Oral Sodium Clodronate for Nonmetastatic Prostate Cancer—Results of a Randomized Double-Blind Placebo-Controlled Trial: Medical Research Council PR04 (ISRCTN61384873)

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For the Medical Research Council PR04 Collaborators

Background The most frequent site of metastases from prostate cancer is bone. Adjuvant bisphosphonate treatment improves outcomes of patients with bone metastasis–negative breast cancer, but the effects of bisphosphonates on bone metastases in prostate cancer are not known.

Methods We performed a randomized double-blind placebo-controlled trial to determine whether a first-generation bisphosphonate could improve symptomatic bone metastasis–free survival (time to symptomatic bone metastases or death from prostate cancer) in men with nonmetastatic prostate cancer who were at high risk of developing bone metastases. Between June 1, 1994, and December 31, 1997, 508 men from 26 UK sites and one New Zealand site who were within 3 years of initial prostate cancer diagnosis with no evidence of metastases from current bone scanning were randomly assigned to daily oral sodium clodronate (2080 mg/day, n = 254) or placebo (n = 254) for a maximum of 5 years. Estimates of outcome risks were compared using Kaplan–Meier analyses.

Results The groups allocated to each treatment were well balanced. After a median follow-up of nearly 10 years, no evidence of benefit to the clodronate group was observed in terms of bone metastases–free survival (clodronate versus placebo, 80 events versus 68 events; hazard ratio [HR] = 1.22; 95% confidence interval [CI] = 0.88 to 1.68) or overall survival (clodronate versus placebo, 130 deaths versus 127 deaths; HR = 1.02; 95% CI = 0.80 to 1.30). Adverse events, notably gastrointestinal problems and increased lactate dehydrogenase levels, were more frequent in the clodronate group than in the placebo group; otherwise, clodronate was well tolerated. Modification of trial drug dose was more frequent in the clodronate group than the placebo group (HR = 1.63, 95% CI = 1.21 to 2.19).

Conclusion Adjuvant sodium clodronate does not modify the natural history of nonmetastatic prostate cancer.

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Prostate cancer remains a challenging disease for the oncologist and urologist to treat. During the 1980s and early 1990s, many men in the United Kingdom had metastatic disease at initial diagnosis; however, during the last 15 years, the proportion has been falling, as it has been in the United States, due to the increasing use of prostate-specific antigen (PSA) testing (1,2). Nonetheless, rates of death from prostate cancer have fallen only slightly (3), and metastatic disease is the most common scenario leading to death from prostate cancer. The skeleton is the preferred site for disease spread, and at least 85% of men with advanced prostate cancer will have bone metastases (4,5). An increasing number of these deaths occur in men who were believed to be metastasis free at their

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See "Notes" for full details of collaborators.

See "Notes" following "References."

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CONTEXT AND CAVEATS

Prior knowledge

In men with metastatic prostate cancer, the other tissue most often involved is bone. Treatment with bisphosphonates improves the outcomes of patients with metastatic breast cancer.

Study design

Randomized double-blind placebo-controlled Phase III trial of clodronate among patients with locally advanced prostate cancer.

Contribution

Clodronate treatment did not improve overall survival or symptomatic bone metastasis–free survival compared with placebo. Although clodronate was well tolerated overall, more men in the clodronate than in the placebo arm reported adverse effects, such as gastrointestinal distress, that led to adjustment of trial medication dosage.

Implications

Clodronate treatment has no effect on the progression of locally advanced prostate cancer.

Limitations

Standards for collecting information about toxic effects are higher now than during the time of the trial. Gleason score and prostate-specific antigen levels were not available. Additional treatments were not reported.

original diagnosis and who, by inference, had occult micrometastatic disease at that time.

The bisphosphonate group of compounds is chemically characterized by a phosphorus–carbon–phosphorus (P–C–P) bond, which has affinity for bone through binding to hydroxyapatite crystals; thus, bisphosphonates localize preferentially to areas of increased bone resorption and regeneration (6). The mechanisms of action are complex and may differ between different compounds, but bisphosphonates are known to reduce the number and activity of osteoclasts, probably through direct effects on osteoclast action and recruitment as well as indirect effects on osteoblasts and macrophages (6). The overall effect of bisphosphonate treatment is the reduction of excessive bone turnover with preservation of bone structure and mineralization (6,7). Bisphosphonates have become the standard management for hypercalcemia of malignancy (8–10), have a role in the management of metastatic bone pain (11–14), and have been shown to statistically significantly reduce skeletal-related events in both myeloma and advanced breast cancer when given in addition to standard chemotherapy or hormonal treatment for metastatic disease (13–15). Some studies (6,16–21) suggest that bisphosphonates may also reduce the rate of development of bone metastases in patients who were thought to be initially metastasis-free and thus to favorably modify the natural history of these malignancies.

Prostate cancer bone metastases are most commonly sclerotic or osteoblastic (bone forming), unlike the osteolytic (bone destroying) bone metastases from other types of cancers (4). However, as with myeloma and breast cancer, data suggest the presence of an osteolytic component that could be inhibited by bisphosphonates (22–26).

We hypothesized that if bisphosphonates could reduce osteolysis in prostate cancer patients, they might also slow the development of symptomatic bone metastases and favorably modify the natural history of the disease. Therefore, in the early 1990s, the UK Medical Research Council (MRC) initiated clinical trials of bisphosphonates for prostate cancer in collaboration with Boehringer Mannheim (subsequently Roche Products Ltd). Because intravenous therapy was not a standard component of prostate cancer treatment at that time, we used the most potent oral bisphosphonate then available, sodium clodronate. Because oral absorption of clodronate is poor, we used the highest dose of drug that was likely to be tolerable. We considered that the agent would be most likely to show a benefit when osteolysis from prostate cancer was at a minimum, i.e., at a time well before any underlying metastases were clinically evident.

Two randomized phase III double-blind placebo-controlled trials were designed. One trial (MRC PR05—ISRCTN38477744) recruited patients with known bone metastases who were just starting first-line hormonal treatment or responding to such treatment. Results of this trial have already been reported (27). The other trial (MRC PR04—ISRCTN61384873) recruited men with locally advanced prostate cancer but who had negative bone scans. Here, we report the results from the MRC PR04 trial and compare them with the published results of MRC PR05.

Patients and Methods

Study Design

The MRC PR04 trial was a randomized multicenter, double-blind, placebo-controlled trial of an oral bisphosphonate (sodium clodronate) for men with a recent diagnosis of tumor stage T2 through T4 prostate cancer and with no evidence of bone metastases. It was coordinated from the MRC Clinical Trials Unit (CTU), London (formerly MRC Cancer Trials Office, Cambridge).

The trial was designed according to MRC Good Clinical Practice guidelines and abided by the Declaration of Helsinki. Approval from the appropriate research ethics committee was obtained for each participating center. All patients gave written informed consent before participating. Because this preparation of sodium clodronate (Loron520 tablets) was being used outside of its licensed indication, the trial was run under a Clinical Trials Marketing Product from the UK Medicines Control Agency. All clinicians were required to register with the MRC CTU before participating.

