

The effectiveness of a treatment protocol for male lower urinary tract symptoms in general practice: a practical randomised controlled trial

Roelf JC Norg, Kees van de Beek, Piet JM Portegijs, CP Onno van Schayck and J André Knottnerus

ABSTRACT

Background

Randomised controlled trials have shown the efficacy of several treatment modalities for lower urinary tract symptoms (LUTS) in selected populations. The effectiveness in daily practice has hardly been investigated, especially in primary care and is dependent on choices between all possible treatment options and best investigated in a comprehensive study, including all treatment modalities (watchful waiting, α -blockers, 5- α -reductase inhibitors, and surgery).

Aim

Assessment of the effectiveness of a comprehensive treatment protocol for LUTS in primary care.

Design of study

Randomised controlled trial.

Setting

Fourteen general practices in the Netherlands.

Method

Intervention: treatment protocol based on a formalised expert opinion. Control condition: usual care. Study population: 208 subjects with moderate to severe LUTS (IPSS ≥ 8 , median = 13). Outcome measures: symptom severity (IPSS [International Prostate Symptom Score]), bother score (Dan-PSS [Danish Prostate Symptom Score]), and maximum urinary flow (Q_{max}); incidence of acute urinary retention and urinary tract infections.

Results

In the intervention group markedly more subjects used an α -blocker at end of follow-up than in the usual care group (24% versus 6%). No significant differences were found between intervention and control group in IPSS, Q_{max} or Dan-PSS.

Conclusion

α -blockers and watchful waiting are the most frequent treatment modalities for LUTS in primary care. Our study showed no evidence that a protocol using well-defined indications for all possible treatment modalities based on a formalised expert opinion procedure has added value. Based on our results, we cannot recommend a broadening of the indication for α -blockers, which, however, seems to be the current trend.

Keywords

family practice; practice guidelines; prostatic hyperplasia; randomized controlled trial; therapy.

INTRODUCTION

The awareness of male lower urinary tract symptoms (LUTS) has increased during the past decade. Ageing and the availability of medication have led to an increase in older men being diagnosed and treated for LUTS. Consequently, costs are increasing.¹ Furthermore, patients visiting both GPs and urologists nowadays are younger and have less severe symptoms.²

Patients with LUTS may be offered four main treatment options: watchful waiting, α -blockers, 5- α -reductase inhibitors, and surgery. α -blockers provide moderate improvement of symptoms and urinary flow measures.^{3,4} 5- α -reductase inhibitors can reduce symptoms and the incidence of acute urinary retention in patients with large prostates.^{5,7} Surgery is the most powerful method of reducing symptoms but carries a higher risk of irreversible side effects.^{8,9} The efficacy of these treatments has been investigated in randomised clinical trials with often well-defined, selected, 'homogeneous' populations from secondary care settings. Inclusion and exclusion criteria required investigations like urinary flow measurements or urodynamics that are not directly available to GPs.^{3,4,8}

Therefore, the efficacy figures of these trials cannot easily be generalised to the heterogeneous situation in

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primary care with its generally less-developed clinical stages.^{10,11} As a result, guidelines fail to provide specific diagnostic criteria and sharp indications for therapy. They leave much room for interpretation.^{9,12,14} Consequently, daily care in primary care varies widely.^{2,15,19} GPs must treat patients on a likely (symptoms of impaired micturition) rather than a confirmed diagnosis (proven infravesicular outflow obstruction). In situations like this, studies into the effectiveness of treatments in daily practice may be of great practical value if they enrol patients on presenting symptoms rather than definitive test results.^{20,21}

Such 'practical' or 'pragmatic' randomised controlled trials may be used to investigate individual treatment options or, alternatively, comprehensive treatment regimens. A comprehensive approach, including various treatment options, may better resemble actual practice: in daily care the decision to start or stop a treatment depends on the physician's assessment of not only an individual treatment option, but of the relative effectiveness and risk of side effects and complications of all available treatments. We present such a study comparing a comprehensive treatment protocol with usual care.

