

Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials

Prostate Cancer Trialists' Collaborative Group*

Summary

Background In advanced prostate cancer, androgen suppression (AS) by surgery or drugs controls testicular hormone secretion, and the further addition of an antiandrogen such as nilutamide, flutamide, or cyproterone acetate is referred to as maximum androgen blockade (MAB). The aim of this overview was to compare the effects on the duration of survival of MAB and of AS alone.

Methods The collaborative meta-analysis of 27 randomised trials involved central reanalysis of the data on each of 8275 men (98% of those ever randomised in trials of MAB vs AS) with metastatic (88%) or locally advanced (12%) prostate cancer. Half were over 70 years of age, and follow-up was typically for about 5 years.

Findings 5932 (72%) men have died; of the deaths for which causes were provided, about 80% were attributed to prostate cancer. 5-year survival was 25.4% with MAB versus 23.6% with AS alone, a non-significant gain of 1.8% (SE 1.3; logrank $2p=0.11$). There was no significant heterogeneity in the treatment effect (MAB vs AS) with respect to age or disease stage. The results for cyproterone acetate, which accounted for only a fifth of the evidence, appeared slightly unfavourable to MAB (5-year survival 15.4% MAB vs 18.1% AS alone; difference $-2.8%$ [SE 2.4]; logrank $2p=0.04$ adverse), whereas those for nilutamide and flutamide appeared slightly favourable (5-year survival 27.6% MAB vs 24.7% AS alone; difference 2.9% [SE 1.3]; logrank $2p=0.005$). Non-prostate-cancer deaths (although not clearly significantly affected by treatment) accounted for some of the apparently adverse effects of cyproterone acetate.

Interpretation In advanced prostate cancer, addition of an antiandrogen to AS improved the 5-year survival by about 2% or 3% (depending on whether the analysis includes or excludes the cyproterone acetate trials), but the range of uncertainty as to the true size of this benefit runs from about 0% to about 5%.

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Introduction

In advanced prostate cancer the main systemic treatment is androgen suppression (AS), either by surgical castration (orchiectomy) or by long-term use of a luteinising-hormone-releasing-hormone agonist. Testosterone from the testes provides much, but not all, of the normal androgenic activity, and this activity can be eliminated by AS. The low plasma concentrations of androgens that remain after AS, which are chiefly of adrenal origin, could still have some stimulatory effect on any hormone-sensitive parts of the prostate cancer, but any such residual effect can be further reduced by addition of long-term treatment with an antiandrogen such as nilutamide, flutamide, or cyproterone acetate. Such combination of AS with an antiandrogen is referred to as maximum androgen blockade (MAB).

Since the early 1980s, there have been many randomised trials comparing MAB with AS alone but, on average, they involved only a few hundred patients each, allowing wide scope for the play of chance to affect their survival results. Hence, unduly selective emphasis on some of the more favourable (or just on the adverse) trial results could well be misleading. A meta-analysis of all these results would, however, involve much larger numbers than any single trial, thereby not only limiting the play of chance but also discouraging unduly selective emphasis on particular trial results (or on other particular subsets of the overall evidence).

This report is of a collaborative meta-analysis (or overview) of the mortality findings from all the available trials of MAB versus AS in advanced prostate cancer, with central reanalysis of the data from each randomised individual. It includes more studies and longer follow-up than the previous such meta-analysis,¹ and hence involves almost twice as many deaths (plus some information as to which of those deaths were thought not to have been caused by prostate cancer).

Methods

Eligible trials and data sought

All properly randomised trials that began before 1991 and compared MAB with AS alone (where MAB involved AS plus the immediate administration of an antiandrogen that was to be given for at least 1 year, or until progression) were eligible for this overview, irrespective of the type of patient and of whether or not the trial had been published. The requirement that treatment last at least 1 year was to exclude short-term studies of the hormonal rather than clinical effects of MAB; such studies would be small and uninformative about survival, and might well be difficult to review thoroughly enough to avoid introduction of selective bias. Moreover, even if such studies had followed up mortality, short-term treatment might have less effect on survival duration than longer-term treatment would.

The methods of trial identification have been described previously and included searches of electronic databases (keywords: prosta*, neoplasm), trial registers, meeting abstracts, and reference lists, plus discussions with the relevant investigators and pharmaceutical companies.^{1,2} The information requested on each randomised patient included stage of disease, age at randomisation,

*Information about collaborators is given at the end of the paper

Correspondence to: PCTCG Secretariat, Biometrics Department, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, Netherlands

