Research article

Finasteride in the treatment of clinical benign prostatic hyperplasia: A systematic review of randomised trials

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Abstract

Background: Benign prostatic hyperplasia affects older men. This systematic review determined efficacy and adverse effects of finasteride.

Review methods: PubMed, the Cochrane Library, reference lists of reports, and reviews were searched for randomised, double-blind trials of finasteride in benign prostatic hyperplasia. Outcomes included symptom score, urinary flow rate, prostate volume, discontinuation, and adverse effects. Relative risk and NNT or NNH were calculated for dichotomous data. Sensitivity analyses assessed influences of baseline symptom severity, initial prostate volume, a dominating trial, and previous interventions.

Results: Three trials had active controls and 19 had placebo. In placebo-controlled trials, 8820 patients received finasteride 5 mg and 5909 placebo over 3–48 months. Over 48 months finasteride produced greater improvements in total symptom score, maximum urinary flow rate, and prostate volume. Significantly more sexual dysfunction, impotence, ejaculation disorder and decreased libido occurred with finasteride at 12 months; the NNH for any sexual dysfunction at 12 months was 14. Significantly fewer men treated with finasteride experienced acute retention or had surgery at 24 or 48 months than with placebo; at 12 months the NNT was 49 (31 to 112) to avoid one acute urinary retention and 31 (21 to 61) to avoid one surgery. Sensitivity analyses showed benefit with finasteride 5 mg to be constant irrespective of the initial prostate volume.

Conclusions: Information from many patients in studies of high quality showed beneficial effects of finasteride in terms of symptoms, flow rate and prostate volume. More utility would result if patient centred outcomes were reported in dichotomous form.

Background

Benign prostatic hyperplasia (BPH) properly describes the histological basis of a diagnosis of prostatic enlargement leading to bladder outflow obstruction that gives rise to symptoms of lower urinary tract obstruction [1]. Symptoms of benign prostatic enlargement occur commonly in older men. In an unselected population of Scottish men prevalence rates increased from 615 per thousand in the fifth decade to 890 per thousand in the eighth decade [2]. With time symptoms generally get worse. Over five years symptom scores in men with predominantly mild symptoms deteriorate by two points [3]. About 18% of men with initially mild symptoms will develop symptoms that are moderate over five years, with about three per thousand becoming severe [3] though severe symptoms can ameliorate with time. Over five years perhaps only 3% of

men with initially mild symptoms might seek treatment [3].

Outcomes chosen in clinical trials of treatments for benign prostatic hyperplasia include not only symptom scores, but maximum urinary flow rate, postvoid volume and prostate volume, as well as clinical outcomes such as acute urinary retention or progression to surgery [4–7]. Changes in these outcomes may occur even without active treatment, with reductions (improvements) in symptoms scores and increases (improvements) in maximum urinary flow rate [8]. For this reason accurate evaluation of potential benefit of interventions for symptomatic BPH require controlled trials of at least two years duration [8].

For many alternative therapies such studies are lacking [4]. Studies of alpha-blockers are generally less than two years [5,9,6]. Studies of interventions like transurethral microwave thermotherapy may have longer follow up of between three and seven years, but the bulk of the information is from nonblinded, uncontrolled studies [10], and in surgical studies men generally have higher initial symptom scores and lower maximum urinary flow rates than is seen in medical interventions.

For finasteride some systematic reviews and meta-analyses already exist [5,11]. A significant proportion of randomised trials of finasteride have lasted one or two years, and at least one large study continued beyond two years [12]. Our aim in this systematic review and meta-analysis was to examine results for the standard dose of 5 mg finasteride according to duration of treatment so that men and their professional advisers would know what to expect, and when, both with and without treatment.

Materials and methods
Searching
PubMed (to April 2001) and the Cochrane Library (Issue 2, 2001) were searched to identify full journal publications of randomised, double blind, placebo and active controlled trials of finasteride in the treatment of benign prostatic hyperplasia. Free text search terms used included 'finasteride', 'proscar', 'clinical trial', and 'benign prostatic hyperplasia'. Systematic reviews of finasteride [5,11] were examined, as was a list of systematic reviews in benign prostatic hyperplasia (additional file 1) for possible references and reference lists of all obtained articles were checked to identify additional trials. Abstracts were not sought. Merck, Sharp and Dohme Ltd, UK, were asked for references of any published randomised trials for finasteride in the context of benign prostatic hyperplasia. Unpublished studies were not sought.

It was anticipated that patient information from major trials may have been published more than once, in part or in full, as information became available from longer use of finasteride. For each trial, the study that provided the fullest amount of information was included in the systematic review and any duplicated information was excluded. Duplicate studies were checked to ensure that relevant information for a particular outcome described in an excluded study was not missing from the included trial. A number of trials had an open-label extension in which men received finasteride only; no open-label information was analysed because the pre-hoc decision was to analyse only information from trials that were both randomised and double blind.

Each report which could possibly be described as a randomised controlled trial was read independently by both authors and scored using a commonly-used, three item, 1–5 score, quality scale [13]. Disagreements were discussed and consensus achieved. The maximum score of an included study was 5 and the minimum score was 2.

Outcomes were abstracted after discussion with a panel of two urologists and three general practitioners with an interest in urology to discuss outcomes likely to be of professional or patient interest. Information extracted from the double blind trials included: (i) number of men on finasteride and placebo, (ii) symptom score (total, obstructive, bother), (iii) prostate volume, (iv) urinary flow rate (maximum, mean), (v) discontinuation (total discontinuations, discontinuations because of lack of efficacy, discontinuations because of adverse effects), (vi) information on adverse effects including episodes of acute urinary retention and prostate surgery, (vii) prostate specific antigen (PSA), (viii) residual volume and (ix) total voided volume. Absolute values and/or mean or median values (with dispersion) were extracted. When provided, this information was extracted for the following time-points regardless of whether it was an intermediate or final assessment: baseline and 3, 6, 12, 18, 24, 36 and 48 months of treatment. The type of symptom score used was noted.

Analysis of data
Not all men in a trial may have had each outcome assessed (e.g. prostate volume), or men may have discontinued. For efficacy analyses, therefore, the number of men for which information was available at a particular point in time was used if this differed from the number randomised; because results were rarely dichotomous, an intention-to-treat analysis was impossible for any beneficial outcome. For analysis of adverse effects and discontinuations, the number of men randomised to treatment was used to provide an intention-to-treat analysis.

When possible, patient information from different studies was pooled. The objective was to enter any continuous

data in Review Manager (RevMan version 4.01; Update Software, Oxford), to calculate weighted mean difference from baseline for finasteride and for placebo, to generate standard deviations or 95% confidence intervals, and to determine statistical significance of differences between treatments at various time points. Weighted mean values (by group size) for continuous outcomes were calculated using Excel:mac 2001 on a Macintosh G4.

When dichotomous information was available, relative risk estimates, with 95% confidence intervals, were calculated using a fixed effects model [14]. A statistically significant difference between active treatment and placebo was assumed when the 95% confidence intervals (CI) of the relative risk did not include unity. Numbers-needed-to-treat, with 95% confidence intervals, were calculated [15]. The confidence interval of the NNT includes no benefit of one treatment over the other when the upper limit includes infinity. NNT is the reciprocal of the absolute risk reduction or increase; for instance, if 75 out of 100 men benefit with treatment and only 25 out of 100 benefit with placebo, the absolute risk increase is 0.75–0.25 = 0.5, and the NNT is 1/0.5 = 2.

