Lower Urinary Tract

The relationship between 5α-reductase inhibitors and blood loss from the prostate has been well described and investigated previously. In a well-conducted study, authors from Sweden show that dutasteride, despite significantly lowering the tissue dihydrotestosterone levels, did not lower blood loss or transfusion rates after TURP.

Blood loss and postoperative complications associated with transurethral resection of the prostate after pretreatment with dutasteride

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OBJECTIVE

To determine whether pretreatment with dutasteride, a dual 5α-reductase inhibitor (5ARI), reduces surgical blood loss or postoperative complications in patients with benign prostatic hyperplasia (BPH) who undergo transurethral resection of the prostate (TURP).

PATIENTS AND METHODS

This double-blind, randomized, placebo-controlled, multicentre study comprised 214 patients with BPH. Placebo was compared with dutasteride 0.5 mg/day 2 weeks before and after TURP, or 4 weeks before and 2 weeks after TURP. Surgical blood loss was measured using a haemoglobin photometer (HemoCue AB, Ängelholm, Sweden) and postoperative adverse events were recorded. Microvessel density (MVD) was calculated by immunostaining and light microscopy of the prostatic chips.

RESULTS

Although dutasteride reduced serum dihydrotestosterone (DHT) by 86–89% in 2–4 weeks, and intraprostatic DHT was ≈10 times lower than in the placebo group, the (adjusted) mean haemoglobin (Hb) loss during surgery was 2.15–2.55 g Hb/g resectate with no significant difference in blood loss between the groups either during or after TURP. Clot retention occurred in 6–11% and urinary incontinence in 14–15% of patients during the 14 weeks after TURP, with no difference between the groups. The MVD at TURP was also similar for all groups.

CONCLUSION

There were no significant reductions in blood loss during or after TURP or complications afterward with dutasteride compared with placebo, despite significant suppression of intraprostatic DHT. Blood loss and transfusion rates in the placebo group were lower than those previously reported in studies where

there was a beneficial effect of a 5ARI, relative to placebo, on bleeding during TURP.

KEYWORDS

blood loss, surgical, blood vessels, double-blind, dutasteride, mannitol, BPH, TURP

INTRODUCTION

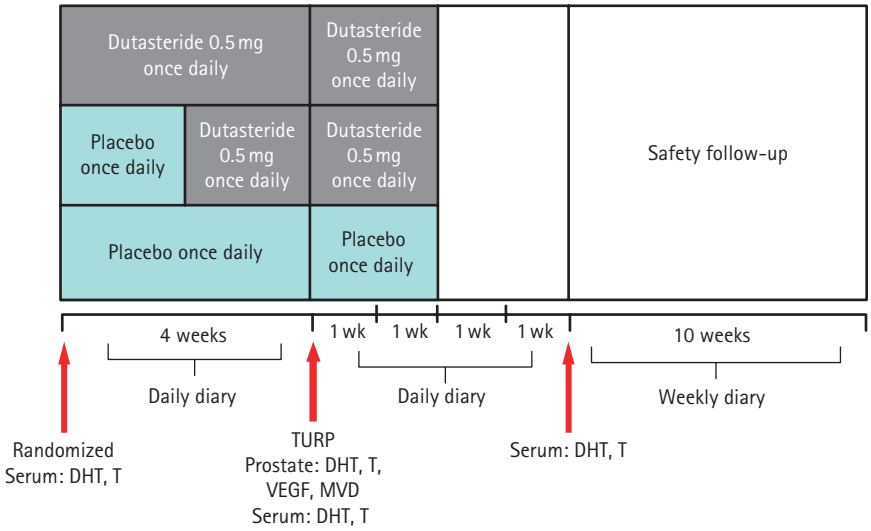
TURP is the standard method for relieving BOO in men with BPH, but the operation still requires in-hospital management due to a relatively high incidence of complications during and afterward, particularly in those with large (>30 mL) prostates [1]. In one study, peri-operative blood loss was >1 L in 13% of the patients [2], increasing the risk of haemodynamic instability and the need for erythrocyte transfusions. Haematuria and clot retention after TURP might prolong the time in hospital, and even necessitate re-operation.

