Dutasteride in localised prostate cancer management: the REDEEM randomised, double-blind, placebo-controlled trial

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Introduction

Prostate cancer accounts for about 25% of newly diagnosed cancers every year in men in the USA.[1] Although men's lifetime risk of development of clinical prostate cancer is high (~16–18%), the corresponding risk of death is only about 3%.[2,3] A study[4] of autopsies in men who died after trauma reported histological evidence of prostate cancer in the fourth decade of life, with lesions becoming more widespread in older men. The lengthy natural history of prostate cancer might contribute to overdiagnosis of indolent disease. Patients with small or indolent cancers might receive no benefit from, and could be harmed by, unnecessary treatment of latent disease.[4] Modelling studies based on incidence data from the USA[5] suggest overdiagnosis rates of 29–44% in all cases detected by prostate-specific antigen screening. In another study,[6] the number needed to treat for 10 years to save one life was 48, although this number might become more favourable over time with longer follow-up.

Several studies suggested that localised prostate cancer is often treated too aggressively, despite the low risk of disease-related death.[7] Data from the Surveillance, Epidemiology, and End Results (SEER) system from 2004 to 2006 showed that more than 75% of men with low-risk disease undergo aggressive local therapy.[7] Data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry[8] suggest that more than 90% of men with very low-risk disease are actively treated with radical prostatectomy, radiation therapy, or androgen suppression. However, active surveillance (conservative management or expectant management) for patients diagnosed with low-volume, low-grade prostate cancer, including assessment of cancer progression with regular prostate examination, prostate-specific antigen measurement, and repeat biopsies, can be a more appropriate option for many of these men.[9] A population-based cohort study suggested a 10 year cancer-specific survival of 94% in men aged 65–74 years with conservatively managed stage T1 or T2 cancers at diagnosis.[10] Furthermore, men with 7–10 year follow-up have a cause-specific survival of 97–100% in large cohort studies.[3] Nevertheless, active surveillance is sometimes received with uncertainty by men confronted with treatment decisions for localised disease.[8]

In men with low-risk, localised prostate cancer, treatment with a 5α-reductase inhibitor might decrease disease progression, extend time to development of aggressive disease, and potentially reduce the need for

active therapy. 5α-reductase inhibitors block the conversion of testosterone to dihydrotestosterone, leading to a reduction in prostate volume and a decrease in prostate-specific antigen concentrations.[11] Dutasteride is a 5α-reductase inhibitor that is approved for the treatment of symptomatic benign prostatic hyperplasia and is the only 5α-reductase inhibitor that inhibits both isoforms (type 1 and type 2) of 5α-reductase.[11] Dutasteride reduced serum dihydrotestosterone by at least 90% in men with localised prostate cancer, a significantly greater reduction (p<0·001) than that reported in men who did not receive dutasteride, and results in a reduction in the volume of some prostate cancers.[12] In the 4 year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study,[13] dutasteride treatment resulted in a relative risk reduction of biopsy-detectable prostate cancer of 22·8% (95% CI 15·2–29·8) compared with placebo in men who were at increased risk of developing prostate cancer (restricted crude rate). During the 4 years, 437 (13·2%) of 3299 patients in the dutasteride group developed biopsy-detectable cancer with a Gleason scale score of 5–6 compared with 617 (18·1%) of 3407 controls (p<0·001); by contrast, 220 (6·7%) dutasteride-treated patients and 233 (6·8%) controls developed cancer scoring 7–10 on the Gleason scale (p=0·81) and 29 treated patients (0·9%) and 19 controls (0·6%) developed cancer scoring 8–10 on the Gleason scale (p=0·15).

In the reduction by dutasteride of clinical progression events in expectant management (REDEEM) trial, we aimed to assess whether treatment with dutasteride decreased the rate of prostate cancer progression (pathological or therapeutic) compared with placebo in men with low-risk, localised disease who would otherwise undergo active surveillance.

Methods

Study design and participants

The design of our multicentre, randomised, double-blind, placebo-controlled REDEEM trial has been reported elsewhere.[14] Briefly, REDEEM was done at 65 academic medical centres or outpatient clinics in North America (USA and Canada) and was designed to assess the efficacy and safety of dutasteride for extension of time to prostate cancer progression (pathological or therapeutic). Men aged 48–82 years old were eligible for inclusion if they had clinically diagnosed (within 14 months before screening) low-risk, prostate cancer (T1c–T2a) and a Gleason score of 6 or less (no Gleason pattern score of ≥4), serum prostate-specific antigen of 11 ng/mL or less, life expectancy of more than 5 years, and had been followed up with active surveillance. The last diagnostic biopsy sample taken for study eligibility had to have been within 8 months of screening. A minimum of ten cores were needed for entry biopsies (with fewer than four cores positive and <50% of any one core involved with cancer); the study pathologist (MSL) confirmed the diagnosis and pathological characteristics of the baseline biopsy. Principal exclusion criteria were previous treatment for prostate cancer with radiotherapy, chemotherapy, or hormonal therapy; use of glucocorticoids (apart from inhaled or topical drugs) within 3 months of screening or gonadotropin-releasing hormone analogues; prostate volume of more than 80 mL; or previous prostatic surgery. Participants with severe benign prostatic hyperplasia symptoms (international prostate symptom score of ≥25 or ≥20 if on α-blocker therapy) were also excluded. Institutional review boards at every site approved the protocol and participants provided written informed consent.