Ref	Start year	Study name	MAB regimen*	AS regimen	Number of men
Trials with nilutamide—1688 men (20%)					
10	1983	F/82/908/03	Orchiectomy+N 150/300 (24)	Orchiectomy+placebo	191
11	1983	F/82/908/01	Orchiectomy or buserelin+N 300 (24)	Orchiectomy or buserelin+placebo	208
12	1984	CDN/83/908/05	Orchiectomy+N 300 (24)	Orchiectomy+placebo	208
13	1984	F/84/908/01	Orchiectomy+N 300 (24)	Orchiectomy+placebo	151
14	1985	ZA/85/908/02	Orchiectomy+N 300 (24)	Orchiectomy+placebo	11
15	1986	FF/86/908/01	Orchiectomy+N 150 (18)†	Orchiectomy+placebo	457
16	1986	CH/85/908/05	Orchiectomy+N 300 (24)	Orchiectomy+placebo	51
17	1986	GHBA-606	Leuprolide+N 150 (18)†	Leuprolide/placebo	411
Trials with flutamide—4803 men (57%)					
18	1985	NCl/INT-0036	Leuprolide+F 750	Leuprolide+placebo	617
19	1985	118, 630/1511/WPSG	Orchiectomy or goserelin+F 750	Orchiectomy or goserelin	110
20	1986	118, 630/1509/IPCSG	Goserelin+F 750	Goserelin	586
21	1986	EORTC-30853	Goserelin+F 750	Orchiectomy	327
22	1986	DAPROCA	Goserelin+F 750	Orchiectomy	262
23	1986	118, 630/1507	Goserelin+F 750	Orchiectomy+placebo	245
24	1986	M85712	Orchiectomy+F 750 (24)	Orchiectomy+placebo	223
25	1986	M85713	Orchiectomy+F 750 (24)	Orchiectomy+placebo	330
26	1987	PONCAP	Goserelin+F 750	Goserelin	319
27	1987	Modena	Buserelin+F 750	Buserelin	122
28	1988	NCl/INT-0105	Orchiectomy+F 750	Orchiectomy+placebo	1385
29	1989	Varese	Leuprolide+F 750	Leuprolide+Fx15 days	277
Trials with cyproterone acetate—1784 men (21%)					
30	1981	EORTC 30805	Orchiectomy+CPA 150	Orchiectomy	238
31	1984	118, 630/1502	Goserelin+CPA 200	Goserelin	195
31	1984	118, 630/1503	Goserelin+CPA 200	Goserelin	133
32	1984	EORTC-30843	Orchiectomy or buserelin+CPA 150	Orchiectomy or buserelin+CPAx14 days	368
33	1984	SPCG-2	Orchiectomy+CPA 150 (36)	Orchiectomy+placebo	285
34	1986	BPCRG1/SCH-262	Goserelin+CPA 300	Goserelin	343
35	1888	SAG-87168	Decapeptyl+CPA 100 (36)	Decapeptyl+placebo	222
Trials with data unavailable—183 men (2%)					
36	1990	WGH-1	Orchiectomy+F 750	Orchiectomy	20
37	1971	Hamburg-1	Orchiectomy+CPA 300	Orchiectomy+placebo	77
38	1977	Hamburg-2	Orchiectomy+CPA 100	Orchiectomy+placebo	42
39	1987	RPMS-2	Orchiectomy+CPA 300	Orchiectomy	44

*Antiandrogen dose is given in mg/day and treatment duration (months) is given in parentheses, unless until progression; N=nilutamide; F=flutamide; CPA=cyproterone acetate.
†N 300 mg/day for first month.

Table 1: Randomised trials of MAB vs AS in advanced prostate cancer

date of randomisation, treatment assigned, date of last follow-up, date of death, and (when available) cause of death. Updated information was requested for trials that had already been included in the first cycle of this overview.

Statistical methods

The statistical methods for meta-analyses of survival duration are standard and described elsewhere.^{3,4} The logrank “Observed minus Expected” (O-E) statistic and its variance (V) were calculated (by use, for the first time, of exact dates of randomisation and of death: previous logrank analyses¹ had used only year of follow-up) for each trial separately, thereby allowing fully for any differences in follow-up duration. The analyses were stratified for age-group (<65 years, 65–74 years, ≥75 years, unknown) and stage of disease (definite metastases or no metastases reported at randomisation). This stratification helps the statistical analyses to compare like with like, and to avoid the slight effects of any chance differences between MAB and AS groups at the time of randomisation. These logrank mortality statistics, one per trial, were then added together to provide an overall comparison of MAB versus AS. A negative value for the logrank O-E statistic favours MAB, because it indicates fewer deaths observed with MAB than expected from the experience of both groups together. Patients were analysed according to the treatment to which they had been randomly assigned, irrespective of what treatment they actually received (“intention-to-treat analysis”). Treatment effects are presented either as pairs of survival curves or as ratios of daily death rates (MAB vs AS), together with their standard errors (SEs). The one-step formula $\exp([O-E]/V)$ was used to calculate the ratio of death rates. The main analyses are of all-cause mortality but, in subsidiary analyses, any deaths described as not being due to prostate cancer were analysed separately (with the remaining deaths analysed by logrank subtraction⁵). Two trials were not randomised evenly; both involved three-way comparisons (two MAB vs one AS or one MAB vs two AS). To maintain balance, the AS groups in these trials were counted double or half in the AS total of deaths/patients, yielding

“adjusted AS” results. No such adjustment was made, or needed, for the logrank analyses. The ratio (Z) of the logrank statistic to the square root of its variance is used to test statistical significance. Two-sided p values (2p) are used throughout, except in heterogeneity tests on more than 1 degree of freedom (where they are not appropriate).

Results

Trials and information available

36 trials that were apparently relevant were identified. However, on further investigation one⁵ was found not to be randomised and four^{6–9} gave the antiandrogen for less than 1 year. The 31 eligible trials are listed in table 1.^{10–39} For four of the trials^{36–39} data could not be obtained, but these small trials included only 183 patients (2% of the total). Individual patients’ data were obtained from the remaining 27 trials, involving 8275 patients (98% of the total).