Eligibility Criteria

Patients had to have been diagnosed within 36 months before study entry with locally advanced adenocarcinoma of the prostate, defined as stages T2 through T4, N0, N+ or NX, M0, following the definition used in a previous MRC trial (28), which was considered at the time of trial development to define a group of men who were at substantial risk of developing subsequent bone metastatses; there was no central review of pathology. Additional eligibility criteria were: World Health Organization (WHO) performance status 0–2, normal calcium levels, and no previous bisphosphonate treatment or long-term hormone therapy.

Random Assignment

Random assignment was undertaken centrally at the MRC CTU. Treatment was allocated in the ratio 1:1, using the method of minimization over five stratification factors: treatment center, tumor stage (T2 versus T3 versus T4), primary therapy (given versus not given), time from primary therapy to random assignment (0 versus 12 months versus >12 months), and PSA value at study entry (<50 ng/mL versus ≥50 ng/mL). The fifth stratification factor (PSA value) was added in 1997 to provide additional balance between trial arms.

Treatment Allocation and Supply

Patients were randomly assigned to receive either oral sodium clodronate (active, A) or a matching placebo (placebo control, C) in addition to conventional management for their prostate cancer. The active regimen consisted of a daily total dose of four 520 mg tablets of sodium clodronate. The placebo regimen consisted of four identical placebo tablets. Both drugs were manufactured by Boeringher Mannheim. Drugs were ordered by the MRC CTU and distributed by Boeringher Mannheim (see "Notes"). Patients were allocated a unique trial number and a unique drug number so that it was not possible to tell which patients had been allocated to which trial arm. No patient details other than drug number and hospital were revealed to the pharmaceutical company.

Treatment Schedules

After random assignment, patients started trial medication as soon as they arrived at the hospital and remained on trial medication for a maximum of 5 years, stopping treatment earlier only if they reached the primary outcome measure of the trial, died, experienced unacceptable toxic effects, or chose to stop trial medication. Patients were instructed to "take four tablets each evening, at least one hour before or after food with a little fluid, not milk".

It was anticipated that the most common adverse reactions in the active group would be gastrointestinal distress and asymptomatic increased levels of lactate dehydrogenase (LDH). Advice was given in the protocol on how to modify dose in the event of these toxic effects, including reducing trial medication dose and temporarily stopping trial medication, with the possibility of progressing to permanent cessation if unacceptable toxic effects continued.

Follow-up and Monitoring

Patients were followed up at 6 weeks after random assignment (after approximately 4 weeks on trial medication) to ensure tolerability. They subsequently returned for clinical assessment at 6 months, then every 6 months until 2 years after random assignment, and then yearly until death. Clinical assessments included a clinical examination plus full blood count, liver function tests (including alkaline phosphatase), renal function tests (serum creatinine and electrolytes), blood biochemistry (calcium, phosphate, and albumin), and a note as to whether there was pain requiring regular use of analgesia. Any relevant abnormalities were reported as adverse events. Adverse event reporting in this trial followed guidelines different to those in current practice. That is, adverse events were defined as events leading to alteration in trial medication, hospitalization, prolongation of hospitalization, or death. These were reported on a separate Adverse Events case report form and were the only source of toxicity data. An indication of severity and/or suspected relatedness of events can be estimated by determining which adverse events led to a modification in the dose of trial medication.

Source data verification was performed on a random sample of patients in each center (10 patients or 20% of patients, whichever was greater). During 2005, all UK trial patients were flagged with a number from the National Health Service Central Register (NHSCR), to aid an independent cause-of-death adjudication in patients who were known to have already died and to confirm long-term status in other patients. This national register is used to assist the National Health Service to manage general practitioner lists and payments in England and Wales. It includes death information and is currently maintained by the Office for National Statistics.

Statistical Analysis

The primary outcome measure of the trial was symptomatic bone metastases–free survival, which was defined as time from random assignment to the development of symptomatic bone metastases or death from prostate cancer. The secondary outcome measures were overall survival, toxicity, rate of events affecting bone during the trial, and type of progressive disease (bone versus nonbone). The cause of death was assigned from data in the case report forms, including a specially designed form that asked about cause of death, place of death, and contribution of prostate cancer to the death, as well as the NHSCR data. Deaths reported only through the NHSCR contributed only to analyses of survival (i.e., all cause mortality, prostate cancer death, and nonprostate cancer death) and not to analyses of composite outcome measures, such as the primary outcome measure. This is because the NHSCR data can only provide death information and cannot provide information on the progression of cancer or the occurrence of other diseases before death. Deaths in England and Wales are generally available on NHSCR within 6 weeks of occurrence and 12 weeks in Scotland. When NHSCR data were used, patients who were not reported as having died were assumed to have been alive 6 weeks previously in England and Wales and 12 weeks previously in Scotland (Office for National Statistics, unpublished data). For the one non-UK center, in New Zealand, survival data from trial case report forms were used instead of national statistics for these analyses.

The trial was designed to be pragmatic, i.e., to fit in with local standard practice, and to have minimal data follow-up requirements. The sample size calculations were based on 80% power to detect a 12% absolute improvement in the proportion of men at 5 years who were free from bony metastases or death from prostate cancer (the primary outcome measure) from 60% to 72% (hazard ratio [HR] = 0.64) at the $\alpha = 0.05$ level. It was anticipated that recruitment of 500 patients for 3 years would provide the 166 events necessary to meet these specifications. (We note that 148 such events are included in this analysis and that the placebo arm event rate was much lower than anticipated.)

Throughout, time to outcome measure events were taken as time from random assignment to the first confirmed report of an event for each patient. Time on trial medication was calculated as the time from random assignment to the first follow-up assessment reporting permanent cessation of trial medication. Patients who did not experience an event were censored at the time at which they were last known to be event free.

All analyses were performed on an intention-to-treat basis using all randomly assigned patients. The analyses were performed at MRC CTU using Stata 9 (StataCorp, College Station, TX) following a prespecified statistical analysis plan that included the use of the -sts- suite of commands. Interval-censored methods were not used. Hazard rates in each treatment group were compared using the log-rank test and plotted using Kaplan–Meier curves. Hazard ratios are presented as point estimates with 95% confidence intervals (CIs), which were calculated using the observed and expected events from the log-rank test. A hazard ratio of less than 1.0 denotes an advantage to the active group. Time-to-event analyses, including those of the primary outcome measure, all-cause mortality, prostate cancer death, nonprostate cancer death, and disease progression were performed. The Royston and Parmar model (29) has been used to estimate the survival difference and its 95% confidence intervals at any time point. The Royston–Parmar model is a flexible parametric model and works by smoothing the baseline log cumulative hazard function using a natural cubic spline function of log time. Consistency of effect across subgroups was tested with a chi-square test of heterogeneity, and the number of df was dependent on whether the subgroups were ordered (test for trend) or unordered (test for overall interaction). The subgroups that were planned for examination were the main disease characteristics and the stratification factors, e.g., T-stage, age. To compare the results from PR04 with those of PR05, a trial of patients with more advanced disease, the PR05 data were not updated but were taken from the primary publication (29). All statistical tests were two-sided, and *P* values less than .05 were considered to be statistically significant.