After the introduction of selective antiandrogens as a medical treatment for BPH, some studies showed that finasteride prevented spontaneous episodes of urothelial bleeding in men with BPH [3–7]. Haematuria or lack of haematuria in patients with BPH appears to be related to the density of microvessels in the prostatic urothelium [8]. 5α-reductase inhibitors (5ARIs) such as dutasteride and finasteride are known to suppress dihydrotestosterone (DHT) levels and thereby prostate growth. Some research suggests that in the cascade of associated effects, the androgen-controlled vascular endothelial growth factor (VEGF) is also suppressed, leading to decreased angiogenesis, offering a possible mechanism for the observed effect with finasteride. Treatment with finasteride or other antiandrogens before TURP was later reported to reduce surgical blood loss [9–13], but not all studies showed a consistent effect [14–16].

While finasteride inhibits only the type II 5AR isoenzyme, at therapeutic doses [17] the dual 5ARI, dutasteride, inhibits both type I and type II isoenzymes. Treatment with dutasteride results in near-maximal and consistent suppression of serum DHT, with >85% of men achieving a ≥90% reduction within 4 weeks, whereas finasteride suppresses serum DHT by ≈70%, with only 49% of treated men achieving this reduction in one series [18]. Recently, a mean suppression of the intraprostatic DHT level of 95% relative to placebo was found after 3 months of treatment with dutasteride [19]. Therefore, if finasteride decreases surgical blood loss, it is logical to also expect this effect with dutasteride.

The aim of the present study was to examine whether dutasteride decreases blood loss and complications after TURP when provided as a 2–4-week treatment before surgery, and continued for 2 weeks afterward.

FIG. 1. A schematic of the study design.



PATIENTS AND METHODS

In this double-blind study we enrolled men aged 52–85 years (mean 67) with a prostate volume of ≥30 mL (measured by TRUS using the ellipsoid formula). Patients were recruited from 23 centres in six countries (Denmark, Finland, Sweden, Norway, Netherlands and the UK) and were scheduled for TURP to treat BPH in a period that allowed 28–32 days of preoperative treatment with study medication.

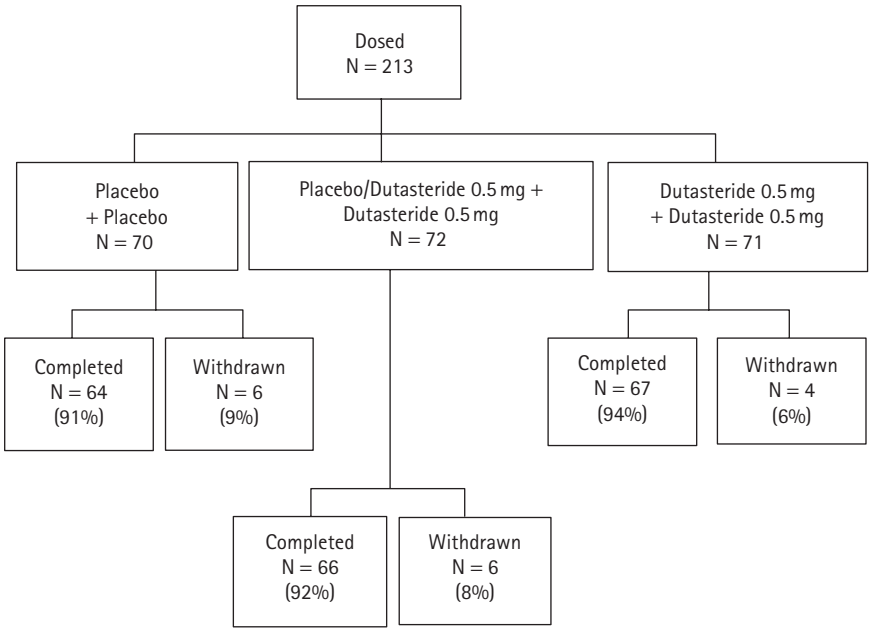
Exclusion criteria included a history or evidence of prostate disease other than BPH, previous prostate surgery, treatment with any 5ARI within 12 months, requirement for treatment with aspirin or NSAIDs during the restricted periods, and severe medical conditions such as liver disease, bleeding disorders (e.g. haemophilia, von Willebrand's disease, etc.) and unstable cardiovascular problems.

