

# Randomised, placebo-controlled, double-blind clinical trial of $\beta$ -sitosterol in patients with benign prostatic hyperplasia

R R Berges, J Windeler, H J Trampisch, Th Senge and the  $\beta$ -sitosterol study group\*

## Summary

Medical treatments have become available for benign hypertrophy of the prostate, including alpha-receptor blocking agents and 5-alpha-reductase inhibitors. Drugs derived from plants, for which no precise mechanism of action has been described, are widely used for this purpose in Europe.

In a randomised, double-blind, placebo-controlled multi-centre study, 200 patients (recruited between April and October 1993) with symptomatic benign prostatic hyperplasia were treated with either 20 mg  $\beta$ -sitosterol (which contains a mixture of phytosterols) three times per day or placebo. Primary end-point was a difference of modified Boyarsky score between treatment groups after 6 months; secondary end-points were changes in International Prostate Symptom Score (IPSS), urine flow, and prostate volume. Modified Boyarsky score decreased significantly with a mean of  $-6.7$  (SD  $4.0$ ) points in the  $\beta$ -sitosterol-treated group versus  $-2.1$  ( $3.2$ ) points in the placebo group  $p < 0.01$ . There was a decrease in IPSS ( $-7.4$  [ $3.8$ ] points in the  $\beta$ -sitosterol-treated group vs  $-2.1$  [ $3.8$ ] points in the placebo group) and changes in urine flow parameters:  $\beta$ -sitosterol treatment resulted in increasing peak flow ( $15.2$  [ $5.7$ ] mL/s from  $9.9$  [ $2.5$ ] mL/s), and decrease of mean residual urinary volume ( $30.4$  [ $39.9$ ] mL from  $65.8$  [ $20.8$ ] mL). These parameters did not change in the placebo group ( $p < 0.01$ ). No relevant reduction of prostatic volume was observed in either group.

Significant improvement in symptoms and urinary flow parameters show the effectiveness of  $\beta$ -sitosterol in the treatment of benign prostatic hyperplasia.

*Lancet* 1995; **345**: 1529–32

## Introduction

The natural history of benign prostatic hyperplasia (BPH) is a slow enlargement of fibromuscular and epithelial structures within the gland, eventually leading to obstructive urinary symptoms experienced to some extent by most men over the age of 50.<sup>1,2</sup>

Transurethral resection of the prostate in men with symptoms of obstruction is the standard treatment for this condition, against which alternative treatments options have to be compared in terms of safety and effectiveness.<sup>3</sup> In recent years, new medical treatments have become available, including alpha-receptor blocking agents<sup>4</sup> and 5-alpha-reductase inhibitors,<sup>5</sup> which have been shown to be effective in randomised clinical trials.<sup>6–8</sup>

Drugs derived from plants have a long tradition in the medical treatment of BPH in Europe; although no mechanism of action nor precise classification of the active compounds for many of these drugs have yet been established, substantial symptom improvement has been reported.<sup>9</sup> We tested  $\beta$ -sitosterol (Harzol, Hoyer, Germany), a phytopharmacological drug containing phytosterols. Although the active substance is termed  $\beta$ -sitosterol, the mixture contains a variety of phytosterols, mainly  $\beta$ -sitosterol, with smaller amounts of campesterol, stigmasterol and other sterols along with their glucosides (Harzol contains 10 mg of  $\beta$ -sitosterol [including standardised 0.1 mg  $\beta$ -sitosterol- $\beta$ -D-glucosidase], glucose, lactose, talc, gelatin, erythrosin E127, quinoline yellow E104, and titanium dioxide E171). It is not known which of its components are responsible for its effect in BPH.

This study was designed in accordance with the suggestions of the international committee on the therapy of BPH held at the 2nd international consultation on benign prostatic hyperplasia in Paris, 1993.<sup>10</sup> Treatment endpoints were chosen so as to match studies on alpha-receptor blocking agents and 5-alpha-reductase inhibitors.