PSA levels were not routinely collected in the United Kingdom when recruitment started. PSA levels before random assignment were mandated, and PSA levels before primary therapy were collected retrospectively for all patients, where available, during the accrual phase of the trial. The complete PSA histories of patients from the two largest centers were collected retrospectively before this analysis. No PSA data were collected prospectively during follow-up, and so no guidance was offered to participating physicians on what to do for men with increasing PSA levels or what constituted a rising PSA level. Therefore, the analyses of the retrospective PSA data are intended to be indicative only. PSA failure was defined as a PSA value of at least 2 ng/mL greater than the nadir. The nadir was the lowest PSA value reported at any time after 3 months before random assignment.

Review of Cause of Death

Causes of death were reviewed because patients with prostate cancer often have comorbidities and die from nonprostate cancer causes and thus, the contribution of prostate cancer to the patient's death is often not apparent. A medically trained member of the trial team (REL), who was blinded to allocated trial arm, reviewed the cause of death based on information reported on the standard case report forms and supplemented with the recorded causes of death from death certificate information collected from NHSCR sources. Each death was classified as having being caused by prostate cancer or a nonprostate cancer cause by considering the reported cause of death and the history of the patient's disease (Supplementary Table 1, available online). The chief investigator (M. D. Mason), who was also blinded to the treatment allocation, was consulted if there was any difficulty in assigning the cause of death, and disagreement was resolved by a consensus.

Overseeing Committees

The day-to-day management of the trial was reviewed routinely by the Trial Management Group. In addition, from November 1999, the trial came under the auspices of an independent MRC Trial Steering Committee. Full blinded interim analyses, including those of the primary and secondary outcome measures, were performed for review by an independent Data Monitoring & Ethics Committee (DMEC) on three occasions (July 1996, July 1997, and September 1999). No formal stopping rules were prespecified. No formal adjustment of *P* values has been performed. The DMEC were to consider recommending stopping the trial only if the results would be sufficiently convincing to a broad range of clinicians. After the first two reviews, the DMEC recommended continuation of trial recruitment. At the third and final review, the DMEC advised continuing follow-up until the protocol-stated number of events had been reached, noting that this would make follow-up longer than initially planned.

Results

Accrual and Maturity

A total of 508 patients were randomly assigned from 26 centers in the United Kingdom and one in New Zealand between June 1, 1994, and December 31, 1997; of whom 254 patients were allocated to receive oral sodium clodronate in the active group and 254 allocated to the placebo (control) group. All patients had stopped trial medication by August 31, 2003. The median follow-up of the patients is nearly 10 years (118 months) for overall survival using NHSCR data. Of the 320 patients last reported alive, 93% and 87% have been followed up for at least 3 and 5 years, respectively. The flow of patients through the trial is summarized in Fig. 1.

Patient Characteristics

The groups were well balanced in terms of disease-related baseline characteristics, general well-being, and primary therapy (Table 1).

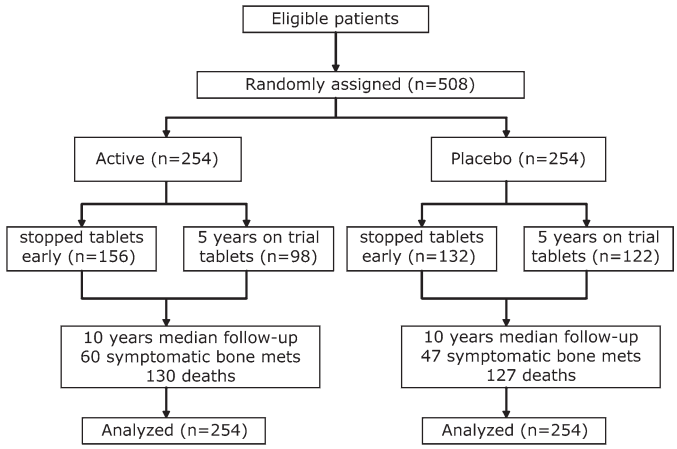

Fig. 1. CONSORT diagram showing the flow of patients through the trial, expressing the maturity of the trial data and the number of randomly assigned patients who are included in these analyses.

Table 1. Baseline characteristics of participants in the Medical Research Council PR04 trial*

Characteristic at time of random assignment	Clodronate, N = 254	Placebo, N = 254
Age, y		
Median (interquartile range)	70 (64–74)	69 (64–74)
Range	49–85	50–87
WHO performance status, No. (%)		
0	200 (79)	201 (79)
1	44 (17)	52 (20)
2	10 (4)	1 (0)
Tumor stage, No. (%)		
T2	136 (54)	135 (53)
T3	106 (42)	108 (43)
T4	12 (5)	11 (4)
Nodal stage, No. (%)		
N0	207 (81)	202 (80)
N+	10 (4)	3 (1)
NX	37 (15)	49 (19)
Bone metastases, No. (%)		
M0	254 (100)	254 (100)
M1	0 (0)	0 (0)
PSA level at random assignment, ng/mL		
Median (quartiles)	13 (3–31)	10 (2–31)
Range	0–316	0–294
No. with missing data	1	3
PSA level before primary therapy, ng/mL		
Median (quartiles)	25 (11–52)	23 (12–46)
Range	0–900	0–208
No. with missing data	94	92
Time from primary therapy to random assignment, days		
Median (quartiles)	83 (20–140)	85 (26–167)
Range	–78 to 1156	–46 to 1158
No. with missing data	15	13
Primary therapy, No. (%)		
RT + long-term hormones	68 (27)	76 (30)
RT alone	107 (42)	104 (41)
Long-term hormones alone	65 (26)	59 (23)
Prostatectomy-based	2 (1)	4 (2)
TURP/no treatment	12 (5)	11 (4)

* WHO = World Health Organization; T = tumor; N = nodal; M = metastases; PSA = prostate-specific antigen; RT = radiotherapy; TURP = transurethral resection of the prostate.

