survival after 2 years of treatment. Data on each drug category are pooled for all studies. Also shown are similar pooled analyses limited to studies that excluded patients without extranodal metastases (stage D2 disease) or double-blind studies that reported intention-to-treat analysis (high-quality studies). DES = diethylstilbestrol; LHRHa = luteinizing hormone–releasing hormone agonists; NSAA = nonsteroidal antiandrogen. Numbers in parentheses are pooled numbers of studies and patients, respectively.

is essentially equivalent to that with orchiectomy (hazard ratio, 1.262 [95% CI, 0.915 to 1.386]). Evidence on disease progression was consistent with evidence on survival.

No trials directly compared the three LHRH agonists. Indirect comparison demonstrated no difference in survival among treatments, although CIs were wide for leuprolide and buserelin. When LHRH agonists were compared with orchiectomy, hazard ratios were 1.0994 (CI, 0.207 to 5.835) for leuprolide, 1.1172 (CI, 0.898 to 1.390) for goserelin, and 1.1315 (CI, 0.533 to 2.404) for buserelin.

The evidence suggested that survival rates are lower with nonsteroidal antiandrogens than with orchiectomy, DES, or LHRH agonists. Of eight trials involving 2717 patients, three found a lower survival rate that was statistically significant and none favored nonsteroidal antiandrogen monotherapy. The hazard ratio relative to orchiectomy was 1.2158 (CI, 0.988 to 1.496) for nonsteroidal antiandrogens compared with 0.9835 (CI, 0.764 to 1.267) for DES and 1.1262 (CI, 0.915 to 1.386) for LHRH agonists. The meta-analysis also found a hazard ratio compared with orchiectomy of 1.2005 (CI, 0.592 to 2.433) for the steroidal antiandrogen cyproterone, suggesting that cyproterone is not superior to nonsteroidal antiandrogens.

No trials directly compared different nonsteroidal antiandrogens. The meta-analysis found a hazard ratio compared with orchiectomy of 1.2027 (CI, 0.973 to 1.487) for bicalutamide and 1.9583 (CI, 0.369 to 10.394) for flutamide. The CI for flutamide was wide, and no trials evaluated nilutamide as monotherapy.

Treatment withdrawals, the most reliable indicator of adverse effects, occurred less with LHRH agonists (0% to 4%) than with nonsteroidal antiandrogens (4% to 10%). Although patients prefer to avoid orchiectomy, there was insufficient evidence to compare the effects of the various monotherapies on quality of life.

## Discussion

The results of our systematic review (see **Table 4** for a list of our data extraction elements) and meta-analysis led us to conclude that the available monotherapies are largely interchangeable in clinical practice. Survival in patients who receive LHRH agonist therapy is equivalent to that in patients who undergo orchiectomy. Although patients prefer to avoid orchiectomy, it is unknown whether the procedure actually decreases quality of life. No evidence shows that survival rates differ among LHRH agonists. No LHRH agonist is superior in terms of

adverse effects. Survival rates may be somewhat lower with nonsteroidal antiandrogen monotherapy.

Although our findings confirm what many practitioners already believe, this report is the first systematic review and meta-analysis of monotherapies for advanced prostate cancer and provides evidence for clinical decision making. One limitation of our report is related to the current state of prostate cancer and its treatment. Patients enrolled in existing trials predominantly had stage D2 or M1 disease, but the number of patients presenting with metastatic disease has decreased substantially (64). An important question is whether to initiate androgen suppression in the absence of symptomatic stage D2 or M1 disease or to wait until symptoms occur. Our comprehensive evidence report (20) found little evidence to address this question. Another limitation is related to gaps in the available literature. For example, the LHRH agonists have not been directly compared. In addition, evidence on two of the three agents is limited, but interest in such studies is now low compared with interest in research on more novel therapeutic approaches.

Our findings contrast with current practice patterns and also suggest that costs of androgen suppression therapy could be considerably reduced without compromising outcomes. When monotherapy is used, the most frequent choice is an LHRH agonist. Although the available LHRH agonists differ substantially in cost, the evidence suggests that none is superior.

Although orchiectomy has been portrayed as a traumatizing surgical procedure, it can be performed in an outpatient setting with minimal patient discomfort, and prostheses can create good cosmesis. Orchiectomy has also been criticized as being irreversible, but it is unclear whether intermittent androgen suppression therapy is as effective as continuous therapy. Although patients prefer to avoid orchiectomy, it is unknown whether patient perceptions regarding this choice are borne out by the realities of life after treatment. Empirical evidence is needed to inform shared decision making.

Although DES may be a good alternative to LHRH agonists and is much less expensive, it is currently unavailable commercially in the United States. Interest in its use has decreased because it is known to be cardiotoxic at high doses. An intermediate dose (3 mg/d) seems to be as effective as orchiectomy and may have an acceptable adverse effect profile, especially when it is used in the setting of contemporary cardiac risk management.

Substantial evidence suggests that available monotherapies have similar outcomes, with the possible exception of nonsteroidal and steroidal antiandrogens. Evidence does not demonstrate clinically mean-

ingful differences among monotherapies, especially within each class of agent.

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*Acknowledgment:* The authors thank Maxine Gere, MS, and Kathleen Ziegler, PharmD, for editorial assistance.

*Grant Support:* This work was developed under contract with the Agency for Healthcare Research and Quality (AHRQ contract number 290-97-0015). The Blue Cross and Blue Shield Association Technology Evaluation Center is an Evidence-based Practice Center of the AHRQ.

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