Lacking an evidence-based protocol with sharp indications, we chose a feasible and useful alternative for the development of a treatment protocol for primary care. The adequate treatment policy for the included patients could be determined using a previously validated algorithm.^{14,22} This algorithm reflects the treatment choices of an international panel of urologists. Such a formalised panel judgement rationalises the individual management choices, and thereby may improve both the efficiency and patient outcome.¹² It also resembles daily practice, where — lacking clear guidelines — GPs are likely to anticipate an (expected) treatment of specialists. If a GP expects the urologist to prescribe medication, he may do so himself. If he expects the urologist to perform surgery, he probably will refer his patient for (assessment of the eligibility for) surgery.

METHOD

Study population

The participants of this study were recruited from a 12-month cohort study, which comprised of all men aged 55 years or older registered in 14 general practices (26 GPs). The participants of the cohort study kept a 3-day micturition diary and filled in questionnaires with general questions (for example, demographics and micturition behaviour), and questions that assessed the symptoms (International Prostate Symptom Score [IPSS], referred to as 'symptom score')²³ and the bother caused by the symptoms (Danish prostate symptom score [Dan-PSS]),²⁴ referred to as 'bother score'). They underwent

How this fits in

For GPs facing their older male patients with lower urinary tract symptoms the decision of who to treat and how is very difficult. Guidelines do not provide primary care physicians with clear-cut criteria indicating the appropriate treatments. An approach based on the (validated) opinion of an expert panel may be the best available alternative.

physical examination, and measurement of urinary flow, PSA (prostate specific antigen), creatinin, post-void residual volume, and prostate size (Figure 1).

Eligible for inclusion in this trial were all subjects with moderate or severe LUTS (IPSS ≥ 8) at the time of recruitment, and at least one earlier occasion (to minimise spontaneous symptom improvement due to regression to the mean). Exclusion criteria were known or increased risk of prostate cancer (PSA >10 ng/ml, or PSA >2.5 ng/ml and a free to total (F/T) ratio $<25\%$); prior prostate surgery; and diabetes mellitus type 1 or heart failure (to prevent disturbances of symptom assessment due to neuropathy or irregular use of diuretics). Since these exclusion criteria are easily available from patient records the study population was easy to recognise in a primary care setting.

Informed consent and randomisation

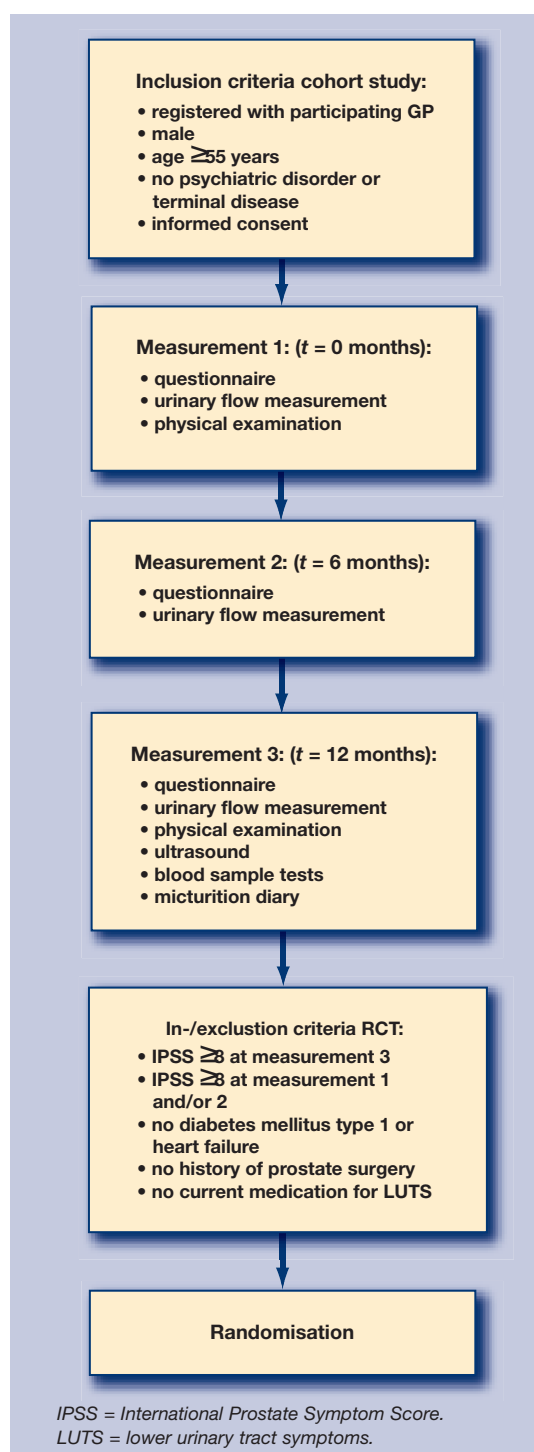
Eligible subjects received written information with neutral information regarding the details of intervention and control condition. They returned signed informed consent forms to the research nurse. The research nurse gave unique patient identification numbers — including practice identifier — to one of the researchers, who performed the randomisation blind for patient data (block randomisation, block size = 4, stratified per general practice).