Randomisation and masking

We randomly allocated participants in a one-to-one ratio with GlaxoSmithKline's central registration and medication ordering system (RAMOS) to receive dutasteride 0·5 mg or matching placebo once daily for 3 years. Randomisation was done by site with a block size of four. At every drug refill visit, RAMOS assigned the container number to be dispensed to the patient. The clinical supplies department at GlaxoSmithKline prepared trial drug containers labelled with numbers linked to randomised treatment and ensured matching of stock at individual sites to RAMOS assignment.

GlaxoSmithKline and site personnel, including participants, were masked to treatment allocation until the study was unmasked, when the study conduct had finished and the database was frozen. An interim analysis was done by a statistician who was independent from the study, and results were provided only to an independent data monitoring committee. This committee met face-to-face every 6 months to review safety data associated with the study.

Procedures

Participants attended follow-up visits every 3 months for the first year and every 6 months thereafter. Participants also received a follow-up telephone call 4 months after their last dose of study drug. We measured serum prostate-specific antigen concentrations at screening and subsequent follow-up visits; actual prostate-specific antigen concentrations were reported to the investigator and patients. Digital rectal examinations were done at screening, at 18 months, and at 3 years.

All participants underwent 12-core transrectal ultrasound-guided prostate biopsy sampling at 18 months and 3 years (and at early study withdrawal if applicable). For study-mandated biopsy procedures, a standard of 12 cores was required. For-cause biopsy sampling was undertaken if, in the investigator's opinion, there was a clinically significant medical trigger (such as adverse change on digital rectal examination or increase in prostate-specific antigen). For-cause biopsy samples that were undertaken within 6 months preceding study-mandated biopsies at 18 months and 3 years replaced study-mandated biopsy