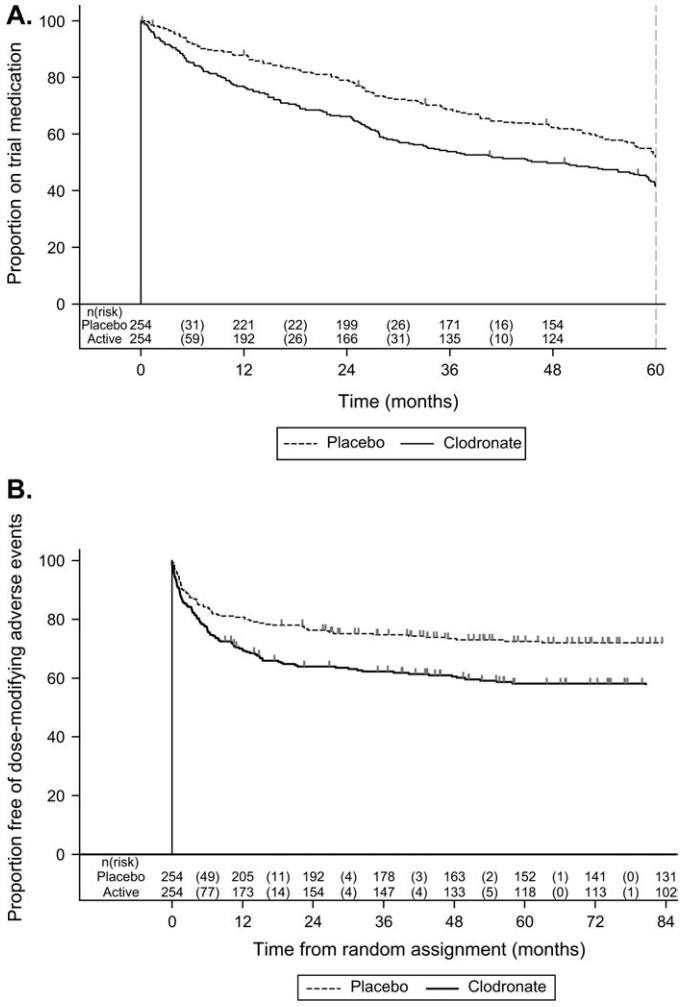

Fig. 2. Time on trial medication and time to dose-modifying adverse events. **A**) Kaplan–Meier plot of time from random assignment to the time of confirmed cessation of trial medication. At random assignment, all patients are presented as being on trial medication; **each downward step in the curves** represents an event, i.e., a patient stopping trial medication. More time was spent on trial medication by the control group (hazard ratio [HR] = 1.40, 95% confidence interval [CI] = 1.11 to 1.79; $P = .005$). The graph is capped at 5 years, which is the maximum time permitted on trial medication. **B**) Kaplan–Meier plot of time from random assignment to the time of the first reported adverse event that led to any modification or cessation of trial medication, whether temporarily or permanently. At random assignment, all patients are presented as being free from dose-modifying adverse events; **each downward step in the curves** represents a patient reported as having a dose-modifying adverse event. The risk of dose-modifying adverse events was higher on the clodronate arm (HR = 1.63, 95% CI = 1.21 to 2.19), and by 3 years, 74% (95% CI = 68% to 79%) of men in the placebo arm and 62% (95% CI = 54% to 68%) in the active arm remained free of having experienced such an event. Estimates and statistics were determined using two-sided log-rank tests.

Overall, the median age was 69 years, 47% had T3/4 disease, 81% were known to be node negative, and 79% had WHO performance status of zero. Forty-two percent of patients were being treated with radiotherapy only, 28% with radiotherapy plus hormone therapy, and 24% with hormone therapy only; the proportion receiving hormone therapy was greater in patients with worse tumor stage.

Compliance

We monitored time from random assignment to cessation of trial medication (Fig. 2, A). Twelve patients never started trial medication (active, n = 9; placebo, n = 3). The median time from random assignment to reported permanent cessation of trial medication was 47 months for the active arm and 60 months for the placebo (HR = 1.40, 95% CI = 1.11 to 1.79; $P = .005$). When the main reasons for stopping trial medication were assessed (Table 2), more patients in the active arm than in the placebo arm stopped for toxicity. The most common reason for stopping was completing 5 years (the maximum time permitted) of trial medication (active,

Table 2. Reasons for stopping trial medication among men in the Medical Research Council PR04 trial

Reason for stopping	Clodronate, N = 254 n (%)	Placebo, N = 254 n (%)
Five years on trial medication	98 (40)	122 (51)
Gastrointestinal problems	37 (15)	20 (8)
Symptomatic bone metastases	26 (11)	23 (10)
Patient choice	25 (10)	16 (7)
Death	9 (4)	20 (8)
Blood counts	8 (3)	1 (0)
Other prostate cancer progression	5 (2)	6 (3)
Other causes	34 (14)	31 (13)
Unknown	12 (n/a*)	15 (n/a*)

* n/a = not applicable.

n = 98 [40%]; placebo, n = 122 [51%]), the second most common reason was gastrointestinal problems (active, n = 37 [15%]; placebo, n = 20 [8%]), and the third most common reason was a primary outcome measure event.

Primary Outcome Measure: Symptomatic Bone Metastases or Death From Prostate Cancer

A primary outcome event was observed in 148 patients (active, n = 80; placebo, n = 68). The development of symptomatic bone metastases (n = 107) was more commonly reported than prostate cancer death (n = 41) as the primary outcome measure.

Comparison of Kaplan–Meier curves of symptomatic bone metastases–free survival suggested that fewer events occurred among men in the placebo arm than in the active arm (HR = 1.22, 95% CI = 0.88 to 1.68; $P = .23$) (Fig. 3; Supplementary Fig. 1, available online). This estimates a non–statistically significant worsening of the relative risk of symptomatic bone metastases or prostate cancer death in patients in the active arm, but the confidence intervals are wide and cannot rule a relative advantage of 12% or a disadvantage of 68%. The median time-to-event was 131 months in the placebo arm, and, from the hazard ratio, 107 months in the active arm. The proportion of patients who were event-free at 5 years was 83% (95% CI = 77% to 87%) in the placebo arm, and, from the hazard ratio, 79% (95% CI = 73% to 84%) in the active arm. This difference represents an absolute decrease in the 5-year symptomatic bone metastases–free survival of 4% in the active arm.

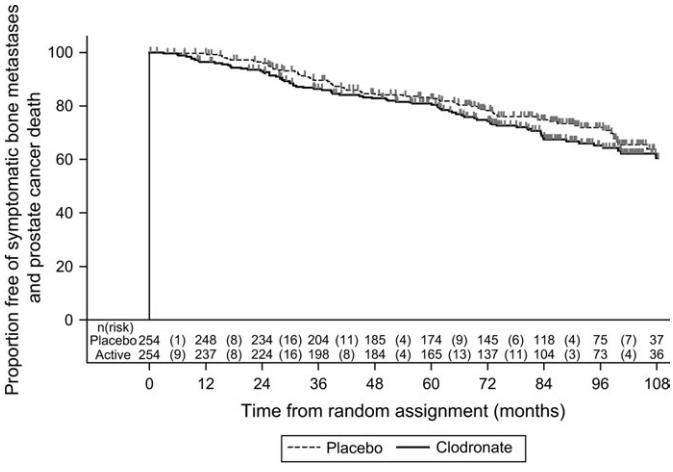

Fig. 3. Kaplan–Meier plot of time from random assignment to the first report of symptomatic bone metastases or death from prostate cancer. **Each downward step in the curves** represents an event. More such events were reported among men in the clodronate arm than in the placebo arm (hazard ratio = 1.22, 95% confidence interval [CI] = 0.88 to 1.68; $P = .23$). The proportion of patients event free at 2 years was 96% (95% CI = 93% to 98%) in the placebo arm and, from the hazard ratio, 96% (95% CI = 92% to 98%) in the clodronate arm, and at 5 years was 83% (95% CI = 77% to 87%) in the placebo arm and, from the hazard ratio, 79% (95% CI = 73% to 84%) in the clodronate arm.