## Patients and methods

### Patients

Patients were recruited from eight private urological practices (table 1). For those currently on medication for prostatic symptoms, a 4-week wash-out period was required. Written informed consent was given by each patient eligible for the trial. Approval was obtained from the ethics committee of the Ruhr University. Treatment with hormones, cimetidine, anticholinergics, psychotherapeutics, sympathicomimetics, parasympatholytics, anticoagulants, diuretics, alpha-receptor-blocking agents, or other phytopharmacological drugs was not allowed during and four weeks before the trial.

### Initial assessment

A history was taken and subjective symptoms evaluated by modified Boyarsky score<sup>11</sup> and IPSS questionnaire.<sup>12</sup> Urinary flow

\*Listed at the end of the paper

Departments of Urology and Biostatistics, Ruhr-University, Bochum, Germany (R R Berges MD, J Windeler MD, H J Trampisch MD, Th Senge MD)

Correspondence to: Dr R R Berges, Department of Urology, Ruhr-University of Bochum, Widumer Strasse 8, 44627 Herne, Germany

<b>Inclusion</b>	Peak urine flow <15 mL/s at a voiding volume of $\geq$ 150 mL Residual volume $\geq$ 30 mL over $\leq$ 150 mL <75 years old
<b>Exclusion</b>	History of acute retention Prostate cancer PSA >10 mg/mL History of transurethral resection Prostatitis Urinary infection Haematuria Urethral stricture Bladder stones Diabetes Abnormal GOT, GPT, or alkaline phosphatase Severe cardiopulmonary disease Neurological or psychological disorders

PSA=prostate specific antigen, GOT= glutamic-oxaloacetic transaminase, GPT= glutamic-pyruvic transaminase.

Table 1: Inclusion and exclusion criteria

(maximum flow, median flow, voiding time, and volume) were recorded with a minimum voiding volume of 150 mL, followed by trans-abdominal ultrasound measurement of residual volume. Prostatic volume was assessed by trans-abdominal or trans-rectal ultrasound.

Each centre was supplied with numbered bottles containing either 20 mg of  $\beta$ -sitosterol in capsules or placebo in capsules of the same size and shape, according to a previously randomised sequence. One copy of the code break (in case of emergency) was held by the responsible investigator at each centre in a sealed envelope.

Laboratory tests included liver function tests, blood urea, creatinine, prostate specific antigen (PSA), blood-cell counts, and urine culture.

#### Follow-up

Patients were assessed monthly. On each visit, compliance, side effects, and modified Boyarsky-score were recorded. After 3 and 6 months, the IPSS questionnaire was recorded as well as urinary flow measurements and prostatic volume. Laboratory testing was repeated after 6 months.

#### Endpoints

The primary outcome variable was the difference in modified Boyarsky scores after 6 months of treatment compared with initial value. IPSS, urine flow, residual urine volume, and prostatic size were secondary end-points.

#### Analysis

To detect a difference of 2.5 modified Boyarsky-score points between the two groups, 100 patients were needed in each

Characteristic	Treatment group	
	Placebo	$\beta$ -sitosterol
Age (years)	65.5 (7.0)	65.2 (6.6)
Height (cm)	173.4 (6.1)	174.7 (6.2)
Body weight (kg)	79.6 (10.9)	78.7 (9.3)
Heart rate (beats/min)	72.4 (5.8)	73.6 (6.6)
BP systolic (mm Hg)	141.6 (15.0)	142.3 (13.1)
BP diastolic (mmHg)	83.8 (9.0)	85.3 (9.0)
Pre-treatment drug therapy (%)	51	51
History of urological surgery/diseases (%)	9	16
Mean voiding vol (mL)	218.5 (84.6)	209.1 (58.7)
Mean urinary flow (mL/s)	5.7 (2.1)	5.7 (2.1)
Peak flow (mL/s)	10.1 (2.8)	9.9 (2.5)
Voiding time (s)	45.5 (2.3)	48.7 (33.3)
Residual volume (mL)	64.8 (24.0)	65.8 (20.8)
Modified Boyarsky score (points)	14.9 (3.7)	15.0 (4.1)
IPSS (points)	15.3 (4.3)	14.9 (4.7)
QOL (points)	3.0 (0.8)	3.1 (0.8)
Prostate volume (mL)	48.7 (29.9)	44.6 (19.4)

Numbers are mean (SD) unless indicated. QOL=quality of life assessed by the IPSS questionnaire.