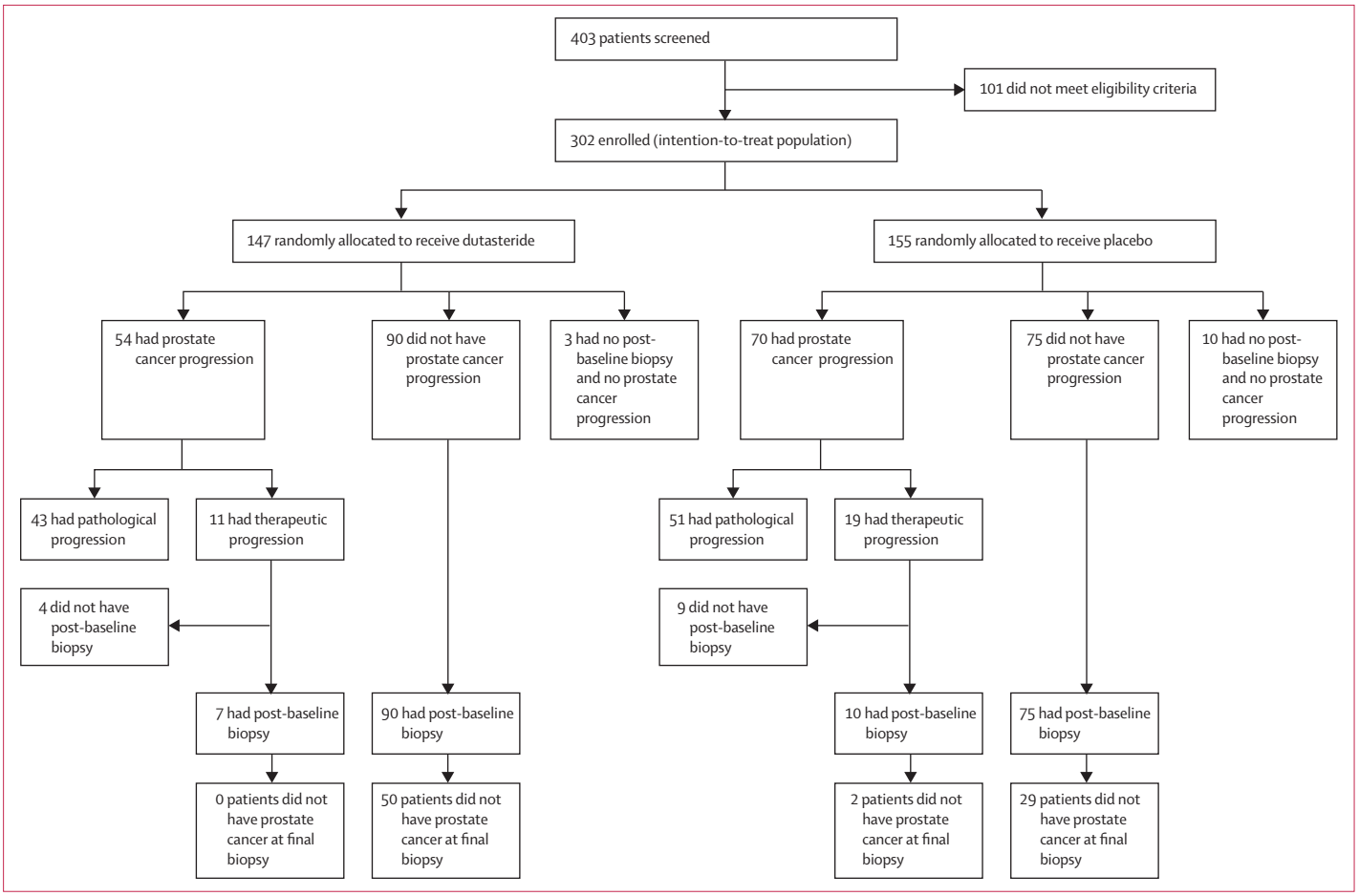


Figure 1: **Study profile**

procedures. One pathologist (MSL), who was masked to study allocation, completed the central pathological review of all histological specimens. The 2005 International Society of Urological Pathologists recommendations for Gleason scoring were used.[15] Biopsy results for the whole study (referred to as final biopsy) are the latest biopsy samples for every patient, irrespective of when that sampling occurred. Follow-up time for study-mandated biopsy sampling (18 months and 3 years) and other study-related assessments (such as digital rectal examination and measurement of prostate-specific antigen) were specified within the study protocol after consultation with a panel of clinicians who use active surveillance in their clinical practice.

We assessed anxiety related to prostate cancer and prostate cancer treatment with the memorial anxiety scale for prostate cancer (MAX-PC) questionnaire. MAX-PC is a validated 24-item scale designed to assess three aspects of prostate cancer-related anxiety: general anxiety, fear of recurrence, and anxiety specifically related to prostate-specific antigen testing.[16] High MAX-PC scores suggest high anxiety.

Statistical analysis

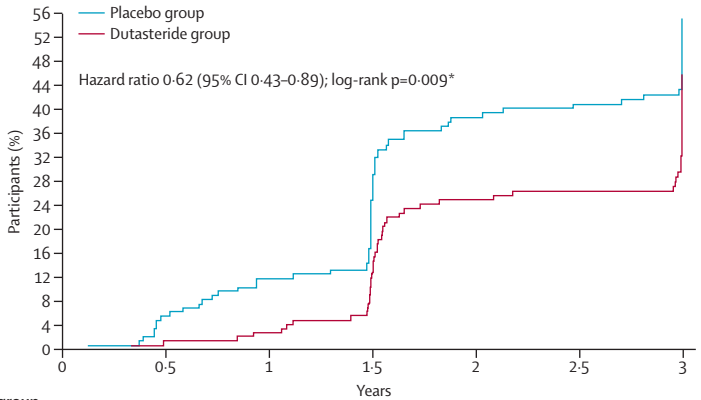
We assumed the rate of progression in the placebo group would be 45% in 3 years, which is consistent with previously reported data after accounting for differences in duration of follow-up.[17] Assuming a crude proportional decrease of 50% in progression rate after treatment with dutasteride compared with placebo (ie, 22·5% progression rate in dutasteride and a 45% progression rate in placebo) which supports a hazard ratio [HR] of 0·535, and that 20% of participants would not contribute to the primary endpoint, about 150 participants would need to be randomly allocated to each treatment group to provide 96% power to show superiority of treatment with 0·5 mg dutasteride compared with placebo at the 0·05 significance level.[14]

The primary endpoint was time to pathological progression (at least one of the predefined criteria: four or more cores involved, ≥50% of any one core involved, or a Gleason pattern score of ≥4) or the institution of definitive medical therapy (referred to as therapeutic progression; eg, prostatectomy, radiation, or hormonal therapy). Secondary endpoints were time to pathological progression, time to therapeutic progression (defined as

	Dutasteride group (n=147)	Placebo group (n=155)
Country		
Canada	84 (57%)	86 (55%)
USA	63 (43%)	69 (45%)
Age, years	65·1 (7·13; 48–80)	65·0 (7·56; 48–81)
Race		
White	132 (90%)	141 (91%)
Non-white	15 (10%)	14 (9%)
Black	8 (5%)	12 (8%)
Body-mass index, kg/m²	28·3 (5·57; 21·3–59·2)	28·9 (4·56; 18·7–46·1)
Family history of prostate cancer	30 (21%)	31 (20%)
Prostate volume, mL	43·2 (15·32; 14·6–79·8)	44·2 (19·17; 13·5–120·1)
Total prostate-specific antigen, ng/mL	5·6 (2·52; 0·4–11·0)	5·8 (2·60; 0·3–10·3)
MAX-PC score	11·3 (8·84; 0·0–45·0)	11·0 (9·28; 0·0–48·0)
Digital rectal examination		
Normal or enlarged	127 (86%)	142 (92%)
Focal abnormality	20 (14%)	13 (8%)
Gleason score		
5	0	1 (1%)
6	147 (100%)	154 (99%)
Median percentage of cancer-positive cores	10·0% (5·3–33·3)	10·0% (4·5–40)
Median maximum percentage of core involved	8·0% (0–48)	8·0% (0–45)
Median tumour length, mm	1·4 (0·2–9·3)	1·3 (0·2–11·0)
International prostate symptom score	7·7 (6·30; 0·0–29·0)	7·8 (5·73; 0·0–24·0)