Secondary Outcome Measures: Disease Progression

Local progression (n = 111) was the most commonly reported first disease event, and symptomatic bone metastasis (n = 42) was the second most common (Table 3). A total of 55 patients died from causes other than prostate cancer and had no disease progression. Men in the placebo arm had longer time to first disease progression (excluding PSA level) than men in the active arm, based on 226 disease events (HR = 1.31, 95% CI = 1.01 to 1.70; $P = .041$). Many patients started hormone therapy before reaching the primary outcome measure. To investigate the potential impact of this treatment, PSA data were collected retrospectively from the two largest trial centers for exploratory analyses. Nadir PSA level could be determined for 202 patients, 101 in each arm. PSA failure events were reported for 77 of 101 patients in the active arm and 66 of 101 of those in the placebo arm (HR = 1.62, 95% CI = 1.16 to 2.25; $P = .005$), with 43% patients in the placebo arm and 24% patients in the active arm being PSA failure free at 5 years. Fewer men in the placebo arm (69 of 101) than in the active arm (79 of 101) had PSA failure or any disease progression (HR = 1.54, 95% CI = 1.11 to 2.13; $P = .008$).

Secondary Outcome Measures: Survival

From trial and NHSCR data, a total of 257 deaths were reported (active, n = 130; placebo, n = 127). Comparison of Kaplan–Meier curves of overall survival showed no difference between arms

Table 3. First disease event reported among men in the Medical Research Council PR04 trial*

First disease progression event reported	Clodronate, N = 254 n (%)	Placebo, N = 254 n (%)
No progressive disease reported	104 (41)	114 (45)
LPD	67 (26)	44 (17)
Symptomatic bone metastasis	23 (9)	19 (7)
Nonbone metastasis	14 (6)	15 (6)
Asymptomatic bone metastasis	7 (3)	11 (4)
Prostate cancer death	5 (2)	8 (3)
Nonbone mets + LPD	4 (2)	3 (1)
Asymptomatic bone mets + LPD	3 (1)	0 (0)
Symptomatic bone mets + LPD	0 (0)	2 (1)
Symptomatic bone mets + other mets + LPD	0 (0)	1 (0)
Nonprostate cancer death	22 (9)	33 (13)
Nonprostate cancer deaths (register)†	5 (2)	4 (2)

* LPD = local progressive disease; mets = metastases.

† The patients with deaths reported only from the National Health Service Central Register are censored at the time of death for analyses based on disease progression but contribute to analyses of survival only.

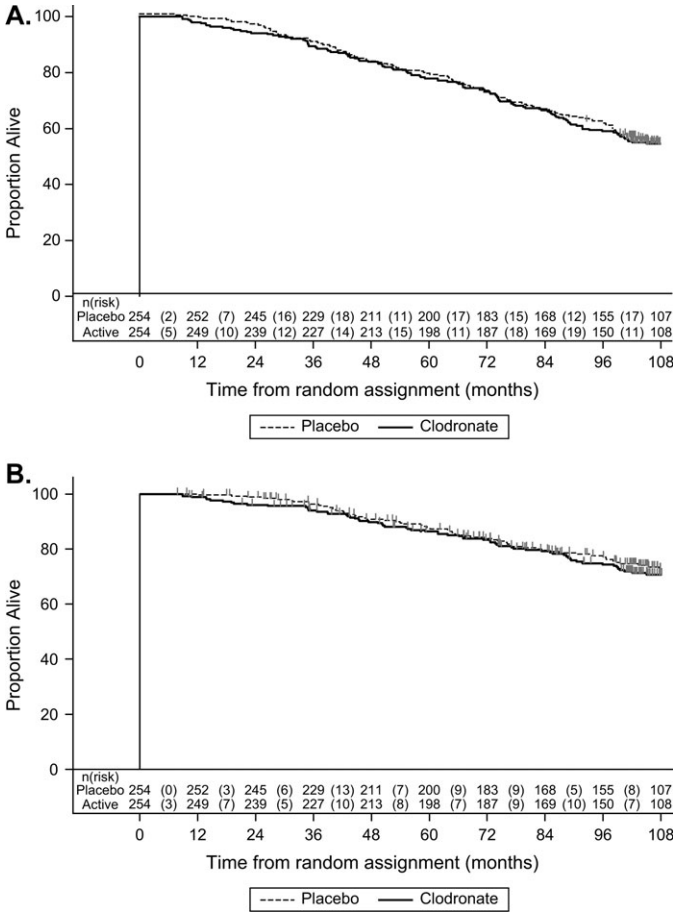

Fig. 4. Kaplan–Meier plot of time from random assignment to death from prostate cancer or from any cause. **Each downward step in the curves** represents a death; patients are censored when assumed to be last alive using National Health Service Central Register data (A only) or at death from causes other than prostate cancer. The hazard ratios (HRs) were similar in each arm. **A**) Death from any cause. For overall survival, HR = 1.02 (95% confidence interval [CI] = 0.80 to 1.30; $P = .90$); the proportion alive at 2 years was 96% (95% CI = 93% to 98%) in the placebo arm and also 96% (95% CI = 93% to 98%) in the clodronate arm and 5 years was 79% (95% CI = 73% to 83%) in the placebo arm and 78% (95% CI = 73% to 83%) in the clodronate arm. **B**) Death from prostate cancer. For death from prostate cancer, HR = 1.07 (95% CI = 0.76 to 1.49; $P = .71$); the proportion of patients not having died of prostate cancer by 2 years was 99% (95% CI = 96% to 100%) in the placebo arm and, from the hazard ratio, also 99% (95% CI = 96% to 100%) in the clodronate arm; and the proportion of patients not having died of prostate cancer at 5 years was 88% (95% CI = 83% to 91%) in the placebo arm and, from the hazard ratio, 87% (95% CI = 82% to 91%) in the clodronate arm. These estimates and statistics were determined using two-sided log-rank tests.

(HR = 1.02, 95% CI = 0.80 to 1.30; $P = .90$) (Fig. 4, A; Supplementary Fig. 2, available online). Median overall survival was 115 months, with 5-year survival of 79% (95% CI = 73% to 83%) in the placebo arm and 78% (95% CI = 73% to 83%) in the active arm. (It should be noted that, using data only on case report forms, i.e., excluding NHSCR data, 188 deaths were reported [HR = 1.00, 95% CI = 0.75 to 1.34].]) Approximately half of the 257 reported deaths were due to prostate cancer (active, n = 72 [55%]; placebo, n = 66 [52%]; Table 4). Comparison of Kaplan–Meier curves of time to prostate cancer death suggested no evidence of a benefit in the active arm (HR = 1.07, 95% CI = 0.76 to 1.49; $P = .71$) (Fig. 4, B; Supplementary Fig. 3, available online).