Intervention

For the intervention group, the treatment protocol followed a stepwise approach (Figure 2). All participants were offered an α -blocker (tamsulosin 0.4 mg once daily) and treatment was evaluated after 3 months. If the α -blocker was well tolerated and the symptom score had improved (≥ 3 points) the medication was prolonged for 6 months. The medication was then stopped for 3 months, and re-evaluated. If symptoms had worsened again, ≥ 3 points (indicating a 'real' effect of the medication), the α -blocker was restarted for 1 year (the rest of the study period).

For those who had not improved after 3 months the indication for other treatment options was established using the algorithm of the formalised expert opinion^{14,22} (Supplementary Table 1). If an indication for a 5- α -reductase inhibitor existed, finasteride (5 mg once daily) was prescribed. Where surgery was indicated

Figure 1. Recruitment of study population.



patients were offered referral to the urologist for this purpose. The intervention was performed by one of the researchers. Subjects were instructed to report and discuss any intermittent health questions related to LUTS to one of the researchers.

Control condition

The control group received 'usual care'. They were not actively offered a certain treatment proposal. Any treatment was coordinated and prescribed by their

own GP. To prevent contamination of their usual care by the intervention, the GPs were blinded to the content of the protocol. It was explained to GPs why they should not have any knowledge of the study protocol, and were instructed not to ask their patients about the study or their treatment. They received no special training on diagnosis or treatment of LUTS.

Data collection

After 12 and 24 months of follow up all subjects completed a questionnaire (symptom and bother scores and any contact with doctors for micturition problems), and underwent urinary flow measurements. Details of consultations, referrals, and prescriptions were obtained from the patient records in the general practice, if necessary. Flow measurements were performed in a private room in the practice using a Da Capo Homeflowmeter® (Danica/Medtronic, Leusden, The Netherlands). Flow measurements with a voided volume below 100 ml were repeated.

Outcome parameters and sample size

The primary outcome parameters were improvement of symptom score and maximum urinary flow rate. The sample size calculation was based on a relevant difference of 2.5 points on the symptom score (with a supposed standard deviation [SD] of 7 points)²⁵ and 2 ml/sec on the maximum urinary flow (supposed SD = 4.9 ml/sec)²⁶. Consequently, 240 subjects were required for analysis ($\alpha = 0.05$, $\beta = 0.80$, equal group sizes, highest needed number).

