This is the authors' final version, post peer-review, of an article published in *Urology* 2013;81(2):390-4. The definitive version is available from www.sciencedirect.com

Baseline symptom score and flow rate can predict failure of medical treatment of LUTS: Prospective 12 years follow-up study.

Said Fadel Mishriki, Omar Aboumarzouk, John T. Graham, Thomas B. Lam, and Bhaskar K. Somani

Introduction:

LUTS is a major cause of impairment in health-related QoL and a driving factor for patients to enquire about treatment options.[1,2] Improved QoL and enhanced patient satisfaction by alleviation of LUTS should have long-lasting outcomes and minimal side effects.[3]

Management options include watchful waiting, medical treatment and surgical interventions and the delicate balance between efficacy, long-lasting therapeutic outcomes and minimal side-effects dictates option choices.[4] Trends in surgical interventions for benign prostatic hypertrophy (BPH) have been declining over the past two decades.[5] With robust evidence demonstrating safety, efficacy and tolerability of alpha blockers and 5 alpha reductase inhibitors, BPH has increasingly become a medically managed condition.[6]

Long-term reports on QoL and satisfaction regarding medical treatment of LUTS are scarce. These are important measures as LUTS is a non-life threatening condition that may require lifelong medical treatment with significant health economic consequences.[7]

Randomised controlled trials (RCTs) such as MTOPS & COMBAT provide invaluable information on the efficacy of medical treatments for LUTS/BPH and evaluate predictors of progressive disease. [8,9,10] However by their very design they have specific participant entry criteria and are restricted in terms of length of follow-up, with the longest follow-up period of recent large RCTs being limited to six years. There is paucity of data to provide practicing clinicians evidence of what happens after this period of time.

This is a real life practice study with 12 years of follow-up of patients and a final notes review at 17 years.

Objectives are twofold:

1. To prospectively assess the long-term outcomes of medical treatment of LUTS/BPH in terms of clinical effectiveness, patient satisfaction rate and QoL
2. To identify potential predictors for failure of medical treatment using baseline variables

Methods:

After approval from the local research ethics committee, 458 men referred with LUTS due to BPE/BPH to a university hospital for evaluation and treatment between January 1993 and September 1994 were recruited into the study following counselling and informed consent. Management options were discussed with each patient. Data was prospectively collected in this single institution study. Routine clinic assessment included digital rectal examination, QMax, PVR and TRUS for prostate size. PSA was not a routine test in Scotland in 1993. Patients completed AUA symptom score, QoL and bother questionnaires (Appendix 1 and 2). Following initial evaluation, treatment options (surgical vs non-surgical) were discussed with the patients. 280 (61%) men were treated by TURP at the outset based on symptom score, flow and PVR. 178 (39%) men were managed with medical (non-surgical) treatment. Men diagnosed with carcinoma of prostate or presenting acutely with urinary retention were excluded. Medical treatment was heterogeneous and included modification of fluid intake, anti-cholinergic agents, alpha blockers, 5 alpha reductase inhibitors or a combination. Medical treatment modes were interchangeable over the 12 years period for all patients. All patients were followed-up as per protocol using objective (flow rates and PVR) and subjective assessments (AUA symptom score, QoL and bother questionnaires). Patients were assessed at baseline, 3 months, 6 months, 6 years and 12 years. At 17 years the hospital records were examined. The 3 month follow-up data were used for questionnaire validation and reliability using the test-retest analysis which also assessed stability of responses over time. The QoL and bother questionnaires designed and used in the present study are similar to the BPH Index questionnaire published later. [3,11,12] Data was prospectively collated into an access database.

Analyses:

Univariate and multivariate analysis were performed using PASW Statistics 18.0.2 (Polar Engineering and Consulting Inc.) with continuous variables analysed in a dichotomous manner. All data was analysed with the intention to deal with bias. The following outcome measures were included: age (<66 years or >66 years), QMax (>15ml/s or <15ml/s), PVR (<70ml or >70ml), prostate volume (<36ml or >36ml), AUA total score (<16 or >16), QoL total score (<7 or >7), and bother total score (<13 or >13). Treatment failure was defined as worsening LUTS despite being on dual therapy (alpha blockers and 5 alpha reductase inhibitors). TURP with patients' consent was offered to those with worsening LUTS despite being on dual therapy. Covariates found to be significantly associated with risk of treatment failure on univariate analysis were entered into the Cox model in a backward, stepwise fashion (i.e. all relevant variables were entered into the model and subsequently non-significant variables were sequentially removed). Cox proportional hazards regression model assumptions (e.g. effects of predictor variables and hazard ratios were constant over time) were assessed using survival curves and complementary log-minus-log curves. A P-value of P=0.05 was considered statistically significant.