Most of the patients took part in the 12 trials of flutamide (4803 men), with smaller numbers in the trials of nilutamide (1688 men) and cyproterone acetate (1784 men). Updated follow-up information was obtained for 13 of the 22 trials included in the previous cycle of this overview,¹ and data were provided for the first time from five additional trials, including two for which data had previously been requested unsuccessfully, two newly identified trials of cyproterone acetate, and the large SWOG (Southwest Oncology Group) trial of flutamide, which was previously still open.

Treatments tested

The trial protocols specified that the antiandrogen (nilutamide, flutamide, or cyproterone acetate) was to be administered for about 24 months (range 18–36 months) in 12 trials (all eight of the nilutamide trials, plus two of the

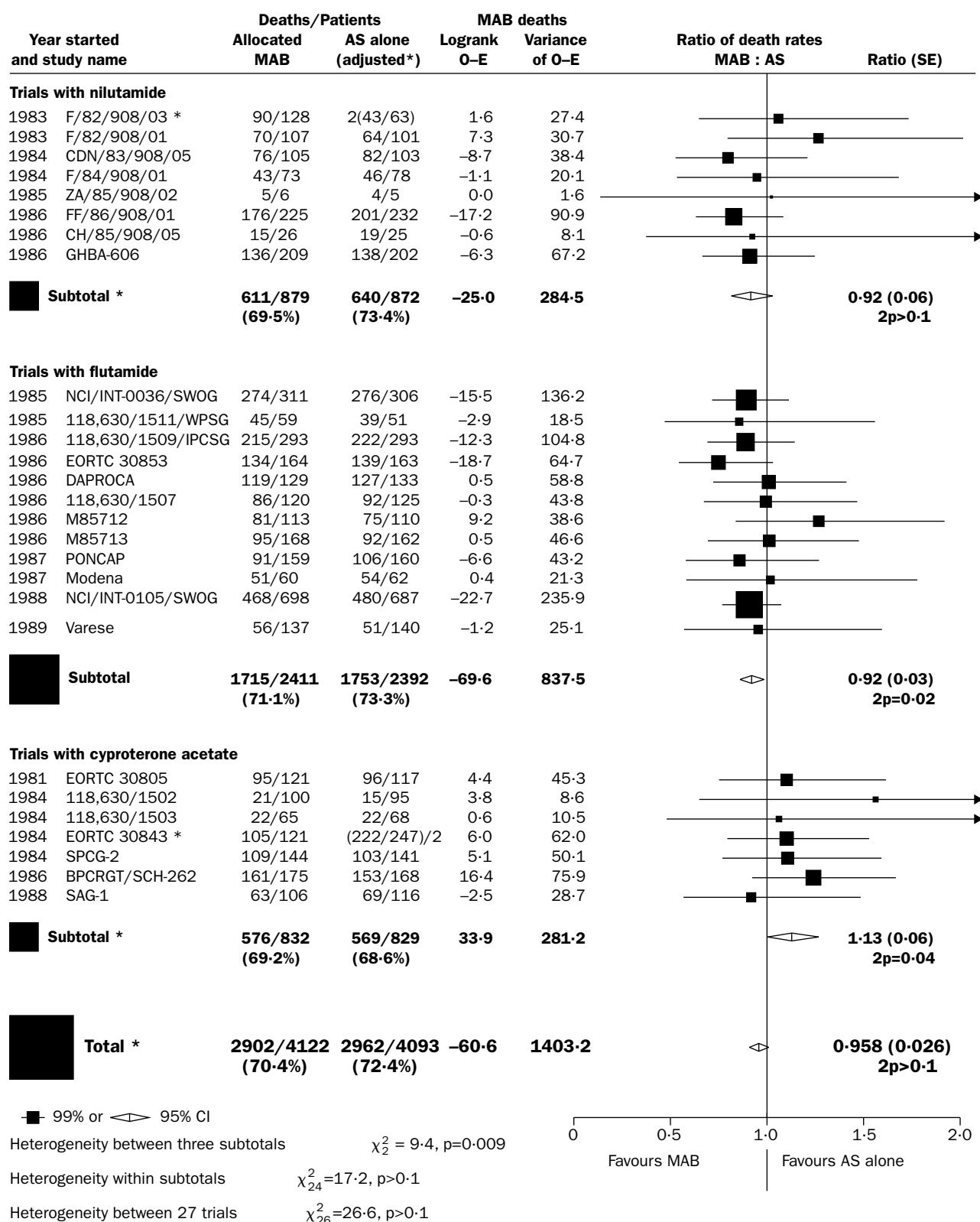


Figure 1: Mortality results from the 27 randomised trials of MAB versus AS alone in advanced prostate cancer

O-E=Observed minus Expected. A black square indicates the ratio of the daily death rates (MAB vs AS), as calculated from the logrank statistics, and the horizontal line gives the corresponding 99% CI. The area of the square is proportional to the amount of information it represents. Ratios less than 1.0 favour MAB and ratios more than 1.0 favour AS alone. A diamond is used to denote the corresponding result and its 95% CI for the total of all trials (and for subtotals). *Adjusted—for balance, control patients in three-way trials count half or twice in subtotals and in the final totals of deaths and patients.