The patients were randomized in a 1 : 1 : 1 ratio to one of three treatment groups. Group 1 received daily placebo for 4 weeks before and 2 weeks after TURP, group 2 received placebo for 2 weeks followed by 0.5 mg of dutasteride (Avodart, GlaxoSmithKline, UK) daily for 2 weeks before and 2 weeks after TURP, and group 3 received dutasteride 0.5 mg for 4 weeks before and 2 weeks after TURP (Fig. 1). A daily 0.5 mg tablet is the therapeutic dose approved for treating symptomatic BPH in over 65 countries spanning Europe, the USA and other regions.

The primary efficacy outcome was total blood loss during TURP (collected in the irrigation fluid in the operating theatre). Secondary efficacy outcomes included measures of bleeding 4 and 14 weeks after TURP, and the incidence of clot retention, transfusions, acute urinary retention, UTI and urinary incontinence after TURP.

During the 4 weeks before and 4 weeks after surgery, all patients completed a daily diary card documenting all bleeding events and clots, and thereafter a weekly diary for a further 10 weeks. The severity of events was subsequently categorized using the grading scale of Puchner and Miller [20]. During hospitalization the investigators also recorded any bleeding considered to be excessive. Every patient visited his urologist on up to nine occasions during the 20 weeks of study participation, and any adverse effect was noted. Bolus doses of anticoagulants for preventing deep vein thromboses were

FIG. 2. The disposition of the randomized patients.



allowed before TURP, but no such drugs were given after the TURP unless clinically indicated. Aspirin and NSAIDs were discontinued 10 days before surgery, aspirin was allowed again 5 days after TURP, but NSAIDs were disallowed for the remainder of the study.

Spinal anaesthesia was used in 98% of the operations. Surgery was supervised by at most two skilled surgeons per site. Blood loss was measured for each bucket used to collect irrigating fluid, using the 'Low Hemoglobin' system (HemoCue AB, Ängelholm, Sweden). This photometer measures low haemoglobin (Hb) concentrations with high precision [7]. About 1000 IU of heparin had been added to each bucket before use and, after manual stirring, two samples were taken from the periphery of the bucket [2]. The Hb content of the bucket was calculated as the product of the irrigating fluid volume (obtained by weighing and assessed independently against a visual volumetric scale), and the mean value of the two Hb samples. The total blood loss was the sum of the Hb content in all buckets used during surgery. The blood loss immediately after surgery was also calculated in the same way. Catheter traction to reduce postoperative blood loss was disallowed unless clinically imperative, a 1% occurrence.

Serum concentrations of testosterone and DHT were measured on the day of recruitment, just before TURP and 4 weeks later. The serum samples were analysed by gas chromatography followed by tandem mass spectrometry (Taylor Technology, Princeton, NJ, USA). The resected prostate chips were also assessed for these hormones, using liquid chromatography and tandem mass spectrometry (PPD, Richmond, VA, USA) and for MVD (Bostwick Laboratories, Richmond, VA, USA). Areas of the prostatic urethra and prostatic nodular hyperplasia were fixed in 10% formalin and stored at 4 °C until incubated with a monoclonal immunohistochemical antibody to CD34 (Dako AB, Glostrup, Denmark) [8]. After mild staining with haematoxylin-eosin, the most microvessels within an area of 0.754 mm^2 was counted by light microscopy at ×200. All measurements were made in a central laboratory, as arranged by the sponsor to reduce inter-site variability for each laboratory variable (e.g. Hb losses, MVD and hormone levels). Medical resource use was recorded in terms of duration of hospital stay, number of unexplained outpatient visits, hospital re-admissions and surgical procedures.

