INTRODUCTION

BPH is common in men aged >40 years; the incidence and prevalence increase with age, and 30% of men aged >70 years have symptoms related to prostatic enlargement [1]. These symptoms impair physiological and functional well-being, and interfere with daily living [2]. Although BPH rarely threatens life, it can contribute to acute urological complications, particularly acute urinary retention (AUR), which is often considered to be the most serious complication of BPH [3]. AUR is relatively common, painful and distressing for the patient, and has considerable economic costs [4]. Early estimates of incidence varied widely, but better estimates now available from population-based studies of men in the community [5] indicate an incidence of 5–25 per 1000 person-years, or 0.5–2.5% per year. The risk is cumulative and increases with age.

AUR is one of the main indications for TURP, reported as the precipitating reason for 25–30% of emergency procedures [6,7]. After an episode of spontaneous AUR (i.e. not caused by a specific event such as surgery, catheterization or drug), 15% of patients in one long-term study had another episode of AUR, and 75% had subsequent surgery [8]. The current management of AUR is to insert a urinary catheter to relieve symptoms, but this can add to the patient’s symptoms if UTI develops. In addition to being uncomfortable for the patient, this is an avoidable risk factor for blood loss after TURP, should surgery become necessary [9]. A trial without catheter (TWOC) is considered preferable to leaving a catheter in place; success rates of 23–28% have been reported [10,11], but significant numbers of patients still require TURP, either as an emergency or electively.

The functional symptoms of BPH can be reduced by α-blockers such as tamsulosin [12], which improve flow rates and bladder emptying, and it is thought likely that they also help to reduce bladder outlet resistance by effects on the sympathetic tone of the bladder neck and prostate stroma [13]. By reducing this resistance, the patient retains sufficient detrusor function, α-blockers could help relieve AUR and improve the chances of a successful TWOC [14]. The optimum duration of treatment with α-blockers has not been fully assessed, and there is controversy about the length of time the catheter should remain in situ for the initial treatment phase. One study suggested that more prolonged use of indwelling catheters has better success rates for TWOC; immediate withdrawal had a 44% success rate compared with 62% if the catheter was left for 7 days [15].

Tamsulosin is an α1-blocker with particular affinity for the α1A receptors that predominate numerically and functionally in...
the prostate, and the $\alpha_{10}$ receptors in the bladder. The present study was designed to investigate the efficacy of modified-release tamsulosin hydrochloride (0.4 mg daily) compared to placebo in the management of patients with AUR who were suitable for a TWOC.

### PATIENTS AND METHODS

Between March 1997 and December 2000, 149 men aged 51–91 years (mean 69.4) were entered into the study, and randomly assigned to receive tamsulosin hydrochloride in a modified-release capsule once daily (75 patients) or placebo (74): the intent-to-treat (ITT) population was 141 patients. All had been admitted to hospital through the Accident and Emergency Department with AUR, and had been catheterized in the Accident and Emergency Department with AUR. The present study was designed to investigate the efficacy of modified-release tamsulosin to make a clinically significant difference it was felt that 60% should be able to void. Thus 42 patients per group would be needed to detect a difference at a two-sided significance level of 0.05 with a power of 80%. Because the data on the effect of $\alpha$-blockers on this facet of patient care are minimal, we decided to recruit 60 patients in each group. After completing the study, but before the coding was broken, it was obvious that few patients had met the original three criteria for a successful TWOC, so we considered several weaker criteria for secondary analyses. In one of these secondary analyses, a successful TWOC was defined as a combination of the patient being allowed to go home without a catheter and the subjective opinion of the investigator. In another, the number of criteria to be met to define a successful TWOC was changed to two, and the maximum allowed residual volume of urine was increased to 250 mL, as higher residual volumes are correlated with an increased risk of patients experiencing a repeat episode of AUR [16].

### RESULTS

The predetermined primary criteria for defining a successful TWOC showed no significant benefit of tamsulosin over placebo (34% vs 24%, $P = 0.193$, Table 1). The results presented are a secondary analysis of this study. Analysing any two free-flow criteria, tamsulosin gave a significantly better outcome than placebo (Fig. 1); 34 patients who received tamsulosin were less likely to need re-catheterization than those who received placebo (Fig. 1): 34 patients who received tamsulosin and 18 who received placebo did not require re-catheterization (48% vs 26% success, $P = 0.011; \text{odds ratio } 2.47, 95\% \text{CI } 1.23–4.97)$.

### TABLE 1 Analysis using free-flow criteria, as n (%) of patients in subgroups with a successful result

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tamsulosin</th>
<th>Placebo</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients</td>
<td>71</td>
<td>70</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome by criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary analysis</td>
<td>24 (34)</td>
<td>17 (24)</td>
<td>41 (29)</td>
<td>0.193</td>
</tr>
<tr>
<td>Any two free-flow criteria</td>
<td>41 (58)</td>
<td>28 (40)</td>
<td>69 (49)</td>
<td>0.020</td>
</tr>
<tr>
<td>Two specified criteria*</td>
<td>37 (52)</td>
<td>24 (34)</td>
<td>61 (43)</td>
<td>0.019</td>
</tr>
<tr>
<td>Any two criteria†</td>
<td>43 (61)</td>
<td>29 (41)</td>
<td>72 (51)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Outcome by age, years (primary analysis)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>3 (38)</td>
<td>5 (50)</td>
<td>8 (50)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>10 (40)</td>
<td>6 (24)</td>
<td>16 (32)</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>10 (33)</td>
<td>5 (16)</td>
<td>15 (25)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>1 (13)</td>
<td>1 (25)</td>
<td>2 (17)</td>
<td></td>
</tr>
</tbody>
</table>