Neither heterogeneity tests nor funnel plots were used since they lack the power to reliably detect statistical heterogeneity or publication bias [16–18]. Instead, pre-planned sensitivity analyses were conducted to detect possible variations in effect of study treatments in men with differing aetiology or baseline severity of their condition.

The four sensitivity analyses were:

1. Comparison of differing severity of symptoms at baseline – results of studies which included men with moderate or severe symptoms at baseline were compared with those which also included men with mild symptoms at baseline.

2. Comparison of differing prostate volume at baseline – results of studies which included men with small prostates (mean less than 40 cm^3) were compared with those which included men with large (mean 40 cm^3 or greater) prostates at baseline. The reason for this is that there is some evidence that finasteride is more effective in men with prostate volumes greater than 40 cm^3 [11].

3. Comparison of the results of other trials with those from a dominating single, large, four year, double blind trial (PLESS) [19].

4. Comparison of the results in men without prior interventional treatments and those who may have had a previous stent or balloon dilatation.

Analyses based on fewer than 500 men are not presented in this report, because the results would not be robust [20].

Results
Trials available for analysis
One hundred and one reports were identified as potential randomised trials of finasteride in the treatment of benign prostatic hyperplasia. Several of these were duplicate publications, with or without reference to previous publications. Eighty studies were excluded and reasons are given in additional file 2. Twenty-two double blind randomised trials from 21 reports were included in the systematic review [19,21–40]. Nineteen trials were placebo controlled, and three compared finasteride with another active treatment. Full details of the included studies, with description of men included, study duration, outcomes, and results are shown in additional file 3, and all the baseline characteristics of study groups in additional file 4.

Finasteride 5 mg daily was assessed in all included trials, though some also included finasteride 1 mg or 10 mg. One trial pooled information from 17 men with finasteride 1 mg and 15 men with finasteride 5 mg [37]; this information was included in the analyses described below.

In placebo controlled trials, 8820 men received finasteride 5 mg given once daily and 5909 men received placebo. Information was available for men followed up for three months in two trials (74 men), six months in nine (366), 12 months in six (6364), 18 months in one (55), 24 months in four (4286), and for 48 months in one (3082). Three trials used an active control; 903 men received finasteride 5 mg once daily, 553 permixon (serenoa repens), and 358 alfluzosin 10 mg daily. Men were followed up for six months in two studies (1870 men) and for 12 months in one trial (489 men). Trials of active comparisons were not followed up further because the comparators were all different and numbers of men were small.

Men included in the trials had a clinical diagnosis of benign prostatic hyperplasia, mostly based on symptoms and urine flow rates. For symptoms, for instance, the American Urological Association symptom scoring scale uses seven questions which can be scored from 0 (no problem) to 5 (severe problem); the scale can be from 0 to 35, split into mild (0–7 points), moderate (8–19 points) or severe (20–35 points) disease. At baseline, symptoms were moderate to severe in 17 trials, and in two studies men with mild symptoms were included. General exclusions in the trials were men with the suggestion of prostate cancer, urinary tract infection, previous prostate surgery, haematuria, or those who required catheterisation for acute urinary retention.

Table 1: Summary of results in the individual randomised, double blind, placebo controlled trials.

Author	Number of patients	Quality score	Duration (months)	ITT or PP	Symptom score	Max urinary flow rate (mL/s)	Prostate volume (cm3)
McConnell et al, 1998 PLESS	3040	4	48	PP	++	++	++
Marbergher et al, 1998 PROWESS	2902	5	24	PP	++	++	++
Byrnes et al, 1995	2417	3	12	ITT	+	No data	
Tenover et al, 1997	2112	3	12	PP	++	No data	
Andersen et al, 1995	707	3	24	PP	++	++	++
Lepor et al, 1996 VA cooperative study.	615	4	12	PP	-	-	++
Nickel et al, 1996 PROSPECT	613	5	24	ITT	++	++	++
Gormley et al, 1992 North American study	598	3	12	ITT	++	++	++
Finasteride study group, 1993 International study	501	3	12	PP	++	+	++
Beisland et al, 1992	182	3	6	ITT	+	+	++
Abrams et al, 1999	121	3	12	PP	-	+	++
Kirby et al, 1992	50	4	3	PP	++	++	-
Yu et al, 1995	50	3	6	PP	+	+	+
Marks et al, 1997	41	4	6	PP	-	-	++
Tammela & Kontturi, 1993	36	3	6	ITT	No data	-	++
Studies with finasteride plus additional interventions							
Lukkarinen et al, 1999	61	3	24	PP	-	-	++
Isotalo et al, 2001	55	4	18	ITT	-	+	++

+ p < 0.05 ++ p < 0.01 – No significant difference between finasteride and placebo ITT Intention to treat analysis – all randomised patients PP Per protocol analysis – may have included men who discontinued treatment

A summary of the included trials, their size at randomisation, quality score, duration, intention-to-treat (by number randomised) or per protocol analysis, and the statistical significance at longest double-blind estimate is given in Table 1. Size varied from 36 to 3040 randomised men; nine trials randomised at least 500 men and four at least 2000. The largest trials were of at least 12 months duration. Most of the larger trials demonstrated a significant superiority of finasteride 5 mg over placebo at the p < 0.01 level for symptom score, maximum urinary flow rate and prostate volume; the notable exception was the VA Cooperative study for symptom scores and maximum urinary flow rate because the inclusion criteria for this study included men with small prostates [31].