Data are n (%), mean (SD; range), or median (range). MAX-PC=Memorial Anxiety Scale for Prostate Cancer.

Table 1: **Baseline characteristics of study participants**



Placebo group							
Cumulative events	0	8	17	50	54	57	70
Number at risk	155	145	136	127	86	82	79
Dutasteride group							
Cumulative events	0	2	4	32	35	37	54
Number at risk	147	144	142	140	106	103	100

Figure 2: **Kaplan-Meier estimates of time to progression of prostate cancer**
*Stratified by country; hazard ratio without stratification by country was 0·66 (95% CI 0·46–0·94).

first surgical or non-surgical intervention for prostate cancer), absence of cancer in repeat biopsy, change in Gleason score from baseline, change in biopsy characteristics from baseline (percentage of cancer-positive cores and total length of cancer), and change in MAX-PC score from baseline. We recorded adverse events, serious adverse events, laboratory data (including total prostate-specific antigen), and physical examinations.

We included all randomly allocated participants in the intention-to-treat population. Participants who withdrew or opted for treatment were not unmasked and were followed up to the end of the study whenever possible. If a patient withdrew from drug therapy, subsequent therapeutic intervention was still included in the analysis on the basis of the original treatment assignment. However, if a patient withdrew and had a subsequent biopsy procedure, these results were not included in the analysis because the biopsy sampling was not done according to protocol or assessed centrally to ascertain pathological progression.

We analysed the primary endpoint on the basis of a restricted crude rate approach,[18] which included participants from the intention-to-treat population who had at least one post-baseline biopsy procedure or documented therapeutic progression. Participants who did not receive primary prostate cancer therapy or have pathological progression were censored at the time of last follow-up information. Participants who completed the study or withdrew prematurely and did not have follow-up telephone contact were censored at the date of their last clinic visit; those who prematurely discontinued the study but were followed up by telephone at least once were censored at the date of last telephone contact. We calculated times to events or censoring from treatment start date. We compared time to prostate cancer progression (pathological or therapeutic) between treatment groups with the log-rank test, stratified by investigative site cluster (defined as the two countries, USA and Canada, in the study). As a supportive analysis, we used a Cox proportional hazards model, stratified by investigative site cluster, with treatment as the only covariate to provide hazard ratio estimates. We used hazard ratios to estimate relative risk. We provide the percentage of participants with prostate cancer progression (pathological or therapeutic) in each treatment group with 95% CI estimates. Time to therapeutic progression and time to pathological progression were analysed in much the same way.

We also did a supportive analysis on the basis of the crude proportion, which included all participants in the intention-to-treat population. In this crude approach, participants in whom the primary endpoint was not assessable (ie, those without post-baseline biopsy or no documented therapeutic progression) were assumed to have an outcome of no progression and were censored on the day of treatment start.

We compared the percentage of participants without prostate cancer on final biopsy and the percentage of participants with a change in clinical stage from baseline between treatment groups with Fisher's exact test. We compared the percentage of cancer-positive cores and total cancer lengths between treatment groups with Wilcoxon's rank sum test. For men without detectable

cancer on biopsy sampling, we regarded the percentage of cancer positive cores and the tumour length as zero.

For MAX-PC analyses, we used the last observation carried forward approach as the primary method of analysis, in which a missing value from a scheduled visit was replaced by the last non-missing value before the particular scheduled visit. We also used an observed-cases approach to ensure robustness of the results. We compared the change in MAX-PC score from baseline at every scheduled post-baseline assessment with a general linear model, which used treatment, investigative site cluster, and baseline MAX-PC score as covariates. We used data from the final assessment to compare changes in MAX-PC scores from baseline between treatment groups. All analyses were done with SAS version 9.0.

This trial is registered with ClinicalTrials.gov, number NCT00363311.

Role of the funding source

The study sponsor (GlaxoSmithKline) had a role in the design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and to the final decision to submit for publication.

Results

Between July 18, 2006, and March 6, 2007, we screened 403 men, of whom 302 were eligible and randomly allocated to treatment groups (figure 1). Mean study drug compliance (assessed by pill count) was 97% in both groups. Baseline characteristics were much the same between treatment groups and were as expected in a population of patients with low-risk prostate cancer (table 1). 140 (95%) of 147 men in the dutasteride group and 136 (88%) of 155 controls had at least one post-baseline biopsy (figure 1). Seven men in the dutasteride group did not undergo biopsy sampling compared with 19 controls.

