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Risk stratification for benign prostatic hyperplasia (BPH) treatment

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- Benign prostatic hyperplasia (BPH) is a common cause of bothersome lower urinary tract symptoms. In the past, the aim of drug treatment was to relieve symptoms until surgery became necessary, predominantly using an α-blocker or a 5α-reductase inhibitor (5ARI) as monotherapy.
- Together with improving knowledge about the pathogenesis of BPH, there is now strong evidence from large randomized trials that risk stratification and appropriate treatment with combined α-blocker/5ARI therapy can significantly reduce the risk of disease progression and avoid long-term complications such as acute urinary retention and surgery.
- BPH will increasingly be managed in primary care in the future and, if new management strategies based on this evidence are to be implemented cost effectively, there is a need to introduce shared care between the primary and secondary care sectors to optimise use of resources and expertise.

What's known on the subject? and What does the study add?
Patients with BPH have traditionally been managed with 'sequential monotherapy' or effectively an intent to treat to failure. Thus watchful waiting strategies, α-blockers, 5α-reductase inhibitors and surgical intervention have been seen as a stepwise progression based on failure of symptom control at each level.

This paper reviews the evidence from large randomized trials which suggest a new approach of risk stratification, allowing the identification of higher risk patients for whom medical management can be optimised at an early stage. If this can be done at a primary care level, this could lead to a dramatic improvement in outcomes in men with BPH.

KEYWORDS

BPH, combined therapy, risk stratification

INTRODUCTION

In men LUTS are common. BPH, a slowly progressive condition, accounts for most of the symptoms and bother associated with LUTS. In the past, the primary aim of treatment was to wait until the symptoms and the bother associated with them was severe enough to warrant surgery. However, the introduction of selective α-blockers and 5α-reductase inhibitors (5ARIs) in the 1990s offered an alternative to the strategy of surgery-now vs surgery-later. Both α-blockers and 5ARIs were initially licensed for the relief of symptoms in the hope that this would lengthen the time to surgery but initially there were no recommendations on whom to treat and when. The resultant therapeutic strategy was what might be described as 'sequential monotherapy', effectively, an intent to treat to failure, after which the patient was switched to another class of drug or offered surgery.

The rationale for combined therapy for BPH is that an α-blocker provides prompt symptom relief and a 5ARI confers a long-term reduction in the risk of disease progression. However, management guidelines usually lacked advice about how to tailor this approach to individual need. This position has now changed. We now know that the pathophysiology of LUTS/BPH is complex. The quality and quantity of the evidence on the comparative effectiveness of different agents/strategies has improved [1,2] and, with a growing evidence base, it is now possible to identify risk factors that are associated with disease progression.

The burden of BPH on healthcare systems and to society is already high but is set to increase in line with greater life expectancy. In an era of universal pressure on healthcare services, new cost-effective management strategies will be needed to preserve patient outcomes in the face of diminishing resources. To assist in realising this goal, we have conducted this review of therapeutic strategies in LUTS/BPH.

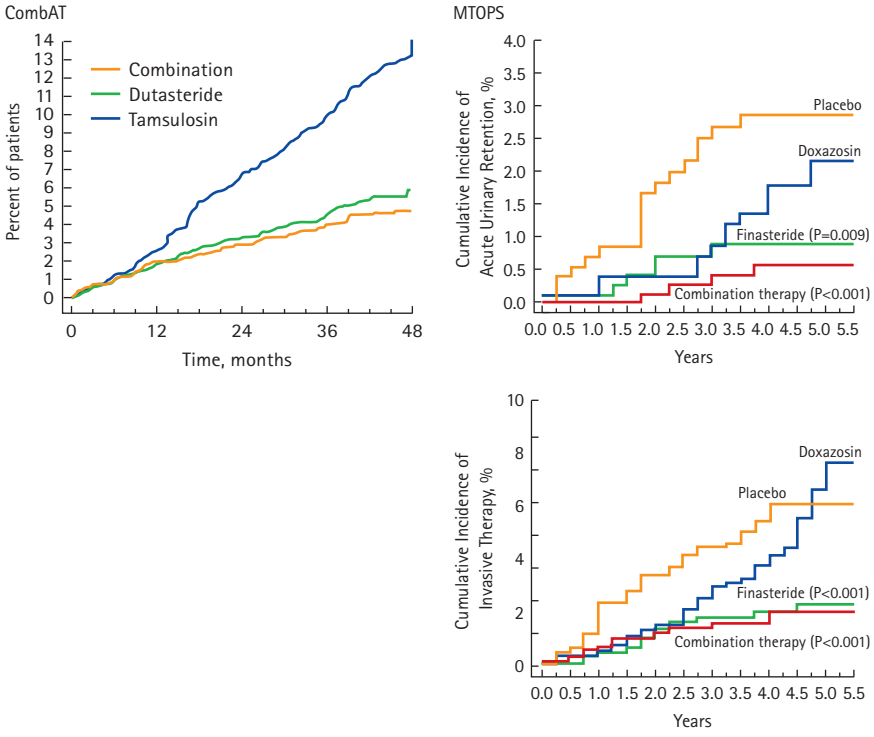
TREATMENT STRATEGIES

SELF-MANAGEMENT

BPH progression is slow, with a mean annual increase in prostate volume of about 2% annually [3,4]. Men whose symptoms are not bothersome and who have no risk factors can be offered watchful waiting. This should include education about BPH, reassurance that the symptoms are not due to prostate cancer, optimisation of concomitant treatments, periodic monitoring and lifestyle advice [5]. However, a 2001 survey of UK urologists, nurse practitioners and continence advisors found large differences in the implementation of these strategies [6].