The power calculations were based on the study by Donohue *et al.* [11], which showed a benefit of finasteride treatment in reducing peri-operative blood loss compared with placebo. The results are reported as the mean (SD or SEM), adjusted for baseline characteristics, unless otherwise noted, and are given for the intent-to-treat population. The study had >90% power to detect a difference in pair-wise comparisons between each active group and placebo in the primary endpoint (blood loss during TURP) using a *t*-test and a general linear regression model with effects for treatment and country. There was 80% power to detect a difference in the secondary endpoint of proportion of patients with peri-TURP bleeding after catheter withdrawal. Multiple stepwise regression analysis was used to identify significant effects in the blood loss model. Complications after TURP were compared using the Fisher's exact test. Pair-wise comparisons of serum and intraprostatic testosterone and DHT were made using the Wilcoxon rank-sum test, with $P < 0.05$ considered to indicate statistical significance.

RESULTS

Of the 214 patients enrolled, 213 took study medication, 202 had a TURP and 197 completed the study. There were no differences among the treatment groups in premature discontinuation (Fig. 2) or demographic variables (Table 1). Patients had had BPH symptoms during the previous 4 years and had received a diagnosis of BPH within the last 2 years (median).

The mean (SD) operative duration was 45 (17) min, during which 25 (15) g of prostatic tissue was resected. There were no statistically significant differences among the treatment groups in the primary endpoint of Hb loss during surgery (Table 2). The resection weight and operating time were significant effects in the blood loss model ($P < 0.004$ and <0.001, respectively) but correction of the Hb loss for these variables showed no significant differences among the groups. Hb loss after TURP was about a third of the total surgical loss (Table 2); 1–3% of the patients in each group received blood transfusions.

Clot retention after TURP occurred in 6–11% of patients, two of whom required further surgery during the initial hospitalization, three were re-admitted as inpatients and one as an outpatient after initial discharge. Acute urinary retention was recorded in 11–17%, UTI in 20–31% and urinary incontinence in 14–15% of the patients over the 14 weeks after TURP (Table 2). The mean hospital stay was 3.1–3.3 days. There were no statistically

TABLE 1 Demographic and background data on the TURP operations (intent-to-treat population)

Characteristic or variable	Group 1 Placebo	Group 2 Placebo + dutasteride	Group 3 Dutasteride	All groups
Number of patients*	70	72	71	213
Mean (SD, range) age, years	66 (7, 54–80)	67 (7, 54–82)	67 (8, 52–85)	67 (7, 52–85)
Weight, kg	80 (11)	84 (15)	82 (12)	82 (12)
Prostate volume, mL	53 (20)	56 (23)	62 (27)	57 (24)
Mean serum PSA level, ng/mL	5.3 (5.8)	4.7 (3.5)	4.9 (2.7)	4.9 (4.2)
Any current medical condition, %	76	90	86	84
Conditions of interest, %				
Hypertension	23	35	28	29
Coronary artery disease	9	10	6	8
Peripheral vascular disease/stroke	1	4	1	2
Other cardiovascular	11	6	6	8
Respiratory	14	11	21	15
Type of irrigating fluid, %				
Mannitol 3%	24	24	26	25
Glycine 1.5%	71	69	64	68
Sorbitol-mannitol	5	7	10	8
Irrigant temperature at 37 °C, %	80	75	78	78
Puncture of prostatic capsule, %	18	10	6	11
Irrigating fluid used, L	18.0 (6.7)	18.0 (7.3)	18.8 (7.3)	18.3 (7.1)
Weight of resected tissue, g	23 (14)	23 (15)	27 (16)	25 (15)
Operating time, min	45 (17)	43 (16)	46 (18)	45 (17)
Histological prostate cancer, %	5	4	4	4

**The number per group varied slightly according to the variable.*

significant differences among the groups in these variables or any of the measures of medical resource use.