One patient in the control group had insertion of Foley catheter recorded as a non-surgical prostate cancer intervention. This mistake in the database was detected after unmasking of treatments. The participant did not have pathological progression or any other intervention for prostate cancer. For this report, we regarded this participant as not having either prostate cancer progression or therapeutic progression.

During the 3 year study, dutasteride significantly delayed prostate cancer progression (pathological or therapeutic) compared with placebo (HR 0·62, 95% CI 0·43–0·89; log-rank p=0·009; figure 2). By 3 years, 54 (38%) of 144 men in the dutasteride group had prostate cancer progression (pathological or therapeutic) compared with 70 (48%) of 145 controls. By 18 months, 142 men in dutasteride group and 144 controls had at least one post-baseline biopsy; 32 (23%) in the dutasteride group had progressed compared with 50 (35%) in the control group (HR 0·56, 95% CI 0·36–0·87).

	Dutasteride group (n=147)	Placebo group (n=155)
Participants with progression	54 (37%)	70 (45%)
Participants with no post-baseline biopsy and no therapeutic progression*	3 (2%)	10 (6%)
Total person-time, days†	133 035	117 450
Median person-time days‡	1092 (1–1183)	987 (1–1143)
Crude rate (cases per total person-time)		
Per day	0·000406	0·000596
Per year	0·15	0·22

Data are n (% based on a crude-rate proportion), n, or n (range), unless otherwise stated. *For calculation of person-time these participants were censored (with no progression) at the first day of treatment. †Follow-up time was time from treatment start date to date of progression or censoring. ‡Some participants had 1 day of follow-up because they did not progress or have a post-baseline biopsy assessment and thus were censored at the first day of treatment.

Table 2: **Summary of prostate cancer progression**

	Dutasteride group	Placebo group
Pathological progression		
n	43	51
≥4 cores involved	19 (44%)	38 (75%)
≥50% of any one core involved	21 (49%)	23 (45%)
Gleason primary or secondary score ≥4	19 (44%)	21 (41%)
Therapeutic progression		
n	11	19
Surgical intervention	8 (73%)	11 (58%)
Prostatectomy	8 (73%)	8 (42%)
Other	0	3 (16%)
Non-surgical intervention	3 (27%)	8 (42%)
Drug therapy	1 (9%)	4 (21%)
External beam radiation	2 (18%)	3 (16%)
Other	0	1 (5%)

Data are n (%).

Table 3: **Rates of prostate cancer progression (pathological and therapeutic)**

	Latest biopsy assessment on or before 18 months		Final biopsy assessment*	
	Dutasteride group (n=139)	Placebo group (n=136)	Dutasteride group (n=140)	Placebo group (n=136)
Gleason scores				
No cancer detected	39 (28%)	42 (31%)	50 (36%)	31 (23%)
5	0	1 (1%)	0	0
6	92 (66%)	77 (57%)	71 (51%)	83 (61%)
7–8	8 (6%)	16 (12%)	19 (14%)	22 (16%)
3+4	7 (5%)	10 (7%)	13 (9%)	15 (11%)
4+3	1 (1%)	4 (3%)	4 (3%)	4 (3%)
8	0	2 (1%)	2 (1%)	3 (2%)
Pathological characteristics†				
Mean percentage of cancer-positive cores	13·6% (12·41)	17·0% (17·43)	13·9% (13·51)	19·0% (17·23)
Mean cumulative length of tumours, mm	3·4 (5·76)	4·7 (6·49)	3·9 (5·75)	5·4 (6·83)

Data are n (%) or mean (SD). *Latest biopsy assessment for a participant, irrespective of when that assessment occurred. †Percentage of cancer-positive cores and tumour length were recorded as zero for biopsy assessments that did not detect cancer.

Table 4: **Biopsy assessment characteristics at 18 months and final biopsy**

	Gleason score ≤6*		Gleason score >6	
	Dutasteride group (n=121)	Placebo group (n=114)	Dutasteride group (n=19)	Placebo group (n=22)
Mean percentage of cancer-positive cores	12·2% (13·15)	16·2% (15·62)	25·1% (10·19)	33·7% (18·08)
Mean cumulative length of tumours, mm	3·4 (5·69)	3·9 (4·78)	7·1 (5·17)	13·4 (9·85)

Data are mean (SD). *Biopsy assessments in which cancer was no longer detected were counted in this category; percentage of cancer-positive cores and tumour lengths were recorded as zero.