Table 2: Demographic and urinary characteristics of placebo and  $\beta$ -sitosterol-treated patients at time of recruitment

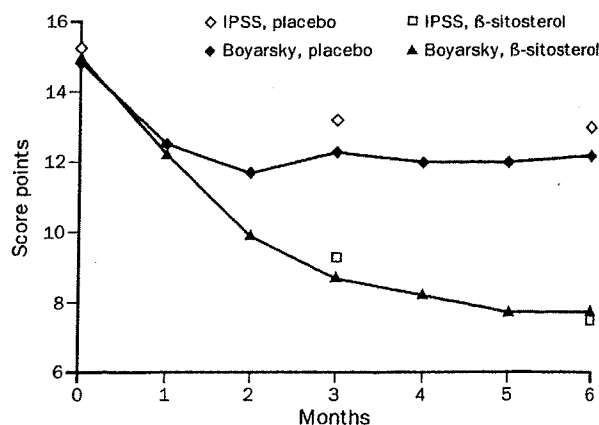


Figure: Modified Boyarsky and IPSS scores during treatment

treatment group to give a power of 80% (unpaired *t* test,  $\alpha=0.05$  two sided,  $\sigma=5$ ).

The statistical method used for the analysis of the primary and secondary outcome variables was the unpaired *t* test. The level of significance was defined as  $\alpha=0.05$  (two sided).

For the primary outcome variable, data were analysed on an intention-to-treat basis including all randomised patients. For patients with incomplete follow-up the last obtainable value of the modified Boyarsky score was used for analysis. If the last obtainable value was lower than the initial value, a difference of 0 points was recorded. If the last obtainable value was higher than the initial value, this last value was recorded. Therefore, all 200 patients enrolled in the study were considered for final analysis of the primary outcome variable Boyarsky score. Reported *p* values for secondary outcome variables are considered as descriptive only. Centre effects were measured by a two-factor analysis of variance (centre, treatment), with initial values and end-of-study values as independent parameters.

## Results

### Recruitment and baseline characteristics

Between April, 1993, and October, 1993, 200 patients were included. All but one centre recruited at least 20 (range 20–40). Inclusion criteria were violated once, by a patient aged 75.6 years. No exclusion criteria were violated. Characteristics were well balanced between the two treatment groups (table 2).

### Follow-up

2, 4, and 6-months follow-ups were completed in 95% of patients. Times of evaluation were at a mean of 93 (SD 25) days for 3-month and 183 (25) days for 6-month evaluation, with no differences between treatment groups.

### Withdrawals

All 200 patients were included in analysis for the primary outcome variable. For secondary outcome variables, only patients with values at six months were considered. Six patients of the placebo group and four patients of the  $\beta$ -sitosterol group did not appear for final evaluation. Four patients underwent surgical interventions during the study period, all in the placebo group, and were excluded. Thus, 91 patients in the placebo group and 96 patients in the  $\beta$ -sitosterol group were considered for analysis of secondary outcome variables. 1 patient in this latter group was unable to void at 6 months; however, residual urinary volume was obtained.

Prostatic volume was not assessed in all participating centres, reducing the number of patients available for