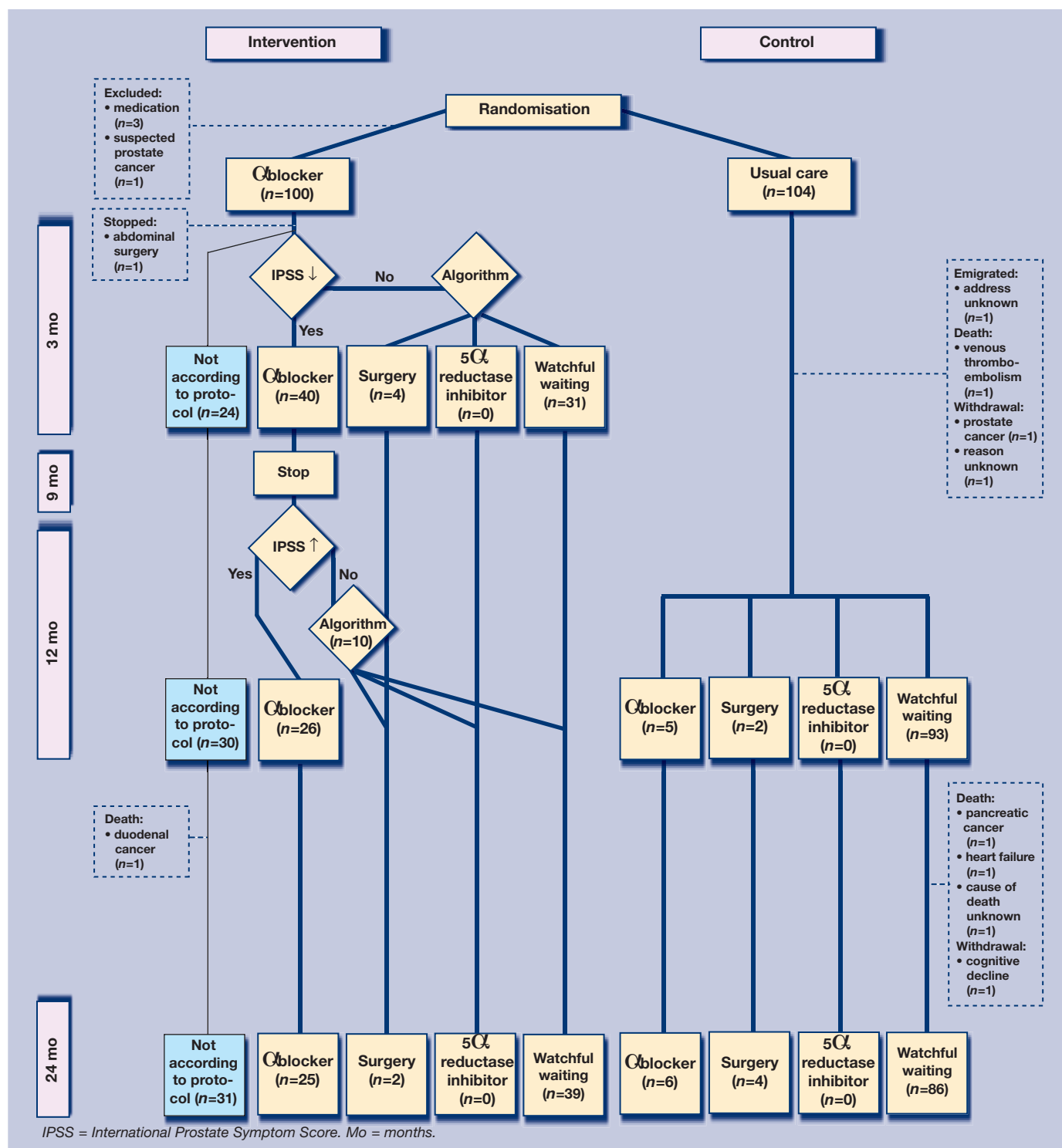
The secondary outcome parameter was improvement on the bother score. Furthermore, the number of acute urinary retentions and urinary tract infections was registered.

Statistical analysis

The difference between intervention and control after 24 months was tested using the Mann-Whitney U test (IPSS, Q_{\max} , Dan-PSS), or the χ^2 test (acute urinary retention and urinary tract infections), based on the intention-to-treat principle.

An analysis of the baseline characteristics of the subjects in the different treatment subgroups was performed at the end of the follow-up period. This was done to explore possible explanations for differences between the intervention and control condition in outcome and the number of patients receiving a certain treatment.