Table 5: **Pathological characteristics of biopsies by Gleason score at final biopsy assessment**

	Dutasteride group (n=147)	Placebo group (n=155)	p value*
Adverse events	122 (83%)	135 (87%)	0·34
Drug-related event	34 (23%)	24 (15%)	0·11
Event leading to study withdrawal	4 (3%)	6 (4%)	0·75
Any serious event	22 (15%)	23 (15%)	1·0
Any fatal event	0	0	NA
Adverse events related to sexual function (composite terms)†			
Impotence	13 (9%)	14 (9%)	1·00
Altered (decreased) libido	11 (7%)	6 (4%)	0·21
Ejaculation disorders	8 (5%)	2 (1%)	0·06
Breast disorders (composite terms)†			
Breast tenderness	8 (5%)	5 (3%)	0·40
Breast enlargement	5 (3%)	1 (1%)	0·11
Cardiovascular (composite terms)†	8 (5%)	7 (5%)	0·79
Ischaemic coronary artery disorders or atherosclerosis	2 (1%)	4 (3%)	0·69
Ischaemic cerebrovascular events	3 (2%)	1 (1%)	0·36
Peripheral vascular disease	2 (1%)	1 (1%)	0·61
Acute coronary syndrome	1 (1%)	0	0·49
Cardiac failure	0	1 (1%)	1·00
Cardiac arrhythmia	0	0	NA

Data are n (%). NA=not applicable. *Calculated with Fisher's exact test. †Adverse events of special interest; participants could have had more than one such event.

Table 6: **Adverse events**

The crude approach also showed that dutasteride delayed prostate cancer progression (pathological or therapeutic; HR 0·62, 95% CI 0·43–0·89; log-rank p=0·009). The crude proportion of such progression in 3 years was 45% (70 of 155 patients) in the placebo group and 37% (54 of 147 patients) in the dutasteride group. The median follow-up time was 987 days for the placebo group and 1092 days for the dutasteride group (table 2). The absolute crude rate of progression (pathological or therapeutic), which accounts for person-time at risk, was 0·22 cases per person-year of follow-up in the placebo group compared with 0·15 cases per person-year of follow-up in the dutasteride group.

Table 3 shows rates of prostate cancer progression owing to pathological or therapeutic progression. Consistent with the decreased incidence of prostate cancer progression (pathological or therapeutic), men in the dutasteride group had a numerically lower incidence of therapeutic as well as pathological progression. 31 (21%) of 147 patients in the dutasteride group chose to have further treatment for prostate cancer compared with 51 (33%) of 155 controls. Time to pathological progression and time to therapeutic progression did not differ between treatment groups (log-rank p=0·079 for pathological progression and log-rank p=0·074 for therapeutic progression).

At final biopsy sampling, 71 (51%) of 140 participants in the dutasteride group and 83 (61%) of 136 controls did not have a change in Gleason score (table 4). More men in the dutasteride group showed no evidence of cancer compared with the placebo group at final biopsy sampling (p=0·024; table 4). Gleason score 8 cancer was detected in final biopsy in two men in the dutasteride group and three controls. We did not note any cases of Gleason score 9 or 10 cancer. In the final biopsy sampling, the dutasteride group had a lower mean percentage of cancer-positive cores and shorter cumulative length of tumours compared with placebo, but neither outcome reached statistical significance (table 4).

In men with cancer with Gleason scores of more than 6 at the final biopsy sampling (19 men in the dutasteride group, 22 controls), we noted a shorter tumour length and a lower percentage of positive cores in men treated with dutasteride than in controls (table 5).

We included 143 patients from the dutasteride group and 148 controls in the prostate cancer anxiety assessment at 3 years. 47 (33%) of 143 measurements in dutasteride group and 70 (47%) of 148 measurements in the placebo group were carried forward from earlier timepoints. Based on total MAX-PC score, overall prostate cancer anxiety remained almost constant for controls and decreased for patients who received dutasteride throughout the study; the adjusted mean change from baseline to 3 years was –1·5 (standard error 0·65) for dutasteride and 0·5 (0·64) for placebo (p=0·036). Of the three MAX-PC subscales, there were no significant differences in anxiety related to prostate cancer or anxiety related to prostate-specific antigen scores. However, patients in the dutasteride group had significantly lower fear of recurrence, with an adjusted mean change from baseline to 3 years of –0·6 (0·19), compared with 0·0 (0·19) for controls (p=0·017).

Overall incidence of adverse events, serious adverse events, and adverse events leading to study withdrawal was much the same between treatment groups (table 6), and the reported safety profile for dutasteride in this study was consistent with that of other studies.[11,13] No deaths were due to prostate cancer or any other adverse event and there were no instances of metastatic disease. The incidence of cardiovascular adverse events was balanced between the treatment groups. Although the difference was not significant, numerically more participants in the dutasteride group had drug-related adverse events compared with controls (table 6). 35 (24%) men in the dutasteride group and 23 (15%) men in the placebo group

had sexual adverse events or breast disorders (table 6). Ejaculation disorders are a commonly noted adverse event seen with 5α-reductase inhibitors; however the difference between treatment groups in ejaculation disorders was not statistically significant (5% *vs* 1%, p=0·06).