Time of withdrawal (days)	Treatment group	Reported reason	Modified Boyarsky score at time of stopping treatment	Intention to treat value used for analysis
na	Placebo	Better voiding without medication	13	0
34*	Placebo	No relief under medication	20	2
125*	Placebo	Two episodes of transurethral bleeding	4	0
1	Placebo	Allergic reactions after medication	16	0
43*	Placebo	Acute urinary retention, suprapubic fistula	25	4
61*	Placebo	Increase of hair growth (hands and eyebrows)	19	3
29*	Placebo	Subjective worsening of symptoms	8	0
52*	Placebo	Hospital admission	15	0
47*	Placebo	Epigastric pain	11	0
1*	Placebo	Not known	13	0
37	Placebo	Pelvic tenderness after medication	13	0
14*	Placebo	Dizziness, finger trembling	11	1
115	Placebo	PSA >10 ng/mL, ?prostate carcinoma	12	0
73	Placebo	Allergic reaction after medication	20	0
14*	$\beta$ -sitosterol	No relief, patient requested another treatment	22	5
111	$\beta$ -sitosterol	Not known	19	1
14*	$\beta$ -sitosterol	Too many medications, no relief	14	1
11	$\beta$ -sitosterol	Nausea after medication	14	0
na*	$\beta$ -sitosterol	Acute heart attack, change of medication	11	0
107*	$\beta$ -sitosterol	Relief of symptoms, medication discontinued	8	0

\*Withdrawn from analysis of secondary outcome variables. na=not assessable.

Table 3: Patients who stopped treatment

analysis of this parameter to 80 in the placebo and 83 in the  $\beta$ -sitosterol groups. 20 patients stopped treatment (table 3).

#### Outcome

There was a significant improvement of modified Boyarsky score in the  $\beta$ -sitosterol group (table 4). Divergence between placebo and treatment group did not occur until about 4 weeks of treatment but was thereafter stable throughout follow-up. Comparison of symptoms with the IPSS questionnaire at 3 and 6 months confirmed the extent and time course of improvement in  $\beta$ -sitosterol treated patients compared with the placebo group (figure).

The quality of life score also improved more in the  $\beta$ -sitosterol treated group (table 1). Urinary flow measurements improved with  $\beta$ -sitosterol: peak flow by 5.2 (4.9) mL/s versus 1.1 (4.1) mL/s in the placebo group; median flow by 3.0 (3.5) mL/s versus 0.3 (2.5) mL/s; and mean voiding time by 15.5 (33.5) versus 2.8 (34.9) s,  $p < 0.01$ .

Residual urinary volume decreased with  $\beta$ -sitosterol therapy from 35.4 (45.2) mL to 11.6 (28.4) mL in the placebo group,  $p < 0.01$ . As with symptom scores, changes in urine flow occurred during the first half of the trial, with no further changes towards the end of the study.

There was a mean decrease of 3.1 (8.8) mL in the  $\beta$ -sitosterol group compared with 0.3 (9.0) mL in the placebo group, which makes it unlikely that  $\beta$ -sitosterol has a substantial effect on prostatic volume.

#### Adverse effects

There were no severe adverse reactions attributed to  $\beta$ -sitosterol. One patient observed erectile dysfunction, and another reported loss of libido, both after 2 months of medication. One patient reported constipation from day 1. One patient experienced several episodes of nausea after 11 days of treatment and stopped medication. In the placebo group, one patient complained of increasing hair growth on hands, abdomen, and eyebrows, leading to discontinuation of medication. One patient suffered from generalised skin rash after the second day of placebo treatment. Both groups experienced minor side-effects and withdrew from the study. Two patients experienced some degree of dizziness on day 3 for 3 h and on day 103 lasting for 10 days. Two patients complained of epigastric pain after medication, starting on day 52 and recurring for several weeks in one case, starting on day 3 and lasting for 30 min in the other case (table 3).

#### Discussion

The effect of phytopharmaceuticals on BPH is controversial because no clear mechanisms of action have been established, and their effect has been attributed to placebo responses. Nevertheless, these drugs are commonly prescribed.<sup>9</sup> Since other forms of medical treatment of BPH have been shown to be effective, it is questionable whether phytopharmaceutical drugs should continue to be prescribed.