Peri-operative bleeding, defined as excessive bleeding, or clot retention (requiring intervention) during the initial hospitalization, or the occurrence of bloody urine and/or clots in the urine as reported by the subject on the diary card, was reported in >90% of subjects in each treatment group, with no statistically significant differences among the groups. Excessive and severe bleeding occurred in relatively few patients per group (Table 2).

Treatment with dutasteride did not alter the MVD in the prostatic urethra or in regions of nodular hyperplasia. However, as expected, the drug decreased the serum concentration of DHT by 86–89% ($P < 0.001$) while increasing the serum testosterone level by 13–15% before treatment ($P < 0.05$). Dutasteride also reduced the intraprostatic concentration of DHT by 10 times compared with placebo (290, 365 and 3155 pg/g DHT in groups 3, 2 and 1, respectively) while increasing the tissue level of testosterone (Table 2). Dutasteride was generally well tolerated, with no severe adverse events recorded that were considered to be drug-related. One cardiac arrest occurred in the placebo group.

DISCUSSION

The primary objective of this randomized, double-blind, placebo-controlled study in men with BPH was to assess whether pretreatment with dutasteride reduces the degree of blood loss during TURP. Despite an 86–89% reduction in serum DHT, neither blood loss during or after TURP, nor the incidence of TURP-associated complications, differed significantly among the treatment groups. The DHT reduction was slightly lower than the 94% achieved after 3 months of treatment with 0.5 mg dutasteride [19], but is significantly greater than for finasteride [18], and as such would be expected to be sufficient for an effect.

The present study is the largest reported to date with a 5ARI, and the first to involve many hospitals from six countries. The range of surgical technique and the complication rates are likely to represent the spectrum of TURP in Europe. If individual results from each country or site within the study are examined, they also reflect the range and lack of consistency of results observed in the previously reported small single-centre studies of finasteride. The overall transfusion rate of ≈3% and the extent of blood loss in the placebo group are as expected from previous reports [2,21]. The incidence of clot retention and urinary incontinence was higher than previously reported, perhaps due to the prospective collection and the extended follow-up after TURP. Also, half of the clot retention events were clustered in just three centres, and for urinary incontinence the liberal definition (Table 2) and active solicitation of reports might have resulted in the higher reported incidence.

The most practical way to quantify blood loss during TURP is by measuring Hb in the irrigating fluid [2]. Although Hb levels are only 5–10% of that found in whole blood, precision is ensured by using a highly

TABLE 2 Blood loss during or after TURP, complications after TURP, and changes in DHT and testosterone

Variable	Group 1 Placebo	Group 2 Placebo + dutasteride	Group 3 Dutasteride
N	70	72	71
Blood loss, g Hb/g resectate			
During TURP			
adjusted mean (SEM)	2.55 (0.41)	2.15 (0.40)	2.55 (0.39)
median (range)	1.54 (0.24–28.89)	1.56 (0.14–15.35)	1.37 (0.11–20.49)
After TURP			
adjusted mean (SEM)	0.85 (0.25)	0.98 (0.25)	0.99 (0.24)
median (range)	0.31 (0.10–7.92)	0.40 (0.02–6.70)	0.38 (0.05–7.12)
Total during and after TURP			
adjusted mean (SEM)	3.09 (0.44)	2.84 (0.44)	3.16 (0.43)
median (range)	1.94 (0.25–28.89)	2.17 (0.14–15.35)	1.75 (0.22–20.71)
Total blood loss during TURP, g Hb			
adjusted mean (SEM)	54.5 (7.45)	45.7 (7.33)	61.1 (7.19)
median (range)	28.8 (3.53–260.05)	31.2 (1.35–225.90)	32.5 (1.05–317.56)
Total blood loss during TURP, L			
adjusted mean (SEM)	0.37 (0.05)	0.32 (0.05)	0.43 (0.05)
median (range)	0.24 (0.03–1.74)	0.21 (0.01–1.64)	0.21 (0.01–2.48)
N (%):			
Excessive/severe bleed after TURP	4 (6)	1 (1)	2 (3%)
Blood transfusions	2 (3)	2 (3)	1 (1)
Clot retention	4 (6)	8 (11)	4 (6)
Acute urinary retention	8 (11)	12 (17)	9 (13)
UTI	14 (20)	19 (26)	22 (31)
Urinary incontinence*	10 (14)	10 (14)	11 (15)
Mean (SEM) highest MVD			
Prostatic urethra	44 (20)	46 (18)	48 (21)
Nodular hyperplasia	53 (22)	50 (21)	55 (21)
Bleeding after TURP			
N	64	67	67
Median (range) total days with bleeding	13 (1–66)	13 (2–50)	15 (1–109)
Median (range) days to last bleeding event	26 (3–103)	25 (5–94)	25 (1–110)
Severity of bleeding†, n (%)			
Mild	48 (75)	53 (79)	50 (75)
Moderate	56 (88)	64 (96)	63 (94)
Severe	7 (11)	2 (3)	5 (7)
Changes in DHT and testosterone			
N	70	72	71
Serum testosterone (adjusted means)			
% change to TURP	3.5	14.5	13.3
% change 4 weeks after TURP	2.7	9.8	9.6
Serum DHT (adjusted means)			
% change to TURP	0.9	–85.9	–88.7
% change 4 weeks after TURP	–10.7	–87.6	–87.4
Intra-prostatic hormones, pg/g			
Adjusted mean testosterone	43	1414	1644
Adjusted mean DHT	3155	365	290