flutamide and two of the cyproterone acetate trials) and until progression of the disease in 15. The maintenance dose of nilutamide was generally 300 mg/day; that of flutamide was 750 mg/day (250 mg three times daily) in all

trials of that drug, and that of cyproterone acetate was generally 150–200 mg/day (range 100–300 mg). In 25 of the trials the method of androgen suppression was the same in the MAB group and in the AS group, but two

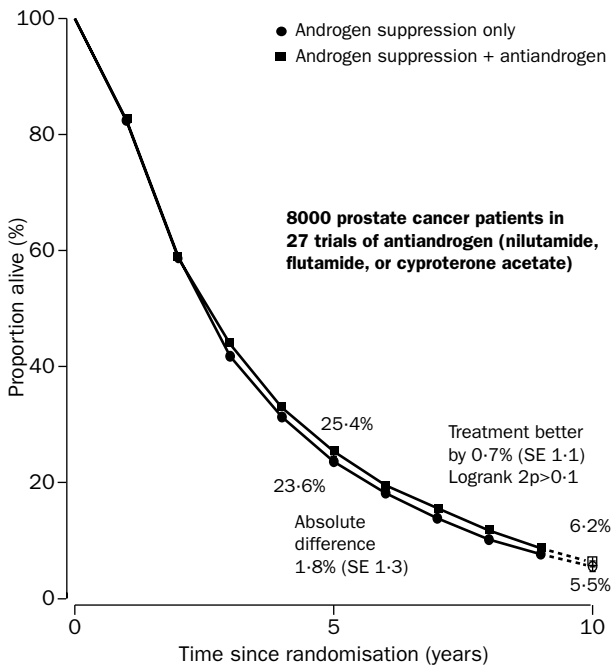


Figure 2: 10-year survival in the 27 randomised trials of MAB versus AS alone

trials compared MAB by drugs alone with AS by orchiectomy.

Mortality

Of just over 8000 men in these 27 trials, almost 6000 are known to have died. Figure 1 presents the mortality results for each separate trial, together with a total for all trials (and three subtotals, for subset analyses). Direct summation of

the numbers of deaths and of patients in the groups allocated MAB yields, in total, 70.4% mortality (2902 deaths among 4122 men) compared with 72.4% mortality (adjusted total 2962/4093) in the groups allocated AS alone. These results indicate an absolute difference of about 2% (difference 2.0% [SE 1.0]; logrank 2p=0.11) in the crude proportions dying. Because the typical follow-up duration was almost 5 years, the crude proportion surviving (29.4%) approximately equals the 5-year survival probability (24.5%).

Figure 2 describes the same results by giving the survival probability at various times after randomisation in the two treatment groups. By 10 years almost all men in both groups will have died, but the 5-year survival was 25.4% with MAB and only 23.6% with AS alone, again suggesting an absolute survival difference of about 2% (1.8% [SE 1.3]). However, the total logrank test in figure 1, which makes use of the mortality data from all periods to compare the patterns of survival with MAB and with AS, shows that the difference is not significant (log-rank total -60.6 with variance 1403.2, indicating a death rate ratio of 0.958 [SE 0.026]; z=1.62, 2p=0.11).

In figure 3 the overall mortality analysis is subdivided by time since randomisation. Although figure 2 indicates no effect on mortality during the first year or two after randomisation (after which the death rate is somewhat lower among those allocated MAB than among those allocated AS), figure 3 shows that the heterogeneity between the four death rate ratios (MAB vs AS) for the four different periods is not significant ($\chi^2_3 = 1.6, p=0.7$). Likewise, the trend in the sizes of these four period-specific treatment effects is not significant. 90% of the information is, however, from the first 5 years after randomisation (years 0-4), with less than 2000 of the 20 000 man-years of follow-up in the overview coming from the period after these 5 years. The