Table 4. Current status and adjudicated causes of death among men in the Medical Research Council PR04 trial*

Status and cause of death	Clodronate, N = 254 n (%)	Placebo, N = 254 n (%)
Alive	123 (48)	126 (50)
Prostate cancer death	72 (28)	66 (26)
Previous symptomatic bone mets	35 (14)	37 (15)
Previous asymptomatic bone mets	1 (0)	0 (0)
Other previous disease progression	21 (8)	19 (7)
No previous reports of progression	15 (6)	10 (4)
Other death	59 (23)	62 (24)
Previous symptomatic bone mets	3 (1)	2 (1)
Previous asymptomatic bone mets	0 (0)	1 (0)
Other previous disease progression	12 (5)	12 (5)
No previous reports of progression	27 (11)	34 (13)
Unable to assess progression	17 (7)	13 (5)

* Includes the conclusion of the death review of two patients who were reported on the case report forms as having died and who were reviewed but for whom National Health Service Central Register confirmation of death was not received. Hence, 259 deaths were included in the cause of death review, above, but only 257 deaths were included in Fig. 4, B. mets = metastases.

We estimated treatment effects with hazard ratios for each of the efficacy outcome measures (Table 5). None of the outcome measures available for all trial patients was statistically significantly different between arms.

Secondary Outcome Measures: Toxicity and Adverse Events

Gastrointestinal problems were the most commonly reported adverse event and dose-modifying adverse event in both arms; raised LDH was more common in the active arm. More patients in the active arm than in the placebo arm reported one or more adverse events (active, n = 132 patients; placebo, n = 117 patients; $P = .18$), and more adverse events overall were reported in the active arm (n = 202 events) than the placebo arm (n = 181 events) (Table 6). Comparison of Kaplan–Meier curves of time from random assignment to the first reported adverse event suggested an increase in the risk of adverse events in the active arm (HR = 1.22, 95% CI = 0.95 to 1.56; $P = .12$).

The severity of an adverse event could be gauged only by whether it led to modification of the trial medication dose. More patients in the active arm reported a dose-modifying adverse event (active, 132 events in 105 patients; placebo, 94 events in 71 patients; $P = .002$); and comparing the Kaplan–Meier curves of time to the first dose–modifying adverse event showed a benefit to the placebo arm (HR = 1.63, 95% CI = 1.21 to 2.19; $P = .0013$) (Fig. 2, B). This represents a 63% increase in the risk of at least one dose-modifying adverse event in the active arm ($P = .0013$).

Exploratory Analyses

Subgroup analyses showed no evidence of differential effects of clodronate treatment across subgroups of characteristics with regard to the primary outcome measure; the possible exceptions were between patients who received radiotherapy only, hormones only, or both (Supplementary Table 2, available online).

Table 5. Summary of hazard ratios for the Medical Research Council PR04 trial*

Trial outcome measure	Clodronate		Placebo		HR (95% CI)	*P*
	No. of events	No. of patients	No. of events	No. of patients		
Symptomatic bone metastases or prostate cancer death	80	254	68	254	1.22 (0.88 to 1.68)	.23
Symptomatic bone metastases	60	254	47	254	1.32 (0.91 to 1.93)	.15
Symptomatic bone metastases or any death	113	254	109	254	1.08 (0.83 to 1.41)	.56
First progression or any death	150	254	140	254	1.18 (0.94 to 1.49)	.15
Death (NHSCR)†	130	254	127	254	1.02 (0.80 to 1.30)	.90
Prostate cancer death (NHSCR)†	71	254	66	254	1.07 (0.76 to 1.49)	.71
First progression	123	254	103	254	1.31 (1.01 to 1.70)	.041
Death (CRF)‡	93	254	95	254	1.00 (0.75 to 1.34)	.98
Nonprostate cancer death (CRF)‡	38	254	44	254	0.89 (0.58 to 1.37)	.59
Prostate cancer death (CRF)‡	55	254	51	254	1.10 (0.75 to 1.61)	.62
Local progression	83	254	62	254	1.45 (1.04 to 2.00)	.027
Nonbone metastases	30	254	34	254	0.91 (0.56 to 1.48)	.69
Nonprostate cancer death (NHSCR)‡	59	254	61	254	0.96 (0.67 to 1.37)	.83
Any progression (including PSA)§	79	101	69	101	1.54 (1.11 to 2.13)	.0081
PSA progression only§	77	101	66	101	1.62 (1.16 to 2.25)	.0034

* *P* values (two-sided) were calculated using the log-rank test. HR = estimate of hazard ratio; CI = confidence interval; NHSCR = National Health Service Central Register, i.e., long-term follow-up and survival data available from national registers; prostate-specific antigen (PSA) progression ≥2 ng/mL greater than the nadir, for which the nadir was the lowest PSA value reported subsequent to 3 months before random assignment; NHSCR = National Health Service Central Register i.e., long-term follow-up and survival data available from national registers.

† The data included in the death analyses suffixed with "NHSCR" were taken from the trial's case report forms and supplemented with data from NHSCR. UK patients in these analyses without a reported event were censored shortly before analysis (see "Patients and Methods").

‡ The data included in the death analyses suffixed with "CRF" were only taken from the trial's case report forms. Patients in these analyses without a reported event were censored at the time of the last follow-up.

§ PSA progression analyses used retrospectively collected data from the two largest participating centers and were intended to be indicative.

No evidence of differential effects of clodronate treatment was observed across subgroups in terms of overall survival or prostate cancer survival.

Comparing Results From MRC PR04 and MRC PR05 Trials

The results of the analyses of MRC PR04 were compared with the previously published results of the MRC PR05 trial, which had performed the same randomized comparison of active and placebo treatments, but for a duration of 3 years and among patients who were already diagnosed with bone metastases. Patients with bone metastases (PR05) appear to benefit from clodronate treatment, whereas patients without metastatic disease (PR04) did not. These differences are shown in the hazard ratios and confidence intervals that are presented as a forest plot (Fig. 5). For example, in terms of symptomatic bone metastases or progression or prostate cancer death, in PR04, the HR was 1.22 (95% CI = 0.88 to 1.68) in favor of the placebo arm, whereas in PR05, the HR was 0.79 (95% CI = 0.61 to 1.02) in favor of the active arm. These values show statistically significant heterogeneity ($P = .038$), indicating a differential effect of clodronate in the two trials in terms of their primary outcome measures.

Table 6. Adverse events reported during the Medical Research Council PR04 trial*

Adverse event	All adverse events		Dose-modifying adverse events	
	Clodronate n (%)	Placebo n (%)	Clodronate n (%)	Placebo n (%)
Gastrointestinal problems	86 (43)	68 (38)	67 (51)	42 (45)
Raised LDH	30 (15)	5 (3)	24 (18)	4 (4)
Cardiovascular problems	12 (6)	15 (8)	5 (4)	5 (5)
Rash or itch	10 (5)	14 (8)	9 (7)	5 (5)
Other conditions†	62 (31)	78 (43)	27 (20)	38 (40)
Missing	2 (1)	1 (1)	0 (0)	0 (0)
Total	202 (100)	181 (100)	132 (100)	94 (100)

* Percentages are given relative to the total number of adverse events reported. LDH = lactate dehydrogenase.