Discussion

We present the first randomised study to investigate the potential benefits of use of a 5α-reductase inhibitor to delay the time to treatment or pathological progression in men undergoing active surveillance for low-risk prostate cancer (panel). Dutasteride delayed the progression of prostate cancer at 18 months and 3 years. Although non-significant differences in favour of dutasteride were noted in the subcategories of therapeutic and pathological progression, we were unable to establish significant differences because of study size constraints. Future studies should include more patients and longer treatment than our study.

In this study, the endpoints used to assess progression and its component parts (ie, therapeutic and pathological progression) act as surrogate markers of prostate cancer progression and might not replicate actual progression of the cancer, which can only be verified through pathological examination of the entire prostate. However, a significantly increased percentage of participants in the dutasteride group had no cancer detected at final biopsy compared with men in the placebo group. The higher percentage of men without cancer in the dutasteride group might be due to dutasteride inhibition of the growth of some tumours compared with placebo, shrinking of tumours (allowing the tumour to be missed on final biopsy), or, less likely, eradication of the cancer in some participants during the course of the study. The trend towards lower indices of cancer volume on biopsy sampling in the dutasteride group (table 4 and table 5) is consistent with these hypotheses.

Results from the REDUCE study[13] and Prostate Cancer Prevention Trial (PCPT)[25] have raised questions about the diagnosis of high-grade tumours in men treated with a 5α-reductase inhibitor.[26,27] Initial results from the 7 year PCPT showed an increased prevalence of Gleason scale score 7–10 prostate cancer in men treated with finasteride compared with placebo, and in the REDUCE study there was an increase in Gleason scale score 8–10 tumours in years 3–4 of the study.[13,26] However, logistic regression analyses accounting for prostate volume and other potential sources of bias in both trials suggested 5α-reductase inhibitor treatment might have a beneficial effect in at least some high-grade cancers.[13,25] In the Combination of Avodart and Tamsulosin (CombAT) study,[28] reduction in prostate cancer was shown across all Gleason scores. In our study, although there was no significant reduction in progression of cancers to Gleason scores of 7 or more in men who received dutasteride compared with placebo, there was also no evidence of increased progression in Gleason grade with dutasteride.

Panel: Research in context

Systematic review

We searched Medline for full articles reporting the results of trials published in any language between Jan 1, 1990, and May 31, 2011, with the terms "dutasteride", "finasteride", "5α-reductase inhibitor", "5ARI", "active surveillance", "expectant management", and "prostate cancer". We did not identify any randomised controlled trials reporting the use of 5α-reductase inhibitors in active surveillance; however, we did identify one retrospective cohort study.[19] We identified four trials that assessed active surveillance for low-risk or localised prostate cancer: one trial[20] compared nutritional supplementation versus placebo on cancer-related gene expression in prostate biopsies; two reported the effect of selenised yeast[21] or high-dose isoflavone supplements[22] on prostate-specific antigen concentrations; and one investigated the effect of diet and stress management interventions on initiation of prostate cancer treatment.[23] Finally, a series of three related randomised trials compared prostate cancer progression in men who were treated with bicalutamide versus placebo undergoing standard of care for prostate cancer, although the standard of care included surgical and medical management in addition to active surveillance.[24]

Interpretation

Previous studies have suggested the importance of delaying disease progression in men who elect to undergo active surveillance for localised prostate cancer. Our study is the first prospective, randomised trial of treatment with 5α-reductase inhibitors in men undergoing active surveillance. We show that dutasteride delays progression of prostate cancer (pathological or therapeutic) and thus provides a treatment option for men with low-risk, localised disease.

For men in whom low-risk disease progressed to higher Gleason grade, those who received dutasteride had a lower mean percentage of cancer-positive cores and shorter cumulative length of tumours compared with placebo on final biopsy. As such, the benefit of dutasteride is to reduce the amount of low-grade cancer, not to reduce the risk of being diagnosed with a higher grade cancer. This reduction leads to fewer men with biopsy-detectable prostate cancer, and therefore fewer treatment interventions. Time to treatment or progression is a clinically relevant outcome; however, future studies should also focus on longer term mortality to fully reveal the prevention potential of 5α-reductase inhibitors.

Men receiving dutasteride reported significantly lower overall anxiety than did controls. This reduction in anxiety seemed to be driven by a reduction in fear of prostate cancer recurrence, in which the dutasteride group had significant reductions compared with the placebo group from 12 months onwards. Although these effects might have been driven by a prostate-specific antigen drop in men randomly allocated to dutasteride, this effect nevertheless represents a real-world benefit of such treatment. Furthermore, given that a prostate-specific antigen drop due to dutasteride occurs earlier than 1 year and improvements in anxiety were noted after this point, the possibility remains that other mechanisms of reduction in anxiety might be responsible (eg, enhanced biopsy status or improvement in lower urinary tract symptoms).

Adverse events were consistent with those reported in previous studies of dutasteride,[11,13] and drug-related adverse events consisted mainly of sexual adverse events. There was no increase in cardiovascular adverse events with dutasteride treatment compared with placebo.