Furthermore, it was acknowledged that the treatment protocol in some ways was a 'black box'. Its overall effectiveness depends on the specific efficacies of the various treatment options and the quality of the decision for which treatment to offer an individual patient. Therefore, the differences in outcome measures were calculated at end of follow up to check



whether the individual treatments were effective in the subgroups identified by the treatment protocol.

RESULTS

Between August 2000 and June 2002, 208 subjects were randomised to the intervention ($n = 104$) and control group ($n = 104$). Baseline characteristics are described in Table 1. The flow of the subjects through the study is shown in Figure 2.

Intervention group

After randomisation four subjects were excluded: three had started using an α -blocker and one had been referred for suspected prostate cancer. The remaining 100 subjects were offered tamsulosin. Of these, 13 did not want medication; 11 stopped because of side effects (dizziness ($n = 4$), sexual problems ($n = 1$), rash ($n = 1$), interaction with co-medication ($n = 1$), increasing LUTS ($n = 3$), leg cramps ($n = 1$). One

Figure 2. Flow of participants through the study.

Table 1. Study population, baseline characteristics of intervention (*n* = 104) and control group (*n* = 104).

	Intervention median (P ₂₅ -P ₇₅)	Control median (P ₂₅ -P ₇₅)	P-value
IPSS	13 (10-17)	13 (10-17)	0.90
Q _{max} (ml/sec)	11.4 (7.6-16.6)	12.8 (8.3-16.5)	0.81
Dan-PSS	10 (5-18)	8 (5-19)	0.91
Age (years)	64 (60-70)	65 (60-71)	0.56
Prostate volume (ml)	25 (19-32)	24 (20-33)	0.35
Post-void residual volume (ml)	34 (15-65)	38 (19-61)	0.68
PSA (ng/ml)	1.0 (0.7-2.0)	1.3 (0.7-2.0)	0.27
Post-void residual volume >100 ml (<i>n</i> [%])	18 (17)	20 (19)	0.70

IPSS = International Prostate Symptom Score. Q_{max} = maximum urinary flow. Dan-PSS = Danish Prostate Symptom Score. PSA = prostate specific antigen. The IPSS is a validated 7-item questionnaire assessing the frequency of lower urinary tract symptoms (0 = never, 5 = (almost) always); The IPSS ranges from 0-35. The Dan-PSS is a 12 item questionnaire multiplying the presence of symptoms (0-3) with a subjective bother score (0-3); the Dan-PSS ranges from 0-108.

subject stopped with the intervention after abdominal surgery for nephrogenic haematuria.

Consequently, 75 patients completed the first 3-month period of α -blocker treatment according to the treatment protocol. Evaluation showed a mean change in symptom score of -2.7 points, with (sufficient) improvement in 40 subjects (mean -6.8 points), and no improvement in 35 subjects (mean +2.1 points).

The 40 'improved' subjects continued the protocol (6 months α -blocker/3 months stop). Re-evaluation at *t* = 12 months showed that 26 had worsened after withdrawal (they therefore restarted the α -blocker); 10 subjects showed no worsening and consequently changed therapy to watchful waiting (*n* = 9) and 5- α -reductase inhibitors (*n* = 1). Four subjects stopped the medication because of 'second thoughts' (*n* = 1), dizziness (*n* = 1), sexual problems (*n* = 1) and angina

pectoris (based on the advice of his cardiologist, *n* = 1).

Of the 35 'unimproved' subjects 31 changed to watchful waiting; the other four were referred for surgery. Two of these were indeed operated on, but the other two did not risk the side effects and complications of surgery, and continued tamsulosin treatment (*n* = 1), and no further treatment (*n* = 1), respectively. One subject of the watchful waiting group died before the end of the study.

Finally, 67 subjects (64%) completed the study according to the protocol; complete data were available from 103 subjects.

Control group

In the first year five subjects received an α -blocker and two were referred for surgery. One subject died and three were lost to follow up (emigration and withdrawal of informed consent). During the second year three participants were prescribed an α -blocker; one subject changed from α -blocker to surgery, and one from watchful waiting to surgery. Three subjects died. Two were lost to follow-up (withdrawal of informed consent, emigration; only returned a questionnaire). As a result 96 subjects completed the study, of which six used an α -blocker, four had undergone surgery and 86 were on watchful waiting. No participant used a 5- α -reductase inhibitor.