Trial reports usually provided dispersion measures (standard deviation, interquartile ranges) at baseline for measures like symptom score, urine flow rate and prostate volume. In almost no case did they provide standard deviations or 95% confidence intervals for intermediate and/or final assessment for these outcome data. Consequently statistical significance of differences between finasteride and placebo could not be assessed for continuous measures.
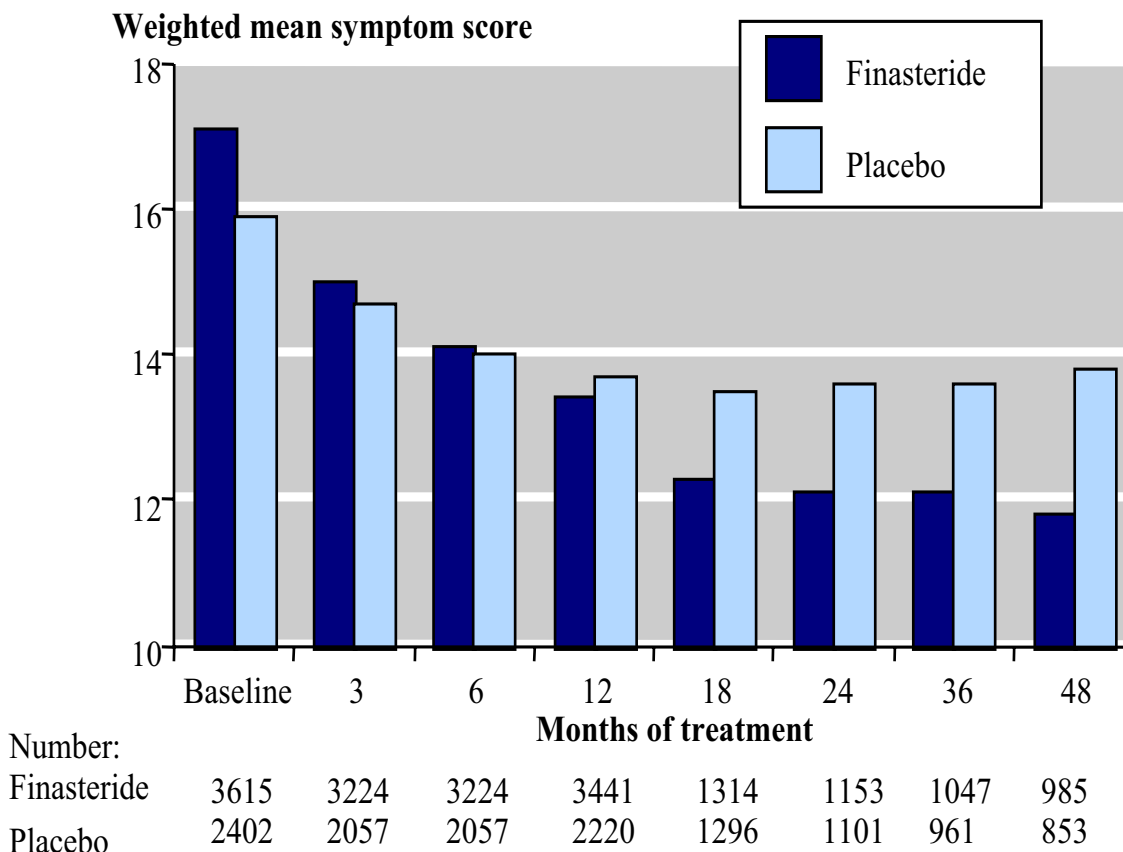
Symptom scores

Weighted mean symptom score

Number:	Baseline	3	6	12	18	24	36	48
Finasteride	3615	3224	3224	3441	1314	1153	1047	985
Placebo	2402	2057	2057	2220	1296	1101	961	853

Figure 1
Total symptom scores using the American Urological Association scale (0–35).

Three different scoring systems were used. In placebo-controlled trials, the Boyarsky scale (0–54) was used in two studies, modified Boyarsky scale (0–36) in nine, and the American Urological Association (AUA; 0–35, similar to the current International Prostate Symptom Score, IPSS) in eight; higher scores show worse symptoms in all three scales. Symptom severity was recorded at baseline and at various stages throughout the study, though not all studies reported this information for all time points, including baseline. Figure 1 shows the weighted mean total symptom scores at different time points with the American Urological Association scale which was used for most men, and the results for all scales are in additional file 5. Total symptom scores were similar at baseline with finas-

teride (17) and placebo (16). They then fell (improved), and by 12 months there was a greater reduction in symptom score with finasteride (by 3.7 points) than with placebo (by 2.3 points), and maintained for 24 to 48 months. Scores continued to decrease with finasteride up to 48 months, whereas they started to increase with placebo after 18 months.

Maximum urinary flow rate
Figure 2 shows the results for maximum urinary flow rate. At baseline the weighted mean maximum urinary flow rate was 11.2 mL/s with finasteride (3960 men) and 10.5 mL/s with placebo (3893 men). This increased (im-
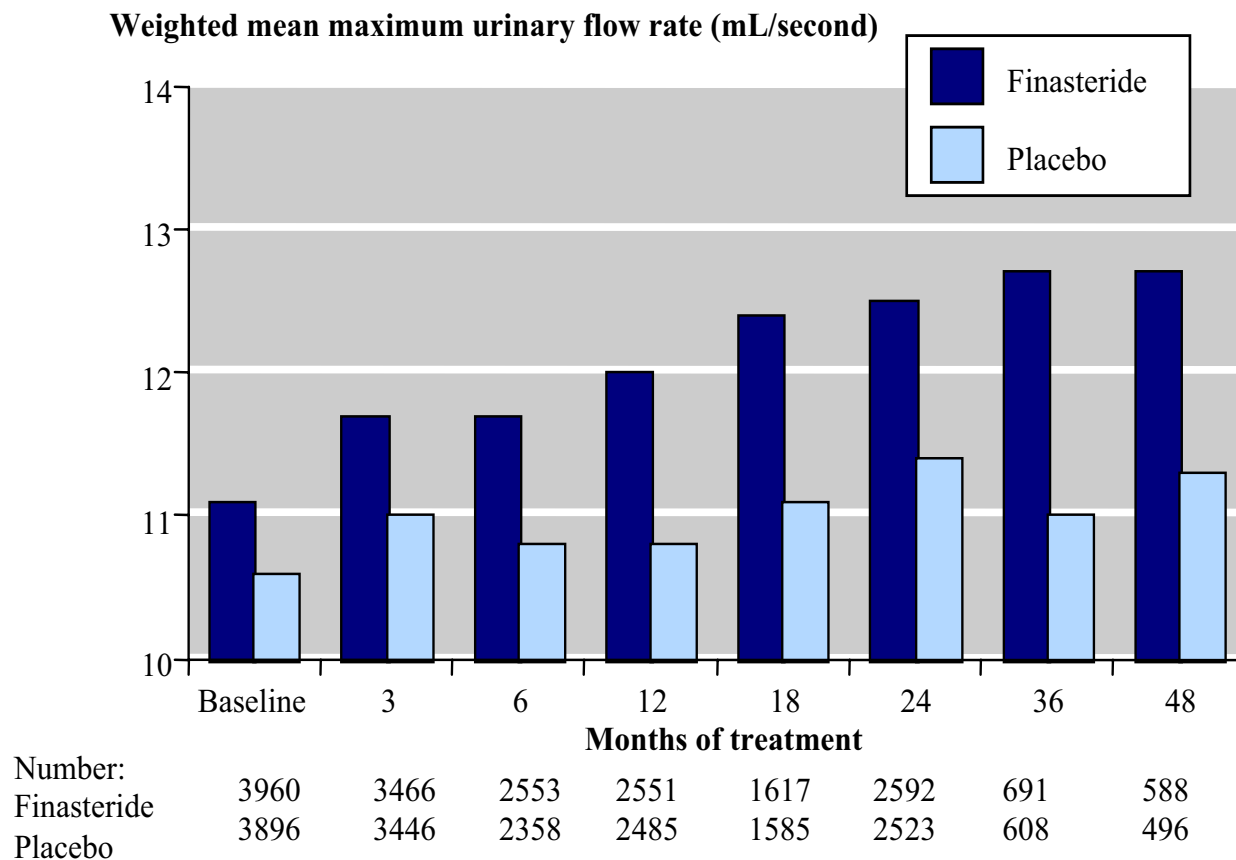
Weighted mean maximum urinary flow rate (mL/second)

Number:	Baseline	3	6	12	18	24	36	48
Finasteride	3960	3466	2553	2551	1617	2592	691	588
Placebo	3896	3446	2358	2485	1585	2523	608	496

Figure 2
Maximum urinary flow rate over time.

proved) with time on treatment and by 24 months weighted mean urinary flow rates were 12.5 mL/s with finasteride (2592 men) and 11.3 mL/s with placebo (2523 men).