Participants in our trial had much the same baseline characteristics (clinical stage range, Gleason score, and prostate-specific antigen) as did those in other prostate cancer active surveillance studies;[3,17] however, the proportion of men with progression in the placebo group (49%) was higher than that of recent surveillance studies (25–30%).[3,29] This difference might be attributable to methodological differences (eg, entry criteria, frequency of a secondary biopsy sampling, definition of progression)[3] or higher rates of patient withdrawal and lower rates of follow-up in surveillance studies compared with REDEEM. In a surveillance study by Carter and colleagues[29] with equivalent pathological progression criteria to that of REDEEM, 25% of men underwent a curative intervention compared with 34% of men in the our placebo group. In the other study,[29] 16% of men were lost to follow-up, withdrew from the study, or died, and therefore had unknown prostate cancer status. Had these men remained in the study (as in REDEEM, in which withdrawn participants were followed up by phone for 3 years), those with disease progression could have contributed to higher rates of men undergoing curative interventions.

One potential cause of treatment bias during this study was that prostate-specific antigen was not centrally corrected (as is normally done in other 5α-reductase inhibitor studies).[14] However, we believe our strategy is a more real-world approach to management of patients. Reporting actual prostate-specific antigen values was necessary because clinicians used prostate-specific antigen as part of active surveillance in line with the National Comprehensive Cancer Network Guidelines.[9] The effects of this bias could be bidirectional. Knowledge of actual prostate-specific antigen results could have led to asymmetric initiation of therapy for prostate cancer, and hence a bias against placebo.[3,29] Conversely, more men might have dropped out of the study in the placebo group because of a rising prostate-specific antigen and would therefore no longer be eligible to be diagnosed with progression. In either event, the proportion of men who could not be assessed for progression was low (13 participants), and study results did not change in post-hoc sensitivity analyses.

Our study design represents the real-world use of dutasteride in an active surveillance setting. Through elimination of prostate-specific antigen increases due to benign prostate tissue and indolent prostate cancers, dutasteride should allow prostate-specific antigen rises to better elucidate the biology of prostate cancers whose growth is no longer controlled by the drug. The improved usefulness of prostate-specific antigen with 5α-reductase inhibitors for the diagnosis of high-grade cancers in both the PCPT and the REDUCE trial supports this hypothesis.[27,30]

In conclusion, our trial is the first study to show the benefits of use of a 5α-reductase inhibitor to reduce the need for aggressive treatment in men undergoing active surveillance for low-risk prostate cancer. Although more robust results would be gained by a larger trial of longer duration (that was powered to investigate both pathological and clinical endpoints) than was possible here, the time to prostate cancer progression (pathological or therapeutic) was improved in men treated with dutasteride in our study. A greater proportion of men who received dutasteride rather than placebo had subsequent prostate biopsies that were no longer positive for cancer, and dutasteride-treated patients had less prostate cancer-related anxiety and fear of recurrence. Although the possibility of adverse events with 5α-reductase inhibitor treatment might be a worry for some patients, findings from our study show that dutasteride could be a beneficial adjunct to active surveillance for men with low-risk prostate cancer, delaying their time to pathological progression and initiation of primary therapy. Furthermore, we believe that future studies of medical therapies for men on active surveillance should use dutasteride as the comparator.

Contributors

NEF, LB, and RSR were involved in study design. NEF, MSL, BE, LA, and GE contributed research data to the study. MSL, IN, LB, and RSR were involved in data collection. All co-authors contributed to data analysis and interpretation. NEF, IN, and RSR drafted sections of the report, and all co-authors critically reviewed and revised the report for scientific content. All authors approved the final version.

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Conflicts of interest

NEF has served as a consultant, adviser, and speaker for GlaxoSmithKline, has served as a speaker for Novartis, and receives royalties from BioAdvantex. MSL reported consultancy for GlaxoSmithKline and his institution has received fee-for-service payments from GlaxoSmithKline for processing and interpreting biopsy samples from the reduction by dutasteride of clinical progression events in expectant management (REDEEM) study. BE has served as an advisory board participant and speaker for GlaxoSmithKline. LA has received travel support and payment for preparation of educational presentations from GlaxoSmithKline and his institution has received study funding and medication from GlaxoSmithKline. GE has served as a consultant or adviser for American Medical Systems, Thermatrx/AMS, and the

American College of Surgeons; has served as an investigator for American Medical Systems, Astellas, Ferring, GlaxoSmithKline, GTx, Lilly, Ortho Urology, and Spectrum Pharmaceuticals; has participated in scientific studies or trials sponsored by Bioniche, Dendreon, ECOG, Pfizer, Sanofi-Aventis, the Southwest Oncology Group; and has participated as a meeting participant or lecturer for American Medical Systems, Astellas, Ferring, GlaxoSmithKline, Indevus, and Lilly. Indrani Nandy, LKB and RSR are employees of GlaxoSmithKline with equity ownership or stock.

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