† No group of events under "other conditions" account for more than 5% of adverse events reported.

Discussion

In this randomized placebo-controlled phase III trial, there was no evidence that 5 years of planned oral adjuvant therapy with sodium clodronate given to men with no clinical evidence of bone metastases prevents the subsequent development of symptomatic bone metastases. If anything, outcomes were worse in patients allocated to clodronate in terms of symptomatic bone metastases–free survival. There was also no advantage to clodronate in terms of prostate cancer mortality or overall mortality.

There is unquestionably a need to identify and treat men with prostate cancer and occult micrometastatic disease in bone so as to prevent or delay the progression to overt metastatic disease. The role of osteoclasts in mediating metastasis-induced bone destruction in prostate cancer was already clear (30), and bisphosphonates represented a promising class of drugs that was effective at inhibiting

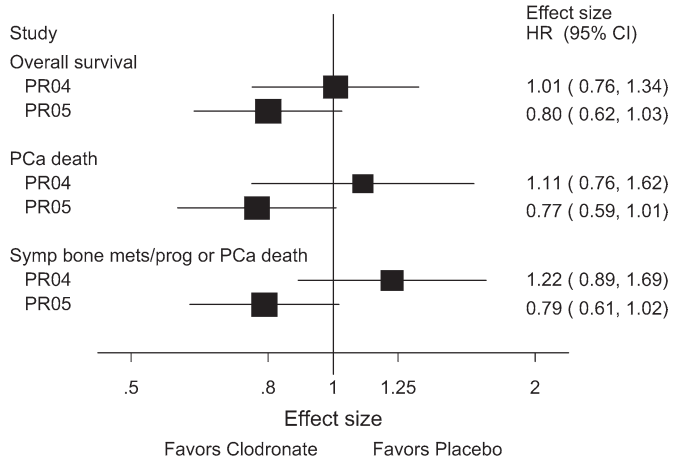

Fig. 5. Forest plots comparing the relative effects in this trial, PR04, and its sister trial, PR05. PR04 included 508 patients with locally advanced disease who received local standard treatment and were randomly assigned to additionally receive 5 years of sodium clodronate or placebo. PR05 (29) included 311 patients with bony metastatic disease who received standard hormone therapy and were randomly assigned to additionally receive 3 years of sodium clodronate or placebo. Three pairs of plots are shown representing the main clinical outcome measures in these trials. The *x*-axis is the hazard ratio (HR) for the comparison, in which a hazard ratio less than 1.0 represents an advantageous effect for the active arm compared with the placebo arm. The **box** represents the point estimate of the hazard ratio, the lines are the 95% confidence intervals (CIs), and the **size of the box** is proportional to the number of events. There is some evidence of heterogeneity of effect between the trials for these outcome measures: for overall survival, heterogeneity $\chi^2_{(1df)} = 1.41$, $P = .23$; for prostate cancer death, heterogeneity $\chi^2_{(1df)} = 2.32$, $P = .13$; for symptomatic bone metastases/progression (mets/prog) or prostate cancer (PCa) death, heterogeneity $\chi^2_{(1df)} = 4.29$, $P = .038$. These statistics were determined using two-sided tests.

osteoclast-mediated bone resorption (22). In the early 1990s, it was believed that patients who were initially diagnosed with T2 through T4, N0/NX/N+, M0 prostate cancer represented a group of patients with approximately 40% risk of developing bone metastases at 5 years after diagnosis, i.e., 60% event free (28). Also at that time, PSA testing was available only in some hospitals in the United Kingdom, and PSA levels could therefore not be included in defining "high-risk" disease or disease progression. Similarly, only some centers used Gleason grade in histopathologic reporting as standard practice. We recognize that practice has changed in the past 13 years but feel that the results of this trial remain clinically relevant and interpretable.

Clodronate was given using the Loron520 preparation at a total dose of 2080 mg/day, which is bioequivalent to 3200 mg/day of the other available preparation of sodium clodronate (Bonefos) (31). In designing the trial, this dose was thought to be the maximum attainable and was twice that selected for the adjuvant trials in breast cancer. Drug-related toxicity in this trial was indeed acceptable (most commonly reported were gastrointestinal problems or an asymptomatic rise in LDH), and any side effects abated with reduction in dosage or cessation of clodronate. Nevertheless, higher doses would likely have been impractical. Adverse events in both arms commonly led to modification of the trial medication dose (by 2 years: active, 35%; placebo, 24%), and the need to modify dose was taken to indicate severity and/or seriousness and/or relatedness to the trial drug itself. The reported occurrence of adverse events was fairly high in the placebo arm, even for gastrointestinal events, although these events were more common in the active arm. This trial was designed in a double-blind placebo-controlled manner to guard against biased reporting of adverse events in one arm; there was no indication that blinding was broken. The prevalence and incidence of adverse events in the placebo arm was striking and reinforces the value of placebo as a tool for protecting against the reporting bias common to open-label studies.

The results from MRC PR04 are in contrast to those seen in some trials of similar design in breast cancer. Breast cancer, like prostate cancer, is a hormone-dependent malignancy in which bone metastases are common, although these are not as strikingly exclusive or as predominantly sclerotic as those in prostate cancer. Two studies using adjuvant clodronate in breast cancer showed reductions in the rate of bone metastases and an improvement in overall survival (20,32,33). However, a third study (21) showed no reduction in the rate of developing bone metastases and no survival benefit with clodronate. The benefits of adjuvant clodronate in breast cancer, although likely, have not been proven (21). Any explanation of our results purely in terms of drug potency and bioavailability must account for those positive results in breast cancer trials, especially because the doses of clodronate used in our trial were equivalent to double those used in the breast cancer studies. This dosage might reasonably have been expected to mitigate against the effects of low potency and oral bioavailability, and other factors probably have a role in determining the results in prostate cancer.

What could these other factors be? First, the selection of patients for inclusion in this trial was, by today's standards, fairly loose. As a consequence, the event rate seen in this study was lower than expected, and by 5 years, 82% of patients remained primary endpoint free as opposed to the 60% primary outcome measure–free expected. It may be argued that, biologically, today's T2 through T4, N0/NX, M0 patient is very different from such a patient seen and diagnosed in the 1980s as a result of stage migration from better imaging, PSA testing, and pathologic examination. However, any biologic differences would have to be enormous in magnitude to account for the failure of clodronate to benefit the patients in this study. Second, prostate cancer may, indeed, be biologically different from breast cancer and perhaps other solid cancers in that, although the osteoclast plays an important role in the behavior of established bone metastases, osteoclast inhibition may not affect the natural history of prostatic micrometastatic disease in bone. The differences between the outcomes of this study and the MRC PR05 study would also argue that there may be important differences in the impact of clodronate in the clinically nonmetastatic and metastatic patient. Formal comparisons of the two trials indicated that there are, indeed, statistically significant quantitative differences between their results. Indeed, the Zometa 704 study (34), a randomized controlled trial comparing zoledronic acid 4 mg versus placebo in men with progressive, hormone-refractory, nonmetastatic prostate cancer, showed no differences in time to development of bone metastases, although the trial was terminated early with 398 patients enrolled due to a lower than expected number of events.