*Primary analysis: three criteria, i.e. flow rate >5 mL/s, voided volume >100 mL, residual ≤ 200 mL; †Flow rate >5 mL/s, voided volume >100 mL; ‡Flow rate > 5 mL/s, voided volume > 100 mL, residual ≤ 250 mL.
Of the patients who received tamsulosin, those taking eight doses before catheter removal were less likely to need re-catheterization than those taking three doses (53% vs 46%). A higher proportion of eight-dose patients had a successful outcome, using the original definitions, than the three-dose patients (38% vs 27%) but this difference was not significant (P > 0.1) and this issue was not factored into any of the subsequent analyses. In all, 120 patients (81%) did not complete both phases of the study; most of these (89, 60%) were because of the need for re-catheterization at the end of the acute phase of the study. Because of the high loss rate there were too few patients remaining in the study after the initial measurements for a valid analysis of long-term efficacy after AUR. There was no significant difference between age groups in the outcome of successful voiding when analysed by the free-flow criteria (Table 1), but the there were too few patients aged >80 years to allow meaningful conclusions to be drawn.

SAFETY

The adverse-event profile was as expected for this class of drug, and the incidence of adverse events similar in the two groups. Exceptions were dizziness and somnolence, which occurred in seven (10%) and four (6%) patients who received tamsulosin, and two (3%) and two (3%) receiving placebo. Both events are recognized with \( \alpha \)-blocker use, although perhaps because there were many elderly patients in the study their incidence was higher than the known tolerability profile of tamsulosin. Fewer than half of the patients had adverse events. More patients who received tamsulosin withdrew for adverse events or adverse experiences (seven, 9%) than those who received placebo (one, 1%), but only five had an adverse event probably related to tamsulosin (three incidences of dizziness, and one each of somnolence and dry mouth). None of these adverse events were serious. One patient in the tamsulosin group died during the study, the cause of death being noted as carcinomatosis, but the site of the primary tumour was not given. This death was classified as unlikely to be related to the test drug.

DISCUSSION

The primary objective of the present study was to evaluate the efficacy of tamsulosin compared with placebo for treating catheterized patients with AUR caused by BPH, by comparing those voiding successfully after removing their catheter. The predetermined primary criteria for defining a successful TWOC showed no significant benefit of tamsulosin. However, because the initial criteria gave few successful TWOCs it was decided, before breaking the randomization code, to use secondary analyses for revised criteria of success. The definition of 'success' in the treatment of AUR has yet to be universally agreed. For patients it must, at least in part, relate to the lack of need for re-catheterization. Patients in the tamsulosin group had an odds ratio in their favour of 2.47 of not requiring re-catheterization before being sent home. For success as defined by the investigator, the odds ratio in favour of tamsulosin was 2.22. When assessed by any two free flow criteria (flow rate, voided volume and residual volume) patients on tamsulosin were more likely to void successfully in the acute phase.

After the present study was designed the use of re-catheterization rates as a clinical marker was reported in two studies comparing alfuzosin and placebo, both taken for 24 h after catheterization. One was a small pilot trial and the other a multicentre randomized controlled trial in which the criteria for assessing the success of TWOC were simply the voiding of urine and lack of need for re-catheterization [17–19]. A similar study with alfuzosin showed a significant difference in outcome by age; younger patients were more likely to have a successful TWOC [17], but in the present study the efficacy was similar across the age range. The patients in the present study were elderly (mean age 69.4 years), but the efficacy results were no different from those expected for younger groups.

In the present trial some patients were catheterized for only 3 days and others for 8; this allowed for variations in practice between hospitals and the distribution was equal for both study groups. Differences in outcome between 3- and 8-day patients were not statistically significant, but the study may not have had the power to detect such a difference. The distribution of patients was equal in both study groups, and so is unlikely to have affected the analysis of whether the treatment effects of tamsulosin differ from those of a placebo.

The safety profile was as expected for an \( \alpha \)-blocker, although the incidence of some adverse events was higher than published for tamsulosin, possibly because of the greater average age of the present men. Less than half of the patients reported adverse events, and none were serious. One patient died from unrelated carcinomatosis, despite any known malignancy being a contraindication to participation.

Many questions remain unanswered about the use of \( \alpha \)-blockers in the clinical setting. It is still not possible to predict which patients are likely to respond to \( \alpha \)-blockers and which are not; the study was not powerful enough to answer this. There were also insufficient data to draw conclusions about long-term outcomes for patients treated with tamsulosin; it is a pity, in retrospect, that the study was not designed to follow patients who were re-catheterized as well as those who were not. Published data from untreated patients suggest that many will require re-catheterization or surgical intervention; 84% had surgery within 5 years in one study [20]. It would be valuable to study the long-term use of tamsulosin after catheterization for AUR. Work with another \( \alpha \)-blocker, alfuzosin, shows that treatment for 6 months was associated with a significantly lower incidence of de novo AUR than with placebo (0.4% vs 2.4% [21]). A retrospective analysis of five studies of the long-term use of \( \alpha \)-blockers for treating BPH showed that the incidence of AUR was significantly lower in patients taking this group of drugs, and there was a possible reduction in the need for surgery [22].

Currently, only one \( \alpha \)-blocker licensed in Europe for treating BPH has the management of AUR as an indication. From the present results, tamsulosin can also be recommended for treating patients after catheterization for AUR, and can significantly reduce the likelihood of the need for re-catheterization, at least acutely.

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Correspondence: Malcolm G. Lucas, Morriston Hospital, Swansea, UK.
E-mail: malcolm.lucas@swansea-tr.wales.nhs.uk

Abbreviations: AUR, acute urinary retention; TWOC, trial without catheter; ITT, intent to treat.