Outcome

Significant changes between baseline and end of follow up in symptom score, bother score, and maximum urinary flow were not found, neither in the intervention, nor in the control group (Table 2). A difference between intervention and control group in change scores was not found either. During the first year of follow up two subjects suffered from an acute urinary retention (intervention (*n* = 1); control (*n* = 1); another three suffered from a urinary tract infection

Table 2. Comparison of symptom score, maximum urinary flow and bother score, and the incidence of acute urinary retention and urinary tract infections between baseline and end of follow-up (*t* = 24 months).

	Intervention (<i>n</i> = 104)			Control (<i>n</i> = 104)			
	Baseline	Outcome	Significance of change baseline - outcome	Baseline	Outcome	Significance of change baseline - outcome	Significance of difference intervention control
Median IPSS (P ₂₅ -P ₇₅)	13 (10-17)	14 (10-18)	<i>P</i> = 0.79 ^a	13 (10-17)	14 (10-17)	<i>P</i> = 0.80 ^a	<i>P</i> = 0.98 ^b
Median Q _{max} (P ₂₅ -P ₇₅)	11.4 (7.6-16.6)	11.3 (8.1-15.8)	<i>P</i> = 0.85 ^a	12.8 (8.3-16.5)	11.8 (8.3-16.0)	<i>P</i> = 0.76 ^a	<i>P</i> = 0.45 ^b
Median Dan-PSS (P ₂₅ -P ₇₅)	9 (4-17)	9 (4-21)	<i>P</i> = 0.92 ^a	8 (5-19)	10 (5-19)	<i>P</i> = 0.25 ^a	<i>P</i> = 0.98 ^b
AUR (<i>n</i> , %)	-	2 (1.9)	-	-	1 (1.0)	-	<i>P</i> = 0.62 ^c
UTI (<i>n</i> , %)	-	2 (1.9)	-	-	5 (4.8)	-	<i>P</i> = 0.45 ^c

IPSS = International Prostate Symptom Score. Q_{max} = maximum urinary flow. Dan-PSS = Danish Prostate Symptom Score. AUR = acute urinary retention. UTI = urinary tract infection. ^aWilcoxon signed rank test; ^bMann-Whitney U test; ^c χ^2 test; due to small numbers the Fisher Exact test was used.

(intervention ($n = 1$); control ($n = 2$). During the second year four subjects were treated for a urinary tract infection (intervention ($n = 1$), control ($n = 3$), and one for an acute urinary retention (intervention).

Our exploratory analysis did not show significant differences in baseline characteristics within the treatment subgroups between intervention and control condition (Supplementary Table 2).

The analysis of the 'black box' showed that in the intervention condition all active treatment subgroups (α -blocker, 5- α -reductase inhibitor, and surgery) symptom and bother scores, and maximum urinary flow had improved, while the watchful waiting group had worsened. This indicates that the protocol was internally consistent. Notably, in the control group the majority of the users of α -blockers at end of follow-up had an increased symptom and bother score, and a decreased maximum urinary flow, leading to an overall (although not statistically significant) worse outcome for this subgroup. Of course, the treatment subgroups in this analysis were defined post-hoc, not beforehand. Due to confounding by indication the results are not suitable for statistical testing of the differences between two treatments or the treatment arms.

DISCUSSION

Summary of main findings

The structured approach of our treatment protocol did not result in a relevant and statistically significant improvement in outcome as compared to current usual care.

Strengths and limitations of the study

Several considerations concerning the generalisability of our results need to be acknowledged. Our study population reflects the heterogeneous population in primary care, which increases the external validity. However, we studied the pool of symptomatic patients from which the consulting population self-selects. Characteristics of consulting patients will vary in time or place, because of cultural aspects, health education or promotional activities, but in general they will be more symptomatic than the subjects in our study. Our results indicate that a more active treatment policy in consulting patients will not improve overall outcome.