The rate of occurrence of symptomatic bone metastases in this trial was also lower than expected, and symptomatic bone metastases were not the most commonly reported first disease event. The most

common first event was local progression, although we suspect that, in the early days of PSA reporting covered by this trial, some PSA failures were erroneously reported as local progression. Many patients reported starting hormone therapy without reporting symptomatic bone metastases. One possibility is that earlier disease progression (notably, unreported PSA failure) in the placebo arm led to an earlier start of androgen deprivation, which in turn led to an improvement in the primary outcome measure. PSA levels were not collected prospectively during follow-up, but for the purpose of exploratory analyses, the complete PSA histories of patients from the two largest centers were retrospectively collected. These data were only used for indicative purposes and was treated in an exploratory fashion, especially because no guidelines for PSA collection, PSA failure, and postfailure treatment had been defined for this trial. However, examining PSA failure specifically and discounting any other disease progression events, the results with clodronate remained unfavorable (HR = 1.62, 95% CI = 1.16 to 2.25). With regard to the choice of outcome measures, there is debate about how best to assess bone metastases.

Asymptomatic bone metastases may not, in general, be a good surrogate for survival, although they have been used as a more objective endpoint than symptomatic bone metastases. However, we would argue for the inclusion of symptomatic bone metastases as endpoints of choice in clinical trials. Asymptomatic bone metastases may not be clinically relevant, e.g., does it matter if time to asymptomatic bone metastases is improved if there is no improvement in time to symptomatic bone metastases? If symptomatic bone metastases are used as study endpoints, it would be desirable to achieve consensus on their definition so that valid comparisons between trials can be made. One possible way to encompass both views would be to obtain routine bone scans in asymptomatic patients but for both the patient and the investigator to remain blind to the results, so that a symptomatic endpoint is not compromised. Blinded estimation of CA125, a blood biomarker for ovarian cancer and somewhat akin to PSA in terms of its use for diagnosis and disease monitoring, is being successfully undertaken in an ongoing MRC trial (MRC OV05, European Organisation for Research and Treatment of Cancer [EORTC] 55955 [ISRCTN87786644]). The successful recruitment to MRC OV05 shows that blinded estimation of clinical investigations are possible in trials and that such an evaluation in prostate cancer may be feasible. Regardless, the inherent difficulties of bone endpoints should not detract from the use of a double-blind randomized controlled trial design as the gold standard, even in a disease like prostate cancer, for which the analyses might be performed many years later, when clinical management may have changed substantially. In addition, with large-scale clinical databases available to inform prognostic nomograms, patients can be selected more appropriately, so that "low-risk" patients can be excluded from metastasis prevention studies.

The trial has several potential limitations. Two of the most important disease measures (Gleason score and serial PSA level) were not available; the trial cohort was heterogeneous and not all these patients may have needed "adjuvant" treatment according to current practice; treatments other than those initiated for clinical disease progression were not reported; the sister study in metastatic disease recorded and saw improved time to deterioration in WHO performance status, but this was not collected here; the exact date of stopping trial medication was not reported; and standards of defining, collecting, and summarizing adverse events and toxic effects were poorer than those in use currently.

One strength of this trial was the review of cause of deaths independent of allocated treatment. All deaths were reviewed because many patients with prostate cancers have comorbidities and often die from nonprostate cancer causes. The contribution of prostate cancer to the patient's death is often not apparent. Therefore, the review was based on information reported on the standard case report forms and supplemented using the registered causes of death supplied through the NHSCR. In the cause-of-death review, each patient was classified as having died from prostate cancer or from nonprostate cancer causes (Supplementary Table 1, available online). This methodology will be helpful for future trials. We note that the lack of treatment effect was similar in terms of both prostate cancer death (HR = 1.07) and nonprostate cancer death (HR = 0.96).

Further data addressing bisphosphonates are available from patients with hormone-refractory prostate cancer. The largest phase III trial to date (35) of bisphosphonates in prostate cancer included 643 men with bone metastases and hormone-refractory disease. Men were randomly assigned to intravenous placebo or to one of two doses of the intravenous third-generation, nitrogen-containing bisphosphonate zoledronic acid, which is 50 times more potent than clodronate. Skeletal-related events were statistically significantly reduced in men receiving the lower dose of zoledronic acid (4 mg; 33% versus 44% with placebo $P = .02$), although a lesser and statistically nonsignificant effect was observed for the higher-dose zoledronic acid group (39% zoledronic acid 8 mg versus 44% placebo $P = .22$) (36). There was some improvement in pain control in the zoledronic acid groups, but there was no difference in clinical disease progression, quality-of-life indices, or performance status between randomized groups. Zoledronic acid caused a statistically significant reduction in markers of bone resorption compared with placebo, and bone alkaline phosphatase (a marker of osteoblastic activity) stabilized rather than falling in the zoledronic acid group and rose in the placebo group.

It remains controversial whether osteoclast activation is a necessary precursor for the development of osteoblastic lesions or occurs in consequence of osteoblastic metastases (37–41). The former hypothesis that suggests that bisphosphonates might have a role in the prevention of osteoblastic bone metastases, whereas the latter implies the value of bisphosphonates would be restricted to an impact on the progression of established metastases. In this case, other targets, such as osteoprotegerin, interleukin-6, and bone morphogenic proteins (41,42) might prove to be useful additional targets to inhibit the development of osteoblastic lesions.

A recent systematic review (43) suggested that bisphosphonates may have a role in reducing pain and skeletal complications in patients with established bone metastases. What of the future? The question of drug potency needs to be addressed, in light of the reduction in skeletal-related events of zoledronic acid in hormone-refractory metastatic disease. Two ongoing studies (44,45) are examining the role of zoledronic acid as adjuvant therapy in men with metastatic or nonmetastatic disease. In the first (44), conducted by the European Association of Urology, men with high-risk

disease are being randomly assigned to zoledronic acid or placebo. In the second (45), the multiarm, multistage MRC Systemic Therapy for Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial, men starting long-term hormone therapy for newly diagnosed advanced nonmetastatic or metastatic prostate cancer or for previously treated local disease are being randomly assigned to receive hormone therapy alone with or without either zoledronic acid, docetaxel or celecoxib, or a combination of these. Some of the patients who enter STAMPEDE (ISRCTN78818544) would have been eligible for either the PR04 or PR05 trials. Furthermore, new drugs, such as RANK-L inhibitors that can target the osteoclast with ever-increasing sophistication (46), are waiting in the wings. Success in targeting the osteoclast is probably assured, but the benefits of such targeting in the adjuvant setting need to be further evaluated.

In conclusion, in the MRC PR04 trial, no benefit for adjuvant therapy with oral clodronate was observed in men with nonmetastatic prostate cancer in terms of modification of the natural history of their disease. Sodium clodronate should not be further used in trials in the adjuvant setting, but more potent bisphosphonates should be investigated.

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