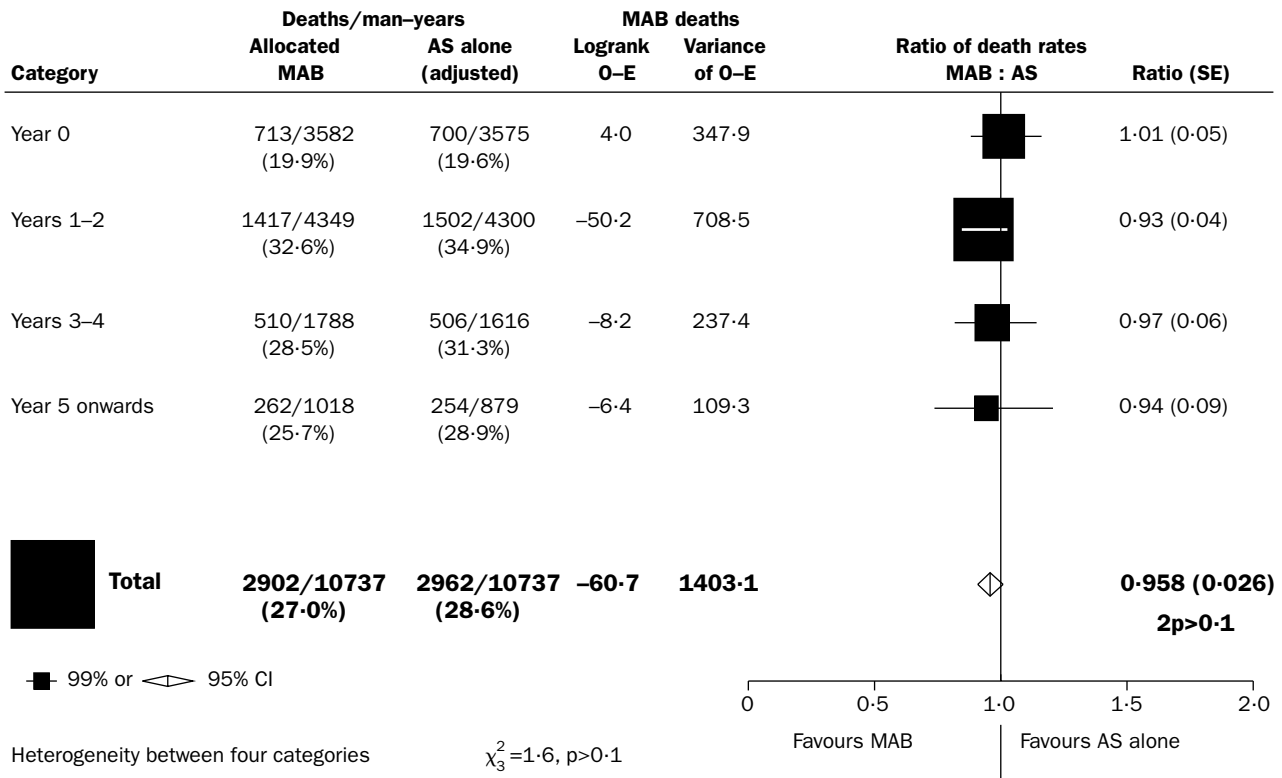


Figure 3: Mortality in the 27 trials of MAB versus AS alone during different periods of follow-up

Numerators are the numbers of deaths occurring in each time period, denominators are man-years. The logrank statistics relate deaths within each period to the numbers then at risk.

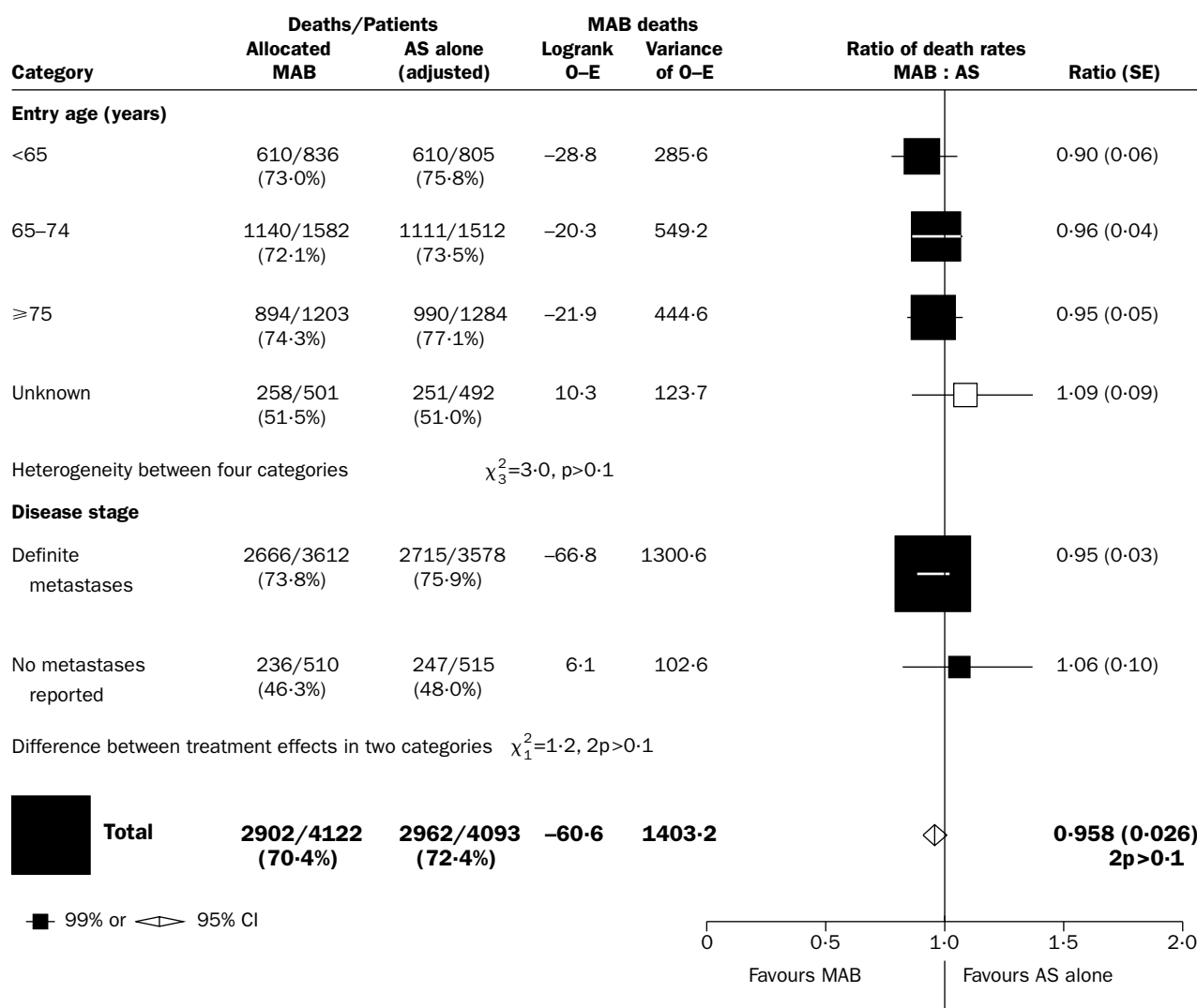


Figure 4: Mortality in the 27 trials of MAB versus AS alone, subdivided by age and by stage of disease