Results:

Of 458 men recruited and assessed, 280 had TURP based on their initial symptoms and flow rates. Data on the TURP group were published previously.[12] Of the remaining patients, 178 were deemed suitable for non-surgical management. Their baseline characteristics are shown in Table 1. Patients had a mixture of irritative and obstructive symptoms. Over the subsequent 12 years, 50 men failed medical treatment and required TURP (Figure 1, Table 2). All men had been tried on either an alpha blocker or 5-alpha reductase inhibitor or a combination. 128 men continued on medical treatment. At the 12 year follow-up, 85 men of this elderly population were alive of which 61 were on medical treatment and 24 had TURP. Out of 61

still on medical treatment, 35 (57%) attended the 12 years follow-up. Out of the 24 patients who failed medical treatment and had TURP, 17 (70.8%) attended the 12 years assessment (Figure 1).

Statistically significant improvements in AUA, bother and QoL were recorded, suggesting long-term efficacy in those patients (Table 2). This also shows a comparison between the baseline characteristics of the two groups that attended at 12 years (medical vs failed medical). Statistically worse baseline AUA, bother and QoL scores were recorded in the group that went on to require surgical intervention.

Table 3 shows predictor variables determined at recruitment that affected risk of treatment failure by univariate analysis. Four variables among the seven tested demonstrated predictive value for treatment failure. These were QMax (>15ml/s or <15ml/s; *P*<0.0001); AUA total score (<16 or >16; *P*=0.002); bother total score (<13 or >13; *P*=0.002); and PVR (<70ml or >70ml; *P*=0.028). The remaining three variables (age, prostate volume and QoL score) did not show statistical significance between baseline and final readings.

Multivariate analysis showed two independent predictors of treatment failure, which were QMax (>15ml/s vs <15ml/s; hazard ratio 3.37, 95% CI 1.74-6.52; *P*<0.0001) and bother score (<13 vs >13; hazard ratio 2.37, 95% CI 1.29-4.35; *P*=0.005). AUA and bother were highly correlated (*P*=0.01), with AUA score being dependant on bother score. At 17 years, no patient continued to require the input of a secondary care physician.

Comment:

Principle findings and strengths of the study:

The uniqueness of this study is the longevity of the follow-up which is 12 years. The first objective of this study was to assess the long-term effectiveness, patient satisfaction and QoL of patients who continued on medical treatment. At 12 years, when the patients were last objectively assessed, those who persisted with medical treatment had statistically significant

improved outcome with respect to their AUA, QoL and bother scores compared with their baseline. In this study, over a 12 year period, 50 men (28%) failed medical treatment and required surgical intervention. Over two thirds (n=36) of medical treatment failures needing TURP occurred within the first three years.

The second objective of this study was to identify potential predictors for medical treatment failure in the long-term, using baseline variables. When predictors for failure of medical treatment were investigated in this cohort, similar predictors of progression were found, although some appeared to be more important than others. Flow of less than 15ml/sec, an IPSS or AUA of >16 and a bother score >13 were all highly significant factors (P<0.001), whilst PVR of >70ml just reached statistical significance (P=0.028). Although age, prostate volume and QoL score were not statistically significant factors, the trends shown appeared to suggest that they approached significance.

Strengths and weaknesses in relation to other studies:

In the 2 most recent large RCTs investigating combination therapy for BPH, the majority of patients who failed treatment did so because of progressive BPH symptoms rather than urinary retention or need for surgery.[8,10] 79% of those who "progressed" in the placebo arm of MTOPS trial did so because of symptom progression.[9] That study reported that doxazosin, finasteride and combination therapy all resulted in significant improvements in symptom scores versus placebo. However, it is not clear what happens after the 4 year trial period. There are few if any other studies supporting the efficacy of medical treatment of LUTS / BPH over this period of time. In 2003 the safety and efficacy of tamsulosin over 6 years was reported.[13] PLESS noted a sustained decrease of acute urinary retention incidence and need for surgery with finasteride over a 6 year duration.[14] Combination studies reveal the benefit of dual treatment with alpha blockers and 5 alpha- reductase inhibitors, but again the evidence does not exceed 6 years.[15] Cumulative incidence of the need for surgery in MTOPS was nearly 5%.[8] In COMBAT, the cumulative incidence of the need for surgery was 7.8%, 3.5% and

2.8% in the alpha-blocker alone, 5-alpha reductase inhibitor alone and combination arms respectively.[10]

Over the first 3 years of this study, 36 men (20.2%) had required TURP. Whilst this figure is higher than those of many other published series, certain factors may explain the apparent discrepancy. This study was performed over an unparalleled period of follow-up. It also commenced in the early 1990s when TURP was the most common form of treatment for BPH. Finasteride was launched in Scotland in 1993, which was the year this study began. As such, awareness of this medication in the early years of the study may have been limited. This study was also commenced before any evidence of the benefit of combination therapy was available.[8,9,10] These factors may account for the high rate of surgical intervention in this study. There has been profound transition of medical and surgical treatment modalities during these 12 years. Less invasiveness of laser prostatectomy may facilitate surgery, while 5-alfa reductase inhibitor would abrogate immediate surgery for an enlarged prostate.