Prostate volume
Figure 3 shows the results for prostate volume, which declined by 25% over 24 months with finasteride compared with a 4% decline with placebo. At baseline the weighted mean prostate volume was 43.7 cm^3 with finasteride (2847 men) and 44.8 cm^3 with placebo (2853 men). This decreased (improved) with duration of finasteride treatment, but generally increased (worsened) with placebo. By 24 months prostate volume was 32.7 cm^3 with finasteride (1705 men) and 43.0 cm^3 with placebo (1724 men). Prostate volumes of about 30 cm^3 or less are generally assumed to be normal in older men and not associated with prostatic hyperplasia [41].

Sensitivity analyses
Symptom severity at baseline
Information was pooled from studies that included men with mild plus moderate symptoms at baseline, and was compared with pooled information from studies including only men with at least moderate symptoms at baseline. Only two trials included men with mild symptoms, with fewer than 500 per group. There was insufficient information to determine whether symptom severity at baseline affected treatment efficacy in terms of prostate volume or urinary flow rate.

Prostate volume at baseline
The sensitivity of results to prostate volume was investigated in two ways. In the first, results were pooled according to whether mean prostate volume of the finasteride-treated group at baseline was less than 40 cm^3 or 40 cm^3 or greater. Prostate volume and maximum urinary flow

Weighted mean prostate volume (cm3)

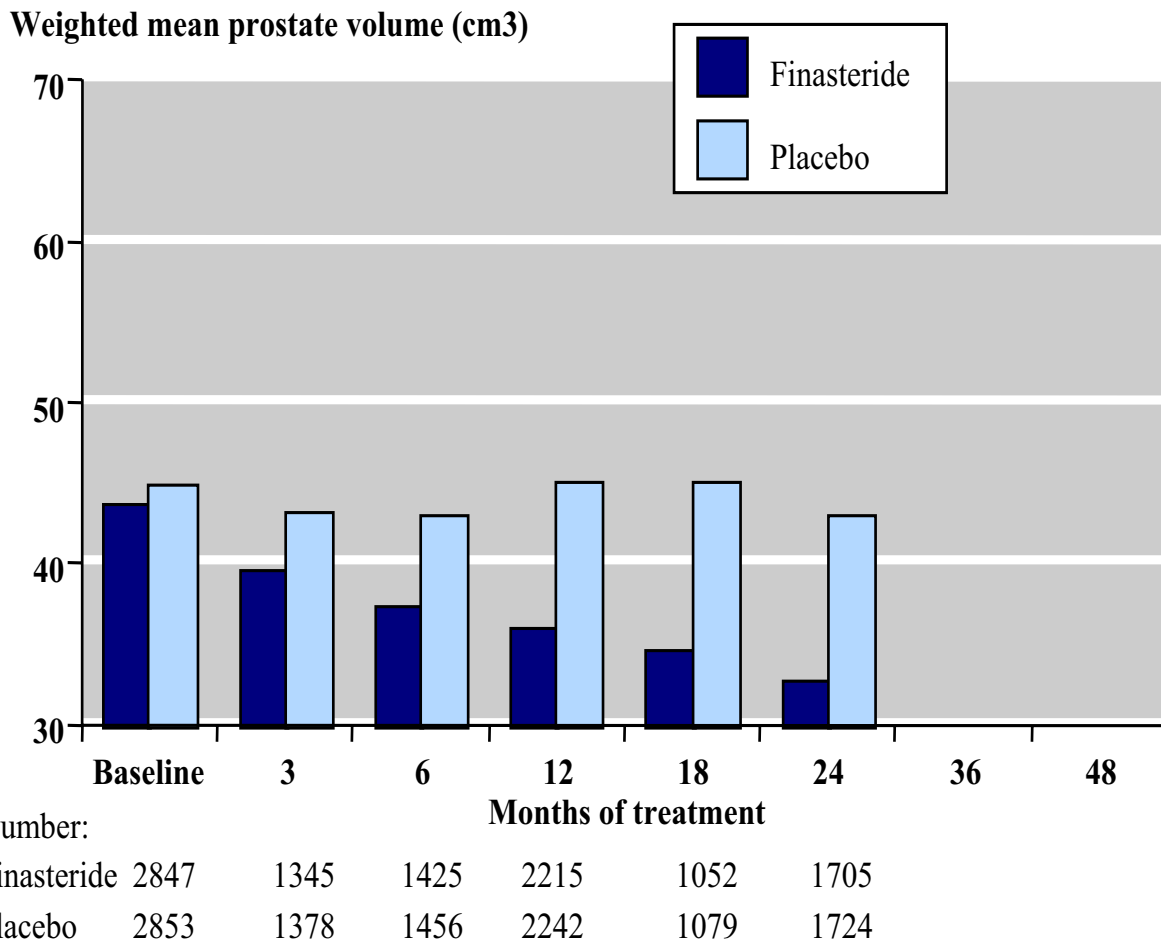| Number:	Baseline	3	6	12	18	24
Finasteride	2847	1345	1425	2215	1052	1705
Placebo	2853	1378	1456	2242	1079	1724

Figure 3
Prostate volume over time.

rate over time were determined for each data set (additional file 6). By 24 months finasteride achieved a similar proportional reduction in prostate volume with larger (79% of placebo) and smaller (75% of placebo) prostates. There was limited data for maximum urinary flow rate in men with smaller prostates, but there was no evidence that the increased flow rate at 24 months was higher with men with larger (110% of placebo) or smaller (108% of placebo) prostates.

In the second, the effect of initial prostate volume on the success of finasteride in increasing maximum urinary flow rate in the individual trials was investigated graphically. Figure 4 replicates the analysis of Boyle and colleagues [11] using all trials with more than 100 men and with 12

or 24 month outcomes. In this analysis the difference between the change in maximum urinary flow rate between baseline and study end with placebo is subtracted from the change in maximum urinary flow rate between baseline and study end with finasteride; what is plotted is the difference between two differences. Higher baseline prostate volume was associated with larger increases in maximum urinary flow rate for finasteride minus placebo.