Several considerations may help to explain the absence of relevant and significant results in this study. The increased attention for LUTS in general practice may have reduced the room for improvement. Although the GPs were not acquainted with the intervention nor involved in its execution, they knew that a study on LUTS was performed. They may have been (or become) more interested in LUTS, which may have influenced their behaviour. They may have already adopted the guidelines, either explicitly or implicitly

because the guideline confirmed their knowledge or clinical experience. Theoretically, any trial with an usual care control group does not provide a fair estimate of the value of an intervention if the usual care has already started to resemble the intervention studied (that is, the guideline). This may be the case with regard to restricted use of 5- α -reductase inhibitors. For α -blockers current treatment guidelines themselves leave a lot of room for interpretation.²⁷ A wider use of these medicines is advocated. However, we noticed that they are prescribed less frequently in the usual care situation without deleterious effect.

Although our intervention was based on the opinion of a large international sample of urologists, one may prefer a different interpretation, and consequently argue some patients should have been treated differently. However, it is unlikely that individual changes in treatments would have changed overall results.

We included 208 subjects and could analyse the data of 199 subjects, and used non-parametric tests. This may have led to loss of statistical power. However, the variance of the IPSS was lower than presumed (standard deviation was 5.2 instead of 7) which sufficiently compensates this (power was actually about 90%).

Comparison with existing literature

Our study primarily aimed at the reduction of symptom severity. A focus on the prevention of complications (like acute urinary retentions) could have led to a somewhat more prominent place for 5- α -reductase inhibitors.¹² However, these are most effective in patients with large prostates. In our sample 16 (7.7%) participants had a prostate size ≥ 50 g. Only one subject (of three) who developed an acute urinary retention had such a prostate size. Therefore, a more rigorous prescription of 5- α -reductase inhibitors to this group probably would not have had the same effect on our primary outcome parameters and conclusions.

Little consensus exists on the appropriateness of α -blocker treatment.¹⁴ Recently published guidelines acknowledge this, stating that 'a trial of treatment is appropriate'.^{12,13} We tried to overcome this problem and select 'real' responders using a trial of treatment combined with a similar trial of withdrawal of treatment. In this way, the effect cannot be attributed to the natural course of the disease, or 'regression to the mean,' although it does not fully protect against the placebo effect. Despite this, the subjects who were treated with tamsulosin at the end of the follow-up period had a relatively small improvement of both symptoms and maximum urinary flow compared to what could be expected if the initial effect after the first 3 months had been sustained throughout the whole study period.

At the end of the follow-up period only six subjects in the control condition were treated with α -blockers. Most of them had worse outcome parameters at the end of follow up compared to baseline. It is likely that GPs reserve medication for those who experience a rapid deterioration. This may be too restrictive; some untreated patients in the control group may have been better off using medication. However, our study results showed no evidence that a protocol starting with an α -blocker has added value. The larger group in the intervention condition who had been prescribed an α -blocker did not have a more favourable outcome than the controls who had not received this treatment.

Implications for clinical practice

A primary care treatment regimen based on the consensus among urologists does not improve effectiveness. Especially for the large 'grey area' in which α -blockers are considered, our study does not support a broadening of the indication for α -blockers, which, however, seems to be the current trend. We should continue to look for sharper criteria for treatment, resulting in adequate therapy for those who may benefit and prevention of overuse of medication for those who may expect little effect.

Supplementary Information

Additional information accompanies this article at <http://www.rcgp.org.uk/bjgp-suppl-info>

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Ethics committee

The study presented in this paper was approved by the Ethics Committee of the Academic Hospital Maastricht / Maastricht University (00-007)

Competing interests

Roelf JC Norg has been paid (250 Euros) for running an educational program by Yamanouchi Pharma B.V. CP Onno van Schayck has been member of the steering committee of the Triumph (TransEuropean Research Into the Management Policies for BPH in Healthcare) study, which was funded by Yamanouchi Europe (at present Astellas). All funding was in accordance with the rules for independent research of Maastricht University.

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