**Socially of hygienically unacceptable leakage of urine; †Patients could be included in more than one severity level.*

sensitive photometer. More experienced resectionists operate faster and remove more tissue than the less experienced, and two-thirds of the variability in peri-operative blood loss was therefore accounted for by the amount of resected tissue and the operative duration [2]. To adjust for such variability, Hb loss can be expressed per amount of resected tissue, or per minute of operating time, but in the present study this did not affect intergroup differences. To recalculate these losses to the volume of blood is cumbersome

because blood Hb levels decrease progressively during surgery [22]. For simplicity, adjustment by preoperative Hb alone is most commonly used, although the blood plasma then becomes underestimated [23]. In the present study, blood Hb was almost identical among the groups, and transformation of Hb loss to actual blood loss showed no hidden differences, but is included for reference (Table 2).

The rationale for the view that 5ARIs reduce blood loss during TURP is that these drugs shrink the prostate by attenuating the number of blood vessels in a way similar to the effect achieved with androgen ablation [24,25]. Many physicians subscribe to this view and it is supported by studies conducted in the late 1990s showing that the 5ARI, finasteride, reduced gross haematuria secondary to prostatic bleeding from the urothelium [3–7]. The entire gland might then be less vascular, with the potential for less bleeding as a result of surgery. However, the results of studies of finasteride on blood loss during TURP have been less consistent and there are several possible explanations.

To the authors' knowledge, only four double-blind placebo-controlled studies (including the present) have been published, two with finasteride and two with dutasteride. A study of 60 patients, in whom the amount of blood lost was actually measured, did *not* confirm that 3 months of finasteride before surgery reduced peri-operative blood loss [14].

In another single-centre study, Donohue *et al.* [11] randomized 70 patients to finasteride 5 mg or placebo for only 2 weeks before TURP, and reported losses of 2.7 and 4.7 g Hb/g resected tissue, respectively. The positive effect of such a short pretreatment period encouraged our use of a treatment arm with only 2 weeks of medication with dutasteride before TURP. The study by Donohue *et al.* differed from other studies based on irrigation fluid measures, in that Hb loss in the placebo group was unusually high, and this might explain the observed difference between the treatment groups. The peri-operative bleeding in a series of up to 700 patients corresponded to a Hb loss of 2.3 g Hb/g resected tissue [2], which is similar to the 2.4 g reported in the present study.

A third multicentre study by Boccon-Gibod *et al.* [16] followed 59 patients randomized to 4 weeks of pretreatment with either placebo or dutasteride 0.5 mg. The mean blood loss during TURP was 1.4 and 1.9 g Hb/g resected tissue, respectively, with no significant difference between treatment groups.