These analyses were performed for the change in maximum urinary flow rate between baseline and study end with finasteride (Figure 5) and the change in maximum urinary flow rate between baseline and study end with placebo (Figure 6). The benefit with finasteride 5 mg was constant irrespective of the initial prostate volume (Figure
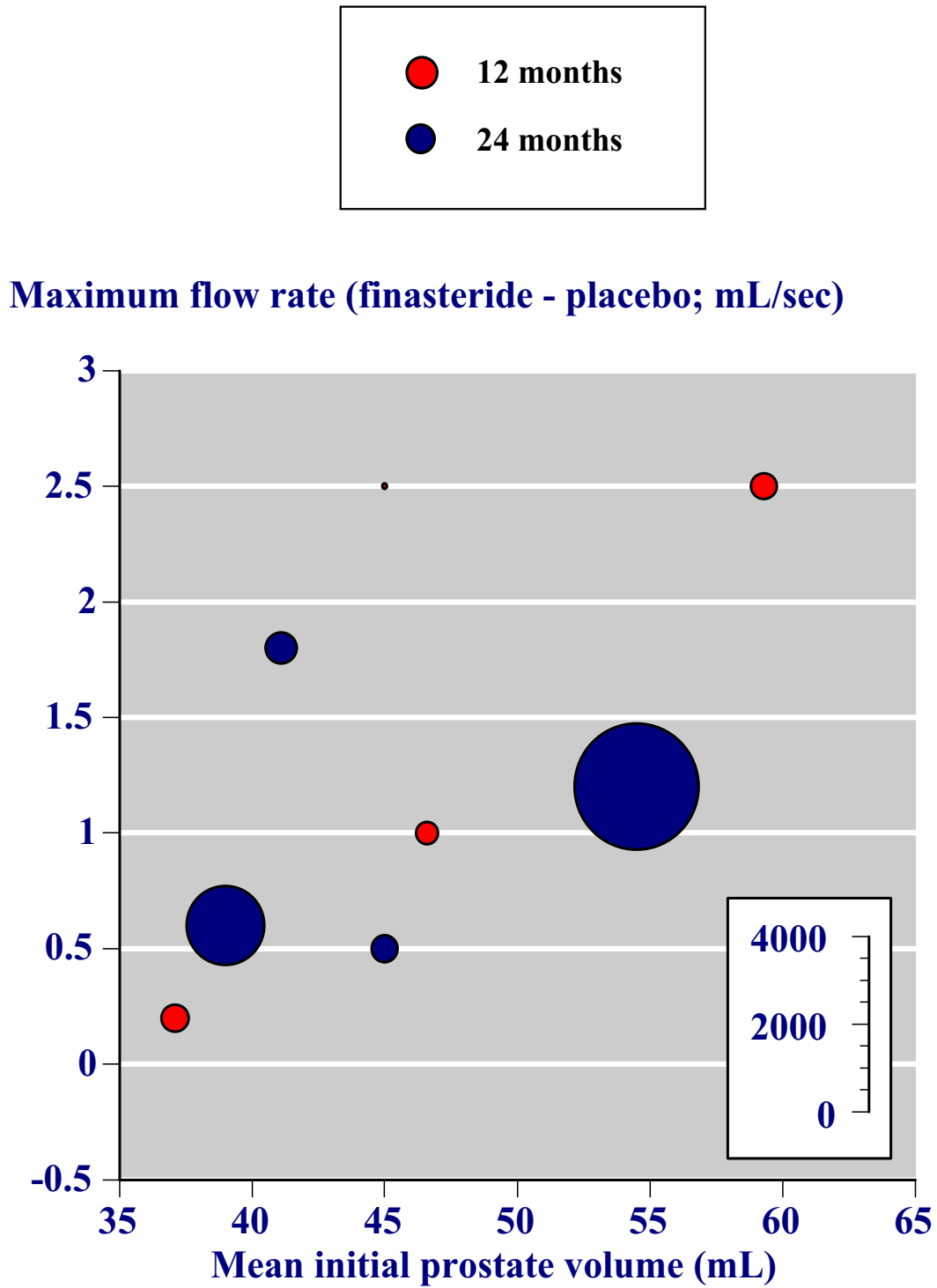
Figure 4
Effect of initial prostate volume – Replication of the analysis by Boyle and colleagues.

5). For placebo, men with higher prostate volumes had little overall change in maximum urinary flow rate, while men with lower prostate volumes had maximum urinary flow rates that increased.

Influence of PLESS
Table 2 shows the results of analyses using the PLESS trial [19] compared with results of other trials (excluding PLESS). Not all men in the PLESS trial had prostate volumes measured. In those in whom it was, the 24 month analysis showed approximately a 10 cm^3 reduction in prostate volume (18% reduction from baseline of 55 cm^3 with finasteride) for PLESS and other trials, compared with a 4 cm^3 (8%) increase in volume with placebo. Maximum urinary flow rates at 24 months rose with finasteride to the same extent (by about 2 mL per second) in the PLESS trial with 1125 men and in the studies with 2991 men given finasteride.

Previous interventions
Only two trials [29,32] included men who had prior interventions like balloon dilatation, or catheterisation with a stent implant. Together these two studies had only 59 men on finasteride and 60 on placebo. Sensible comparisons were not possible.

Discontinuation
Discontinuation was well reported in the trials.

Significantly fewer men discontinued with finasteride than with placebo at 12 months or 48 months (Table 3A). After 12 months, all cause discontinuation rates were 13% (553/4098 men) with finasteride and 17% (299/1764) with placebo; number-needed-to-treat to prevent one discontinuation was 29 (18 to 71). After 48 months, discontinuation rates were 34% (524/1524 men) with finasteride and 42% (633/1516) with placebo; NNH to prevent one discontinuation was 13 (9.0 to 27).

There was no significant difference between groups at any time point for discontinuation because of lack of efficacy (Table 3B), with 24 month discontinuations because of lack of efficacy at 4% with finasteride and 5% with placebo. There was no significant difference between groups at any time point for discontinuation because of adverse effects (Table 3C), with 24 month discontinuations because of adverse effects at 8% with finasteride and 14% with placebo.

Specific adverse effects
The most commonly reported adverse effects were impotence, decreased libido and ejaculation disorder. Definitions of these adverse effects were generally not provided in the trials. Since cumulative adverse effect information was not available after year one in some studies, analyses were conducted for different time points up to one year for most adverse effects. Numbers-needed-to-harm are shown in Table 4 for analyses for which there were adequate data. Serious adverse effects occurred at similar frequencies with finasteride (12%; 437/3557 men) as with placebo (13%; 150/1175 men).

Significantly more men reported any sexual dysfunction, decreased libido, impotence, or ejaculation disorder with finasteride than with placebo at 12 months of treatment. Incidence rates ranged between 2–14% with finasteride and 0.6–7% with placebo, and NNHs for particular adverse events ranged between 14 and 55 (Table 4). This means, for instance, that for every 24 men treated with 5 mg finasteride for 12 months impotence would occur in one in whom it would not have occurred with placebo.

Avoiding AUR and surgery
Significantly fewer men suffered acute urinary retention or surgery related to benign prostatic hyperplasia after 24 months (Table 4), though much of this information was derived from the PLESS trial. Acute urinary retention and surgery related to benign prostatic hypertrophy occurred in less than 1% of men over the first 12 months of treatment. By 24 months their occurrence was significantly lower with finasteride than with placebo. The NNTs for avoiding acute urinary retention were 49 (31 to 112) over 24 months and 26 (19 to 44) over 48 months. The NNTs for avoiding prostate related surgery were 31 (21 to 61) over 24 months and 18 (14 to 27) over 48 months. This means, for instance, that for every 31 men treated with 5 mg finasteride for 24 months prostate surgery would be avoided in one in whom it would have occurred with placebo.

It was not possible to calculate results for a combined end point of avoiding acute urinary retention or surgery.

There was no statistically significant difference in the incidence of prostate cancer with finasteride compared with placebo. Rates were under 0.5% at 12 months, and in one four year study [19] rates were 1–2% at 24 months and 0.5% at 48 months.