denominators in figure 3 are man-years, so the percentages are the death rates per man-year; on average, the all-cause death rate is about 25% per year.

Analyses of various subsets

For comparisons of the treatment effects in different subsets of the trials or patients, the death rate ratios (MAB *vs* AS) in particular subsets are used. Figure 2 illustrates the meaning of a death rate ratio of 0.96, the overall result for all trials; this ratio corresponds to an absolute difference of almost 2% in the 5-year survival. Likewise, the death rate ratios of 0.92 in particular subsets of the trials in figure 1 correspond to an absolute difference of about 3% in the 5-year survival.

If testicular androgen production is suppressed by orchiectomy, the suppression is complete and permanent, whereas pharmacologically produced suppression may not be complete and permanent and may therefore allow greater scope for improvement in the hormonal treatment by the addition of an antiandrogen. From table 1 and figure 1, however, it can be calculated that the death rate ratio (MAB *vs* AS) was 0.96 for the 11 trials in which AS was produced by orchiectomy only and 0.96 in the 16 other trials, indicating no heterogeneity of effect.

Overall mortality in the different age and stage subgroups is shown in figure 4. The crude mortality was similar in middle age and in old age, because in each age-group most

of the deaths were due to the prostate cancer. Hence, as might be expected, there is no evidence of heterogeneity of the treatment effect among the three age-groups; there are non-significant death rate ratios (MAB *vs* AS) of 0.90 (SE 0.06) in men aged less than 65 years, 0.96 (SE 0.04) in men aged 65-74 years, and 0.95 (SE 0.05) in men aged 75 years or older.

Most of the trials were designed to include only patients with metastatic disease, and only 12% of the men in this overview were classified as having locally advanced disease without any record of definite metastases at the time of randomisation. Moreover, the crude mortality was higher in those with metastatic disease than in those with no metastases reported, so 92% of all deaths were in men with metastatic disease. Hence, the treatment effect in men with metastatic disease was almost the same as that in all men. Among the 1000 men with no metastases reported (half of whom are known to have died) the overall mortality was slightly, but not significantly, higher with MAB than with AS alone (death rate ratio 1.06 [SE 0.10; 95% CI 0.87-1.29]).

Non-prostate-cancer deaths

No information about causes of death was available for seven trials (six of flutamide, one of cyproterone acetate), chiefly because this information was not recorded. In the other 20

Study name	Non-prostate cancer deaths		logrank O-E	Variance of O-E
	MAB	AS alone		
Nilutamide trials				
F/82/908/03	13	2×6*	0.3	3.8
F/82/908/01	15	16	2.1	7.1
CDN/83/908/05	8	9	-1.2	4.1
F/84/908/01	12	18	-1.9	6.4
ZA/85/908/02	0	2	-0.6	0.2
FF/86/908/01	49	45	2.0	22.8
CH/85/908/05	4	3	0.6	1.7
GHBA-606	36	38	-3.2	17.8
Subtotal	137/879	143/872	-1.9	63.8
Flutamide trials				
118,630/1511	10	9	0.2	4.5
118,630/1509	50	64	-7.1	27.5
EORTC-30853	22	16	0.8	9.1
DAPROCA	18	21	-0.1	9.2
118,630/1507	20	15	2.8	8.7
Varese	7	8	-0.9	3.7
Subtotal†	127/902	133/905	-4.2	62.9
Cyproterone acetate trials				
EORTC 30805	17	13	2.9	6.9
118,630/1502	4	1	1.6	1.2
118,630/1503	8	4	2.1	3.0
EORTC-30843	16	33/2*	1.1	9.6
SPCG-2	25	21	3.4	10.3
SAG-87168	11	11	0.6	4.3
Subtotal‡	81/657	67/661	11.7	35.3‡
Total†	345/2438	343/2438	5.6	162.0

*For balance, control patients in three-way trials count half or twice in totals.

†Omission of seven trials without data on causes: six flutamide trials^{18,24-26} (2996 men) and one trial of cyproterone acetate³⁴ (343 men). ‡2p=0.05. All other subtotals not significant. Heterogeneity between three subtotals $\chi^2_3=4.0$, p=0.14.

Table 2: Causes of death other than prostate cancer

trials, 697 (20%) of the 3475 deaths were reported to be due to causes other than prostate cancer. There must, of course, be many deaths for which the cause was uncertain, and finer division of the non-prostate-cancer deaths into specific causes was, in general, not possible. However, in these 20 trials age was strongly predictive of the risk of death only from non-prostate-cancer causes (with 7%, 13%, and 21% mortality in men aged less than 65 years, 65–74 years, and 75 years and older) and was not predictive of death from prostate cancer, so our classification of causes has some validity.