In this trial, we investigated the effects of a typical phytopharmaceutical, a plant extract whose composition

	Placebo				$\beta$ -sitosterol			
	n	At start	After 6 months	Difference	n	At start	After 6 months	Difference
<b>Primary outcome variable</b>								
Modified Boyarsky score (points)	100	14.9 (3.7)	12.2 (3.9)	2.1 (3.2)	100	15.0 (4.1)	7.7 (4.2)	6.7 (4.0)*
<b>Secondary outcome variables (mean [SD])</b>								
IPSS (points)	91	15.1 (4.2)	12.8 (4.5)	2.1 (3.8)	96	14.9 (4.7)	7.5 (4.4)	7.4 (3.8)*
QOL (points)	91	3.0 (0.8)	2.8 (0.9)	0.2 (1.0)	96	3.1 (0.8)	1.8 (0.8)	1.4 (0.8)*
Peak flow (mL/s)	91	10.2 (2.8)	11.4 (4.7)	-1.1 (3.9)	95	9.9 (2.5)	15.2 (5.7)	-5.2 (4.9)*
Median flow (mL/s)	91	5.8 (2.4)	6.2 (3.1)	-0.3 (2.5)	95	5.7 (2.2)	8.8 (4.2)	-3.0 (3.5)*
Voiding time (s)	91	45.4 (22.2)	47.5 (34.4)	-2.8 (34.9)	95	48.7 (33.9)	33.2 (18.9)	15.5 (33.5)*
Residual volume (mL)	91	64.8 (23.5)	54.3 (27.6)	11.6 (28.4)	96	65.8 (20.8)	30.4 (39.9)	35.4 (45.2)*
Prostate volume (mL)	80	48.0 (27.9)	48.8 (26.5)	0.3 (9.0)	83	44.6 (19.4)	42.3 (18.2)	3.1 (8.8)

Note that modified Boyarsky scores were analysed on an intention-to-treat basis including all randomised patients (see text). For all other indices, patients with missing values were excluded from analysis. P values reported for these indices are considered descriptive only. \* $p < 0.01$  compared with placebo.

Table 4: Outcome variables at initial presentation and 6 months of placebo or  $\beta$ -sitosterol treatment

is not exactly defined, and which may vary between doses. Furthermore, no exact biochemical mechanism of action has been established for the various phytosterols in  $\beta$ -sitosterol. The trial was designed as suggested by the international consensus-conference on therapy of BPH in Paris in 1993.<sup>10</sup> The results show a significant effect of  $\beta$ -sitosterol in patients with symptomatic BPH on symptoms, as measured by the modified Boyarsky-score questionnaire. Objective parameters of urine flow were also improved more than in the placebo group.

Finasteride, a 5- $\alpha$ -reductase inhibitor reduced prostatic volume by up to 30% over 12 months and improved Boyarsky scores with a reduction of up to 4 points,<sup>6</sup> which is within the range we achieved with  $\beta$ -sitosterol. Finasteride also increased peak urinary flow by a mean of 1.3 mL/s. The increase reached 3.6 mL/s after 36 months in the uncontrolled long-term follow-up,<sup>6</sup> similar to that observed in patients treated for 6 months with  $\beta$ -sitosterol (5.2 [4.9] mL/s). Median flow and residual urinary volume also improved. This improvement was achieved with  $\beta$ -sitosterol with no reduction of prostatic volume, demonstrating again that obstruction and subjective symptoms are not necessarily correlated with prostatic size. It should be noted that our study investigated few patients and only over 6 months. It is well known that subjective as well as obstructive symptoms may vary within the first 6 months after initial appearance of symptoms in patients with symptomatic BPH, leading to substantial improvement in many patients even without any form of therapy.<sup>13</sup>

Data from randomised trials with alpha-receptor blocking agents are also comparable with our results. Jardin et al<sup>14</sup> investigated alfuzosine in 518 patients, and reported a 3.1 mL/sec improvement of peak urinary flow. Doxazosine, a long-acting alpha-receptor blocker, improved peak flow up to 1.5 mL/s in a study of Christensen et al,<sup>15</sup> and to 2.6 mL/s in a study by Chapple et al.<sup>16</sup> The best results were reported by Caine et al<sup>7</sup> with phenoxybenzamine (improvement of peak flow by 6.2 mL/sec),<sup>7</sup> and Martorana et al<sup>17</sup> with prazosine (improvement of peak flow 6.9 mL/s). However, both studies had a short follow-up of only 2 weeks and no evaluation of residual volume or symptom score was reported. By contrast with  $\beta$ -sitosterol treatment, adverse effects such as dizziness, decreasing blood pressure, tachycardia, or orthostatic problems, were reported frequently.