Discussion
Clinical trials set out to determine whether an intervention is better than no treatment (placebo) or another treatment. Their conduct is governed by rules of evidence, and in the main they will need to be randomised and double blind to minimize bias, have a valid design, measure useful clinical outcomes over a sensible period, and be of sufficient size to minimize the effects of random chance or to have a reasonable expectation of seeing a difference if one exists. How clinical trials are designed will often depend on what happens without treatment. For instance,
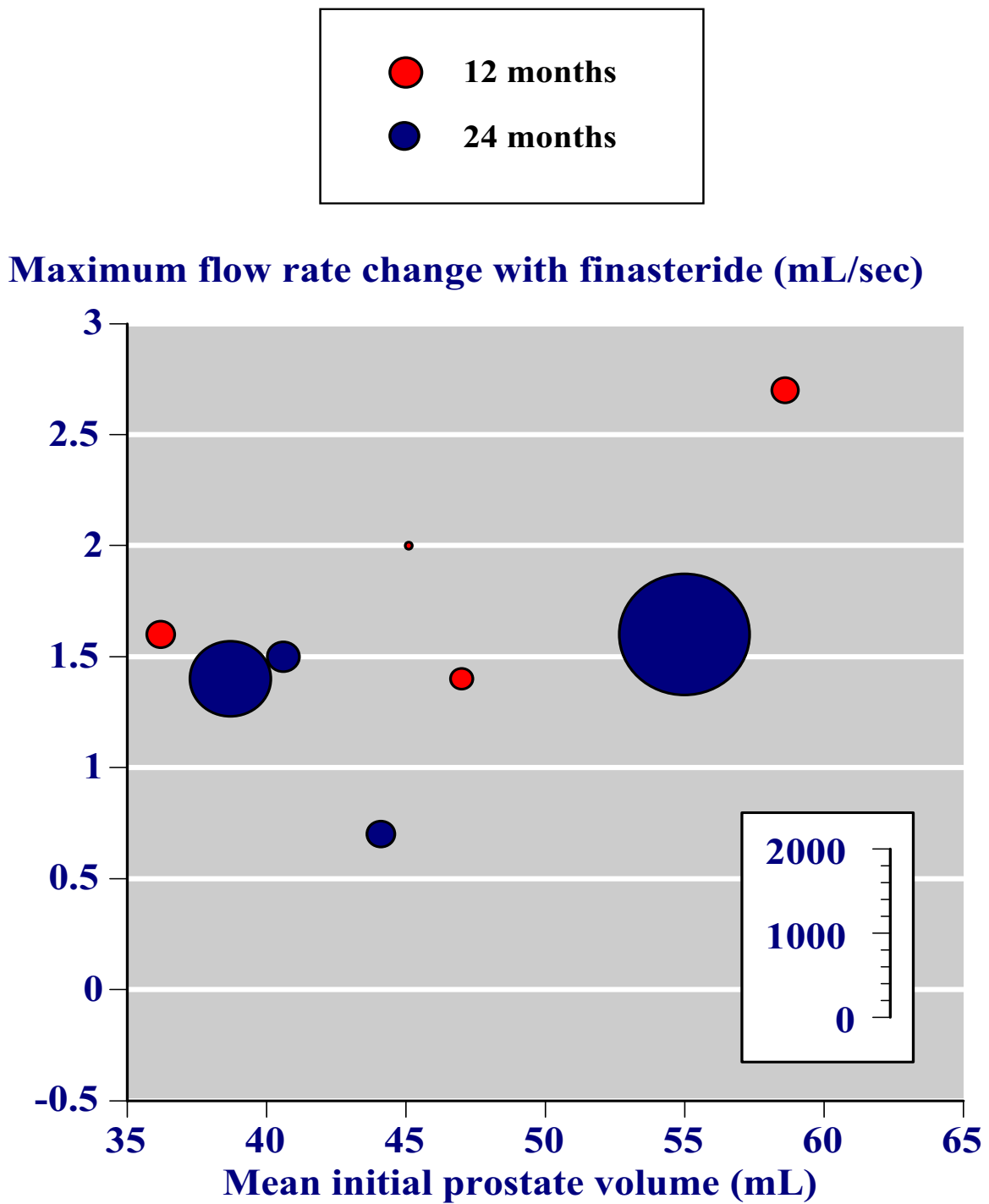
Figure 5
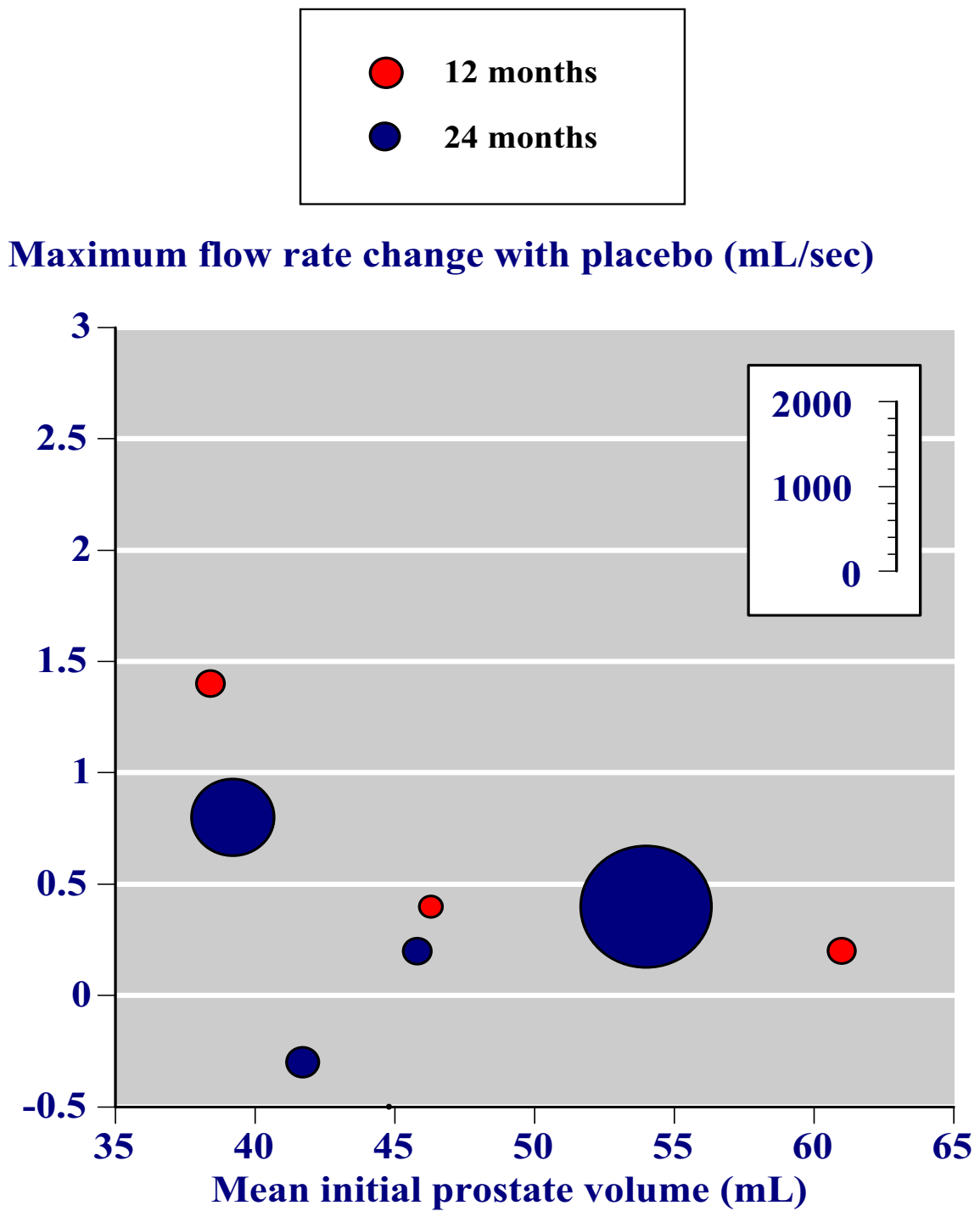Effect of initial prostate volume – finasteride.