Table 2 presents logrank analyses of the deaths attributed to causes other than prostate cancer in these 20 trials. Overall, there was a slight, non-significant excess of non-prostate-cancer deaths among the men allocated MAB (logrank O-E=5.6 with variance 162.0; 2p=0.7). This excess with MAB was not significantly related to age, disease stage, or follow-up year (although there were 118 MAB vs 104 AS non-prostate-cancer deaths in year 0), so omission of such deaths would have made no material difference to the analyses of age, disease stage, or follow-up period in figures 3 and 4. Likewise, the slight excess of non-prostate-cancer deaths was not significantly related to the antiandrogen used (test for heterogeneity between effects of nilutamide, flutamide, and cyproterone acetate in table 2, $\chi^2_2=4.0$, p=0.14). Of the cyproterone acetate trials, only two provided information on cardiovascular deaths (13 MAB vs nine AS in EORTC 30805, 11 vs 26/2 in EORTC 30843). This small amount of information does not indicate any net cardiovascular hazard.

Effects of the three different antiandrogens

Although the heterogeneity between the three subtotals in table 2 is not significant, an apparent excess of non-prostate-cancer deaths was seen in the trials of cyproterone acetate, but not in those of nilutamide or flutamide. If, therefore (by

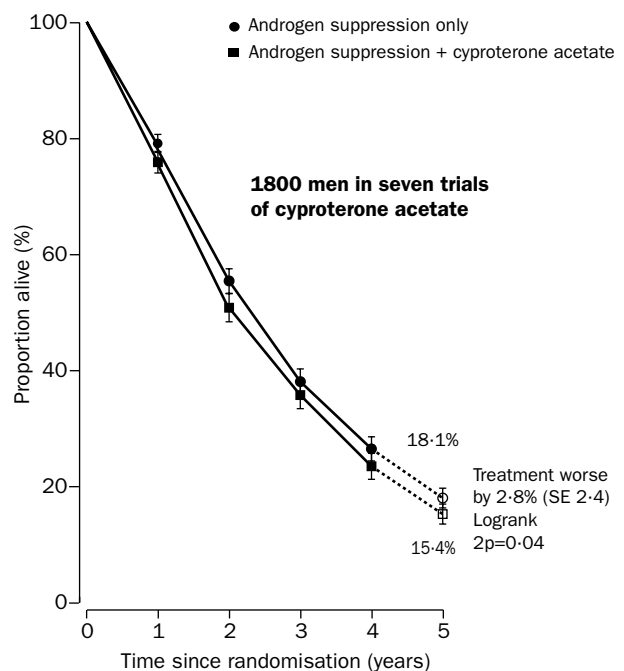
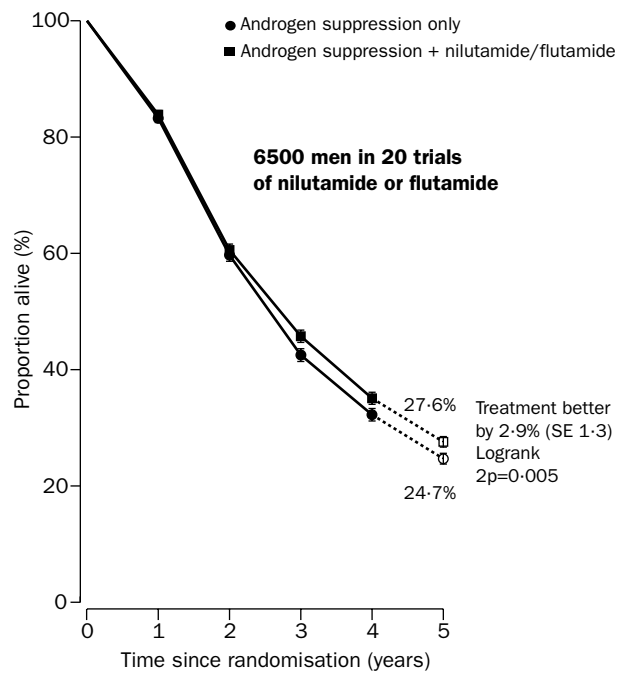


Figure 5: 5-year survival curves for 20 trials of AS plus nilutamide or flutamide versus AS alone, and seven trials of AS plus cyproterone acetate versus AS alone

logrank subtraction) the results for non-prostate-cancer deaths in table 2 are removed from those for overall mortality in figure 1, the remaining results (which would chiefly involve prostate cancer) become slightly more favourable to MAB, although the benefit is still not conventionally significant (O-E=-66.2 with variance 1241.2; $z=1.88$, 2p=0.06), and the apparent heterogeneity between the effects of the three antiandrogens becomes less extreme ($\chi^2_2=6.4$, p=0.04) than in the analysis shown in figure 1. A third of the apparent excess mortality in figure 1 among men allocated cyproterone acetate was accounted for by this slight excess of death from causes other than prostate cancer.