Investigation should now focus on evaluating specific compounds within the mixture of phytosterols in

$\beta$ -sitosterol, and on possible biochemical mechanisms. The effects of long-term treatment with  $\beta$ -sitosterol have also to be assessed.

*The  $\beta$ -sitosterol study group:* B Aekens, J Albrecht, C Becker, P Brundig, D Dreyer, W Kaldewey, H Latka, A Reek, HJ Schneider, P Schöter, C Schumacher.

This study was sponsored by Hoyer GmbH & Co, Neuss, Germany.

## References

- Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1994; 132: 474-79.
- Lytton B, Emery JM, Howard BM. The incidence of benign prostatic hypertrophy. *J Urol* 1968; 99: 639-45.
- Fowler FJ, Wenneberg JE, Timothy RP, et al. Symptom status and quality of life following prostatectomy. *JAMA* 1988; 259: 3018-22.
- Lepor H. Role of alpha-adrenergic blockers in the treatment of benign prostatic hyperplasia. *Prostate* 1990; 3 (suppl): 75-84.
- McConnell JD, Wilson JD, George FW, et al. An inhibitor of 5- $\alpha$ -reductase, MK-906, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. *J Urol* 1989; 141: 239.
- Finasteride Study Group. Finasteride (MK-906) in the treatment of benign prostatic hyperplasia. *Prostate* 1993; 22: 291-99.
- Caine M, Perlberg S, Meretyk S. A placebo-controlled double-blind study of the effect of phenoxybenzamine in benign prostatic obstruction. *Br J Urol* 1978; 50: 551-54.
- Jardin A, Bensadoun H, Delauvauche-Cavallier MC, Attali P. Alfuzosin for treatment of benign prostatic hypertrophy. The BPH-ALF Group. *Lancet* 1991; 337: 1457-61.
- Dreikorn K, Richter R, Schonhofer PS. Konservative, nicht-hormonelle Behandlung der benignen Prostata-hyperplasie. *Urologe* 1990; 29: 8-16.
- Aso Y, Boccon-Gibob L, Brendler CB, et al. Clinical research criteria. In: Cockett AT, Aso Y, Chatelain C, Denis L, Griffith K, Murphy G, eds. Proceedings of the second international consultation on benign prostatic hyperplasia (BPH). Paris: SCI, 1993: 345-55.
- Boyarsky S. Guide lines for investigation of benign prostatic hypertrophy. *Trans Am Assoc Gen Urin Surg* 1977; 68: 29-32.
- Cockett AT, Aso Y, Denis L, Khoury S. The international prostate symptom score (I-PSS) and quality of life assessment. In: Proceedings of the international consultation of benign prostatic hyperplasia. Paris 1991: 280-81.
- Schulze H, Berges RR, Paschold K, Senge Th. Neue Therapieansätze bei der benignen Prostatahyperplasie. *Urologe* 1992; 31: 8-13.
- Jardin A, Bensadoun H, Delauvauche-Cavallier MC, Attali P. Alfuzosin for treatment of benign prostatic hypertrophy. The BPH-ALF Group. *Lancet* 1991; 337: 1457-61.
- Christensen MM, Bendix Holme J, Rasmussen PC, et al. Doxazosin treatment in patients with obstruction. A double blind placebo-controlled study. *Scand J Urol Nephrol* 1993; 27: 39-44.
- Chapple CR, Carter P, Christmas TJ, et al. A three month double-blind study of Doxazosin as treatment of benign prostatic bladder outlet obstruction. *Br J Urol* 1994; 74: 471-77.
- Martorana G, Giberti C, Damonte P. The effect of prazosin in benign prostatic hypertrophy: a placebo-controlled double-blind study. *IRCS Med Sci* 1984; 12: 11-12.