Figure 6
Effect of initial prostate volume – placebo.

Table 2: Comparison of other studies with information from PLESS

A. Prostate volume (cm^3)

		PLESS		Other studies (without PLESS)	
		Finasteride	Placebo	Finasteride	Placebo
Baseline	Number	157	155	2719	2696
	Value	55.0	54.0	43.1	44.2
24 months	Number	130	119	2146	2140
	Value	45.1	58.3	31.5	41.5
Mean change from baseline at 24 mths		-9.9	4.3	-10.6	3.3

B. Maximum urinary flow rate (mL/s)

		PLESS		Other studies (without PLESS)	
		Finasteride	Placebo	Finasteride	Placebo
Baseline	Number	1125	1127	2991	2923
	Value	11.0	11.0	10.5	10.3
24 months	Number	786	720	1806	1803
	Value	12.6	11.4	12.4	11.3
Mean change from baseline at 24 mths		1.6	0.4	1.9	1.0

Number of patients at baseline, or remained in the studies at 24 months

after surgery some patients do not get pain [42], and so trials of analgesics recruit only patients who have moderate or severe pain in the first place [43]. For men with mild or moderate symptoms of BPH long duration placebo-controlled trials are essential; while the natural history is for symptoms to worsen with time [8], lifestyle changes or tolerance mean that in some men improvement occurs spontaneously [3].

Clinical practice is different because the choice is whether to use an intervention or not, or which of several interventions to use. Placebo is not an option, though watchful waiting may be a sensible decision for many men [44]. The choice made will be a product of how much symptoms interfere with aspects of daily living, professional advice, and individual preference. Knowledge of the natural history [45] will be part of the decision-making, together with knowledge of what to expect from treatment.

This review sought to explore whether randomised trials of finasteride 5 mg (the standard licensed dose in the UK) could be used to provide an adequate estimate of what to expect from treatment in terms of benefits (symptoms, flow rates) and harm (acute retention, progression to surgery, and adverse event discontinuation). The 19 trials available comparing finasteride 5 mg with placebo all had quality scores of 3 out of 5 or higher, indication that they were likely to be free of major bias [46,47]. Ten trials, with the bulk of the patients randomised, were of at least 12

month's duration and included more than 500 patients. Almost all showed finasteride 5 mg to be significantly better than placebo for each of three efficacy outcomes (symptoms, maximum urinary flow rate and prostate volume), and mostly at a significance level of 1%. The evidence is that finasteride is effective.

The question is, what can a man expect from treatment with finasteride?

At baseline the individual studies recruited men with mean symptom scores of 8 to 19 points, usually described as moderate. Treatment with finasteride 5 mg for 12 months resulted in a 4 point decrease and for 24 months in a 5 point decrease, so that using the American Urological Association score mean values fell from 17 points at baseline to 12 points. The range of scores for moderate symptoms is 8–19 points, so on average men could expect symptoms to reduce from just under severe to just over mild. Mean urinary flow rates would rise from a mean baseline value of 11.2 mL/s with finasteride 5 mg to 12.5 mL/s after 24 months of treatment; a flow rate of 12 mL/sec is seen by some as a threshold for BPH [41]. This would be accompanied by a reduction in prostate volume by a mean of 8 cm^3 to an average of about 33 cm^3, and though this would not be apparent to the patient it comes close to the one threshold of normality for prostate volume [41]. Quality of life was looked at in several trials, but

Table 3: Discontinuations in double blind, placebo controlled trials of 3–48 months duration Significantly fewer discontinuations with finasteride than with placebo.

A. Total number of patients who discontinued

Number of studies	Time point (months)	Discontinued with finasteride 5 mg		Discontinued with placebo		Relative risk (95% CI)	NNT (95% CI)
		Number	Percent	Number	Percent		
1	3			No data			
5	12	553/4098	13	299/1764	17	0.8 (0.7 to 0.9)	29 (18 to 71)
4	24	467/2146	22	507/2140	24	0.9 (0.8 to 1.03)	n/c
1	48	524/1524	34	633/1516	42	0.8 (0.7 to 0.9)	13 (9 to 27)

B. Discontinuations because of lack of efficacy

Number of studies	Time point (months)	Discontinued with finasteride 5 mg		Discontinued with placebo		Relative risk (95% CI)	NNT (95% CI)
		Number	Percent	Number	Percent		
1	3			No data			
4	12	116/3788	3	46/1459	3	0.9 (0.7 to 1.4)	n/c
4	24	81/2146	4	107/2140	5	0.8 (0.6 to 1.0)	n/c
1	48	99/1524	6	104/1516	7	0.9 (0.7 to 1.2)	n/c

C. Discontinuations because of adverse effects

Number of studies	Time point (months)	Discontinued with finasteride 5 mg		Discontinued with placebo		Relative risk (95% CI)	NNT (95% CI)
		Number	Percent	Number	Percent		
1	3			No data			
5	12	251/4098	6	89/1764	5	1.2 (0.9 to 1.5)	n/c
1	18			No data			
4	24	178/2146	8	210/2140	14	0.8 (0.7 to 1.02)	n/c
1	48	176/1524	12	166/1516	11	1.0 (0.9 to 1.3)	n/c

NB: Number-needed-to-treat to prevent one discontinuation with finasteride compared with placebo

the challenge is to find an acceptable disease-related instrument that adds to current disease measures [48].

Out of every 100 men with moderate symptoms treated with finasteride 5 mg over two years, 34 would discontinue treatment for any reason. For six men it would be because of lack of treatment benefit, for 12 it would be because of adverse events. Four men out of 100 would become impotent, who would not have done with no treatment. Additional benefits would be that out of 100 men treated for two years two would avoid an episode of acute urinary retention and three would avoid prostate-related surgery.

The adverse events seen with finasteride have to be seen in context. Firstly they appear to be reversible on stopping treatment, and we found no evidence of rare, major and irreversible adverse events, important for treatment taken for the rest of a man's life. Discontinuations due to adverse events were the same in finasteride and placebo-

treated men, and at 8% with finasteride after 24 months about the same as seen in alpha-blockers in trials generally of much shorter duration [49]. The sexual adverse events have to be seen against the natural history of reducing sexual performance with age. For instance, sexual dysfunction in men is common [50] and increases with age [51]; men aged 55 years without erectile dysfunction consider intercourse frequency as being less than adequate [52]. The men in the finasteride trials had an average age of about 65 years.