In figure 1 the death rate ratios (MAB *vs* AS) for the effects on overall mortality of the three different antiandrogens were 0.92 (SE 0.06; 2p=0.14) for nilutamide, 0.92 (SE 0.03; 2p=0.02) for flutamide, and 1.13 (SE 0.06; 2p=0.04 adverse) for cyproterone acetate. The separate analyses of the non-prostate-cancer deaths and the other deaths indicate, however, that although the heterogeneity between these three results is significant ($\chi^2=9.4$, p=0.009), the apparently adverse result for cyproterone acetate may be largely or wholly due to a chance adverse effect on the non-prostate-cancer deaths plus a chance adverse effect on the other deaths. If so, for all three drugs the appropriate analysis may be that of figure 2, which indicates a non-significant gain of only 2% in the 5-year survival. If, however, flutamide or nilutamide really do produce better survival than cyproterone acetate, separate analyses are appropriate. Survival curves for the trials that used a pure antiandrogen (nilutamide or flutamide) and for those that used cyproterone acetate are shown in figure 5. MAB is associated with a 3% increase in 5-year survival in the trials of nilutamide or flutamide (27.6% MAB *vs* 24.7% AS; difference 2.9% [SE 1.3], logrank 2p=0.005), but with a 3% decrease in 5-year survival in the trials of cyproterone acetate (15.4% MAB *vs* 18.1% AS; difference -2.8% [SE 2.4], logrank 2p=0.04). The absolute benefit indicated by the pair of survival curves for MAB versus AS is similar for the trials of nilutamide and those of flutamide (death rate ratio 0.92 for each drug; figure 1) and the survival curves for nilutamide trials and for flutamide trials are not shown separately.

Discussion

These results, which involve 98% of the worldwide randomised evidence, suggest that, in advanced prostate cancer, the addition of an antiandrogen will improve the absolute 5-year survival by about 2% or 3%, with a range of uncertainty that runs from about 0% to about 5%. One particular difficulty in interpreting these results is the question of whether, as originally intended, to base inference on all trials (in which case the survival difference is not conventionally significant, and the apparent benefit of 2% has a 95% CI of 0-4), or whether, in the light of the apparently slightly adverse results for cyproterone acetate, to exclude the trials of that drug (in which case the apparent survival difference in the trials of flutamide or nilutamide is 3%, with a 95% CI of 0.4-5.4). Some may prefer to emphasise the overall findings, and conclude that these trials suggest an absolute benefit of about 2% that is not clearly significant. Others⁴⁰⁻⁴² may prefer to emphasise the results just for flutamide or nilutamide (or just for flutamide), concluding that these trials suggest an absolute benefit of 3%, albeit with a lower confidence limit that only just exceeds zero. The appropriate conclusion seems to be that although the real survival difference could well be anywhere from about 0% to 5%, the effects on survival cannot be substantially worse for MAB than for AS, the gain in 5-year survival with MAB cannot be much better than 5%, and it may well be only about 2% or 3%, irrespective of whether AS was achieved by drugs or by orchiectomy.

One particular limitation is that most of the evidence was from patients who already had definite metastases when randomised, and some investigators have hypothesised that the benefits of MAB might be larger in other types of patient.^{14,18,21} The results for patients without any record of metastases were, however, slightly worse for MAB than for AS alone, although only about 1000 such patients were

randomised so there is still a possibility of benefit among them (95% CI for death rate ratio 0.87-1.29).

Although this overview brought together all available randomised evidence on survival, it did not assess other medical outcomes, quality of life, or treatment costs, and the collaborative group makes no comment on whether, if real, a difference of a few percent in 5-year survival should be considered clinically significant. The chief aim was simply to assess any effects on survival as accurately as possible. In retrospect,^{14,43} excessive optimism about the possible size of the effects of MAB on survival can be seen to have led to trials that were too small to demonstrate or refute realistically moderate differences of just a few percent in 5-year survival. Trials of future hypotheses about such improvements in survival duration should ideally randomise several thousand patients with prostate cancer, to minimise the risk of a false-negative result. Nevertheless, it is important not to let excessive pessimism replace excessive optimism. If, after AS in advanced prostate cancer, the addition of an antiandrogen for 2 or 3 years does produce an improvement of about 2% or 3% in overall survival, more effective hormonal regimens might produce somewhat greater absolute benefits, particularly if ways to identify the prostate cancers most likely to respond to prolonged hormonal treatment become available (as has happened with breast cancer⁴⁴).

PCTCG study organisation

Writing committee—O Dalesio, H van Tinteren (Netherlands Cancer Institute, Amsterdam, Netherlands), M Clarke, R Peto (Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, UK), F H Schröder (Erasmus University, Rotterdam, Netherlands). The writing committee accepts full responsibility for the overall content of this report.

Other members of the Secretariat—I Dechering (Netherlands Cancer Institute, Amsterdam), V Evans, J Godwin (Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford), B A Blumenstein (Fred Hutchinson Cancer Center, Seattle, WA, USA), E D Crawford (University of Colorado, Denver, CO, USA), L Denis (Middelheim General Hospital, Antwerp, Belgium), R Hall (Freeman Hospital, Newcastle upon Tyne, UK), C Hill (Institut Gustave-Roussy, Villejuif, France), P Iversen (Rigshospitalet, Copenhagen, Denmark), W U Shipley (Massachusetts General Hospital, Boston, MA, USA), M Soloway (University of Miami, Miami, FL, USA), R Sylvester (EORTC Data Center, Brussels, Belgium).

Collaborators—Other collaborators are listed on www.thelancet.com

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