72% failure within the first 3 years would suggest that the 4 - 6 year follow-up duration undertaken in large RCTs and observational studies could capture the vast majority of patients who are destined to fail medical treatment. After this initial period, when the majority fail because of unresponding symptom improvement, it would appear that the risk of failure is relatively low. In this study, only 14 men required TURP in the latter 9 years of the study. Evaluating predictors of progressive disease and stratifying patients into risk groups influences treatment options and aids appropriate follow-up regimes. Current EAU guidelines suggest annual review of every patient who has been referred with LUTS / BPH regardless of risk factors. This is not practical within all health care systems. There is no guidance as to how long these patients should be followed-up for.[4] Observational studies and the placebo arms of RCTs provide evidence regarding predictors of progressive disease in BPH. Age, prostate volume and PSA are often reported as the strongest predictors of progressive disease.[16] However, most have relatively short duration of follow-up. Based on this study, it

would appear reasonable to conclude that those men commenced on medical treatment with significant risk factors should be followed up in secondary care for potentially 3 years. Thereafter, with subsequent low incidence of treatment failure, it would appear to be appropriate for the primary care physician to continue annual review in the community. Larger comparative studies with an equal length of follow-up may be required.

Limitations of the study*:*

Limitations include those patients switching various medical treatments. It is also possible that the results were biased by the selection of patients who completed follow-up. Furthermore, the results might have been biased by the selection of patients who completed the follow-up who may be more motivated than others to persist with medical therapy. Non-attendance at 12 years is likely to present attrition bias, however these patients were calculated in the final analyses based on an intention to treat bias and the assumption that they did not attend because their symptoms were controlled. Data from observational studies suggest that BPH is a progressive condition; as such, intuitively one could reasonably assume that the incidence of the need for surgical intervention would have been higher had they not been medically treated in this study.[1] It is theoretically conceivable that some men would have had symptomatic relief even without medication after 12 years.

Despite the limitations, this study represents the longest follow-up of patients medically treated for LUTS/BPH to-date. Furthermore, it underscores four variables that can be used to predict therapy failure or success. A randomised controlled trial with long follow-up is required to further evaluate the role of medical therapy of these patients.

Conclusions:

In those patients that medical treatment for LUTS / BPH was successful the objective symptomatic beneficial effect remained for up to 12 years by comparison to baseline, thereby supporting the long-term efficacy of medical treatment of LUTS / BPH. Patients with worse

baseline flow rates, AUA and bother scores were more likely to fail medical treatment for LUTS / BPH and require TURP, the majority within the first three years of follow-up.

References:

1. Jacobsen SJ, Girman CJ, Lieber MM. Natural history of benign prostatic hyperplasia. Urology. 2001; 58(6 Suppl 1): 5-16

2. Kaplan SA, Roehrborn CG, Chapple CR et al. Implications of recent epidemiology studies for the clinical management of lower urinary tract symptoms. BJU Int. 2009; 103 (Suppl 3): 48-57.

3. Mishriki SF, Grimsley SJ, Nabi G et al. Partners agree that the treatment of LUTS reduces patients' bother and improves their quality of life: prospective 12 years follow-up study. World J Urol 2010; 28: 123-32.

4. Madersbacher S, Alivizatos G, Nordling J et al. EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). Eur Urol 2004; 46: 547-54.

5.Vella-Navarrete R, Gonzalez-Enguita C, Garcia-Cardoza,JVet al. The impact of medical therapy on surgery for benign prostatic hyperplasia: a study comparing changes in a decade (1992–2002) BJUI 2005; 96:1045-8.

6. Hutchison A , Farmer R, Chapple C et al. Characteristics of patients presenting with LUTS/BPH in Six European Countries. Eur Urol 2006; 50: 555-61.

7. Chirikos TN, Sanford E. Cost consequences of surveillance, medical management or surgery for benign prostatic hyperplasia. JUrol 1996; 155: 1311-6.

8. McConnell JD, Roehrborn CG, Bautista OM et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. N Engl J Med 2003 18;349 :2387-98.

9. Crawford ED, Wilson SS, McConnell JD et al., MTOPS RESEARCH Group. Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. J Urol 2006; 175:1422-6; discussion 1426-7.

10. Roehrborn CG, Siami P, Barkin J et al. CombAT Study Group. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol 2010;57 :123-31.

11. Barry MJ, Fowler FJ Jr, O'Leary MP et al. American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 1992; 148; 1549-57; discussion 1564.

12. Mishriki SF, Grimsley JS, Nabi G et al. Improved quality of life and enhanced satisfaction after TURP: Prospective 12-Year follow-up study. Urology 2008; 72: 322-6.

13. Narayan P, Evans CP, Moon T. Long-term safety and efficacy of tamsulosin for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. J Urol. 2003; 170: 498-502.

14. Roehrborn CG, Bruskewitz R, Nickel JC et al. Long-Term Efficacy and Safety Study Group. Sustained decrease in incidence of acute urinary retention and surgery with finasteride for 6 years in men with benign prostatic hyperplasia. J Urol 2004; 171: 1194-8.

15. Narayan P, Tununtla HSGR. Long-term efficacy and safety of tamsulosin for benign prostatic hyperplasia. Rev Urol. 2005; 7(suppl 4):S42–S48.
16. Roehrborn CG, Boyle P, Bergner D et al. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. Urology 1999; 54:662-9.

Figure legends:

Figure 1: Summary of all patients recruited