It is clear that increasing prostate volume is the cause of clinical benign prostatic hyperplasia [45]. Prostate volume is not usually measurable in general practice because the required ultrasound equipment is not available. However, PSA acts as a surrogate measure for prostate volume, and as a predictor for increased risk of acute urinary retention [53]. It should be noted, however, that finasteride decreases PSA values by a factor of about two, important to remember if prostate cancer were suspected [54].

Table 4: Adverse effects reported in double blind, placebo controlled trials of 3–48 months duration Significantly fewer adverse effects with finasteride than with placebo.

Adverse effect	Number of studies	Time point (months)	Harmed with finasteride 5 mg		Harmed with placebo		Relative risk (95% CI)	NNT (95% CI)
			Number	Percent	Number	Percent		
Serious adverse effects	2	12	437/3557	12	150/1175	13	1.0 (0.8 to 1.1)	n/c
Any sexual dysfunction	1	12	239/1736	14	38/579	7	2.1 (1.5 to 2.9)	14 (10 to 22)
Decreased libido	5	12	269/5688	5	86/3296	3	2.0 (1.6 to 2.5)	47 (35 to 74)
Impotence	6	12	439/5394	8	117/3551	3	2.2 (1.8 to 2.7)	24 (20 to 31)
Ejaculation disorder	5	12	137/5688	2	19/3296	0.6	3.6 (2.2 to 6.0)	55 (43 to 74)
Acute urinary retention	3	12	17/3803	0.4	9/1430	0.6	0.8 (0.4 to 1.9)	n/c
	1	24	24/1450	2	54/1452	4	0.5 (0.3 to 0.7)	49 (31 to 112)
	1	48	42/1542	3	99/1516	7	0.4 (0.3 to 0.6)	26 (19 to 44)
BPH related surgery	5	12	54/4410	1	24/2035	1	1.1 (0.7 to 1.7)	n/c
	2	24	85/1760	5	142/1755	8	0.6 (0.5 to 0.8)	31 (21 to 61)
	1	48	69/1542	4	152/1516	10	0.5 (0.3 to 0.6)	18 14 to 27)
Prostate cancer	2	12	9/3557	0.3	5/1175	0.4	0.6 (0.2 to 0.8)	n/c
	1	24	3/310	1	6/303	2	0.5 (0.1 to 1.9)	n/c
	1	48	76/1524	0.5	76/1516	0.5	1.0 (0.7 to 1.4)	n/c

n/c Not calculable **NB:** For acute urinary retention, prostate surgery, and prostate cancer the NNT represents the number-needed-to-treat to prevent one episode of acute urinary retention or prostate surgery

The relationship between efficacy of finasteride and prostate volume [55] has been important in making decisions about treatment [11]. Based on an individual patient analysis of six trials Boyle and colleagues showed that while men treated with finasteride 5 mg all had the same average increase in flow rate over one year, statistical significance from placebo occurred only with prostate volumes above 40 cm^3. Improvements in symptom score tended to be higher in men with larger prostates. Analysing mean data from all trials with more than 100 men per treatment group confirms this (Figures 4,5,6). With finasteride 5 mg a mean improvement in maximum flow rate of about 1.5 mL/sec can be expected (Figure 5) irrespective of initial prostate size (Figure 5).

Dependence of treatment efficacy on prostate size is likely be related to mechanism of action, as no such relationship has yet been demonstrated with the alpha-adrenergic receptor antagonist terazosin [9]. In terms of choosing who should be treated, the largest and longest randomised trial of finasteride suggest that men with higher symptom scores and a baseline PSA of above 1.4 ng/mL will benefit most [12]. This is confirmed by a combined analysis of all

men given placebo in finasteride trials [53]. Spontaneous acute urinary retention over two or four years was low when the initial PSA was less than 1.3 ng/mL, but occurred in 2% of men with initial PSA between 1.4 and 3.2 ng/mL and was over 5% in men with a PSA above 3.3 ng/mL. PSA alone was as effective as more complicated algorithms at predicting acute retention [53].

Limitations of the review lie mainly in the way that efficacy trials in BPH are conducted and reported. For outcomes like adverse events, discontinuations or events like acute retention or prostate surgery, the number of men with the event is reported; with the number of men randomised an intention-to-treat analysis becomes possible, and pooling of data using standard methods is possible. Not all trials reported any or all of these outcomes, but they were reported in most of the larger trials in a reasonably consistent manner.

Efficacy outcomes were another matter. There are three problems. First is the relevance of the outcomes themselves. For instance, maximum urinary flow rate is a useful measure of urinary outlet obstruction, though multiple

measures are probably more useful than a single measure [56]. A maximum flow rate of less than 15 mL/sec is generally considered suboptimal, though some now use a flow rate of 12 mL/sec. So a useful outcome might be the number of men at each time point who achieve a maximum urinary flow rate of 15 mL/sec (or 12 mL/sec [41], or whatever is deemed clinically useful). Trials report only mean flow rates, and, with some exceptions at baseline, without any dispersion data in the form of standard deviations or confidence intervals. So, despite many trials involving nearly 14,000 men with BPH, it is not possible to say what proportion can achieve any given maximum flow rate with finasteride or placebo, and when. Reporting of symptom scores is similar, so we cannot say what proportion of men with initially moderate symptoms would have symptoms reverting to mild with finasteride or placebo, or when.

Conclusions
Reporting problems in BPH treatments is not limited to finasteride trials, and is common with all treatments [5], including alpha-blockers [9], as well as other remedies [4]. What would be useful would be some clear indications of patient-centred outcomes, as has been done for migraine [57]. Reporting these outcomes in dichotomous form (success or failure) would greatly aid understanding of the benefits for men, and for healthcare systems.

Competing interests
RAM has been a consultant for MSD, though not in the area of benign prostatic hyperplasia. RAM & JE have received lecture fees from pharmaceutical companies, thought not in the area of benign prostatic hyperplasia. The authors have received research support from charities, government and industry sources at various times, but no such support was received for this work. Neither author has any direct stock holding in any pharmaceutical company. The terms of the financial support from MSD included freedom for authors to reach their own conclusions, and an absolute right to publish the results of their research, irrespective of any conclusions reached. MSD did have the right to view the final manuscript before publication, and did so; MSD made no substantive comments, and the manuscript was not changed as a result.

Authors' contributions
JE performed the searches and extracted data which was checked by RAM. Both authors read the papers, and contributed equally to analysis, and writing and reviewing the paper.

Additional material

> ### Additional File 1
> *Systematic reviews and meta-analyses on benign prostatic hyperplasia.*
> Click here for file
> [http://www.biomedcentral.com/content/supplementary/1471-2490-2-14-S1.pdf]
>
> ### Additional File 2
> *Excluded studies.*
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>
> ### Additional File 3
> *Details of included studies.*
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>
> ### Additional File 4
> *Baseline characteristics of men in the included studies.*
> Click here for file
> [http://www.biomedcentral.com/content/supplementary/1471-2490-2-14-S4.pdf]
>
> ### Additional File 5
> *Absolute total symptom score.*
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>
> ### Additional File 6
> *Effect of large or small prostate volume at baseline on response.*
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