Other recent and less robust studies have generated further differing results. In one study, 30 patients treated with finasteride for 8–10 weeks before TURP had less blood loss than had untreated patients [12]. The amount of resected tissue was large, 45 g, but it is unclear whether treatment was randomized. Furthermore, blood loss was assessed as the decrease in blood Hb, which is affected by the extent of anaesthesia intravenous fluid therapy. The transfusion rate in the untreated group was high, at 12%. Similar results were reported in a study conducted by Özdal *et al.* [13], using 4 weeks of finasteride treatment. However, in a randomized study of 33 patients, Lund *et al.* [15] reported no difference in blood loss between finasteride and placebo given for 3 months. It is unclear how blood loss was assessed and operating times tended to be longer, with more prostatic tissue resected in the placebo group, resulting in numerically greater blood loss than the finasteride group.

The antiandrogen chlormadinone acetate given orally for 1 month before TURP did not reduce the crude blood loss during surgery, nor the blood loss corrected for operating time, compared with placebo, but did result in a significant difference in blood loss per gram of resected tissue. The MVD was lower in those who received chlormadinone acetate [14].

In an open study of a subgroup of patients with resected weights of >30 g, Hagerty *et al.* [9] reported that 12 patients who received finasteride 2–4 months before TURP needed fewer blood transfusions and had a lower incidence of clot retention than 19 who did not receive the drug. Factors contributing to these findings might have been the high overall rate of transfusion and high resected weight. Exploratory analyses by Sandfeldt *et al.* [14] also support the existence of a benefit in larger resections. However, further studies are required to fully assess the hypothesis that the effect and benefit of 5ARI treatment would manifest at resected weights of >30 or >40 g.

The lack of observable effect of treatment with dutasteride for 2 or 4 weeks on median MVD in prostatic tissue was not unexpected. It is consistent with findings from another dutasteride study, which suggested that a minimum of 6 weeks of treatment is necessary to effect these changes [26]. It is also consistent with the findings of Haggstrom *et al.* [27], who found no reduction in human prostate MVD even after 3 months of previous treatment with finasteride, and similar to the findings of Canda *et al.* [28] in rats. This might be because shrinkage of the gland occurred concomitantly with the drug treatment, and that the drug reduced the total number of blood vessels in the prostate but not their density. As finasteride shrinks the prostate by 10% within 3 months [14], gland shrinkage is unlikely to be the reason why antiandrogen treatment has been effective in previous studies; these discrepancies are presently unexplained.

The reduction in VEGF levels in resected suburethral prostate tissue that has been documented in two finasteride studies [27,29] did not occur in the present study (data not shown). The reason is not likely to be the short duration of treatment (unlike MVD), as an effect on VEGF might be expected within days of starting treatment. However, the qualitative assessment of the immunohistochemistry used in the present study is unlikely to give the same degree of differentiation between treatment groups as would have been achieved with the originally planned Western blot and densitometer approach (which was replaced due to technical difficulties). Donohue *et al.* [30] recently reported significant changes in VEGF and MVD after 2 weeks of finasteride treatment. The sensitivity of their assays might have been enhanced by using 10 views per region (compared with only three per region used in the present study), and also by preparing and staining all tissue in one day (personal communication).

In conclusion, dutasteride 0.5 mg is well tolerated and effective in reducing intraprostatic DHT within 4 weeks. However, the present study showed no effect of pretreatment with oral dutasteride daily for 2 weeks or 4 weeks before TURP, followed by 2 weeks continued medication after TURP, on blood loss during or after TURP, or on the complication rate. This study adds to the body of conflicting evidence on the efficacy of 5ARIs in reducing TURP-associated blood loss. It is possible that 5ARIs might be effective

against a background of high blood loss and in subpopulations, but further well-controlled studies are required to examine this hypothesis.

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CONFLICT OF INTEREST

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Abbreviations: **5AR(I)**, 5α-reductase (inhibitor); **DHT**, dihydrotestosterone; **VEGF**, vascular endothelial growth factor; **MVD**, microvessel density; **Hb**, haemoglobin.