Self-management strategies improve health status in people with chronic disease. They are

FIG. 1. Time to first episode of acute urinary retention or BPH-related surgery/invasive therapy MTOPS [1] and CombAT [2].



considered integral to long-term care in chronic conditions [7] and they have been incorporated into management guidelines for long-term conditions (see http://www.nice.org.uk for examples). As with other chronic conditions, self-management is useful for men with BPH because their condition must be managed over a long period; the patient must use more than one strategy for health care; the patient knows best about his condition and needs to apply that knowledge to treatment; and he needs to share his knowledge and expertise with health professionals [8].

Compared with standard care alone, standard care plus self-management (education, lifestyle modification, and training in problem solving and goal setting skills) significantly reduced treatment failure and symptom scores in men with LUTS at 3, 6 and 12 months [9]. Lifestyle modification involved fluid management and avoiding caffeine and alcohol; behaviour modification involved bladder retraining, double voiding and urethral milking. Self-management can be delivered in the community, by lay experts or remotely using electronic media [10,11].

SEQUENTIAL MONOTHERAPY

BPH has traditionally been treated with monotherapy. A survey of six European countries in 2000–2002 found that 74% of 4979 men newly diagnosed with BPH were prescribed medication. Of these, 83% were treated with a single agent; α-blockers accounted for 75% of prescribed medicines [12].

Compared with placebo, α-blockers rapidly reduce symptom severity in men with moderate-to-severe symptoms and increase urinary flow more quickly than 5ARIs [1,2,13] By contrast, 5ARI monotherapy reduces prostate volume and increases urine flow but the impact on symptoms is delayed, with consistent improvement only after 10–12 months [14]. Symptoms continue to worsen as BPH progresses [13]. Therefore, α-blockers have been preferred for first-choice monotherapy.

Symptoms are the main reason why men with BPH seek medical help [15], so first-line treatment with an α-blocker appeared to be rational. However, treatment to failure has not been tested in a randomized trial to determine whether it offers the best management strategy, nor is it a patient-focused endpoint. Men are worried less about early symptom relief than long-term risk [15,16]. By contrast, a 2002/03 European survey showed that most urologists did not think that men were more worried about long-term complications than symptom relief, consistent with their prescribing practice [15].

TREATMENT ALLOCATION BY RISK STRATIFICATION

EFFICACY OF COMBINED VS MONOTHERAPY

The Medical Therapy of Prostate Symptoms (MTOPS) [1] and Combination therapy of Avodart (dutasteride) and Tamsulosin (CombAT) [2] studies provide definitive evidence of the advantages of long-term combined treatment. Both studies show that, over 4 years, α-blocker monotherapy did not prevent progression to acute urinary retention or surgery whereas a 5ARI did; and both showed substantially greater symptomatic improvement with combined therapy than any monotherapy (Fig. 1) [1,2]. Participants in CombAT had more advanced BPH (larger prostate volume and higher PSA levels) than in MTOPS and the earlier trials of combined therapy, and therefore represented men at higher risk of progression.

CLINICAL IMPLICATIONS

Men can be stratified by the risk of BPH progression, and therefore of long-term complications, according to baseline and dynamic variables (Table 1) [17–26]. The most recent systematic review of clinical trials of BPH treatment concluded that risk stratification using baseline variables (symptom severity and bothersomeness, prostate volume and PSA level) should determine the choice of monotherapy or combined therapy with an α-blocker or a 5ARI [27] and these findings have been incorporated into a management guideline (Table 2) [5].

SHARED CARE

Recent proposals in the UK to shift NHS control of funding to primary care [28] are illustrative of a general trend to increase the provision of healthcare in the community

away from hospitals and to increase the integration of primary and secondary care sectors. Shared care arrangements are becoming more widely used, but if this is to succeed, GPs will need the support of specialists.

The prevalence of LUTS and the effectiveness of medical management mean it is feasible to provide most management in primary care, with appropriate support. To date, shared care has largely been a concept for discussion and small scale trials rather than for widespread implementation. The National Institute for Health and Clinical Excellence (NICE) LUTS guideline purposefully avoids distinction between primary and secondary care [5], recognising that the traditional boundaries between GPs and urologists are being blurred by commissioning (as various models of primary care diagnostic urology services are developed) and the emergence of GPs with special interest in urology. UK Government policy will further blur these boundaries [28] as commissioners recognise that BPH can now largely be managed in the community without specialist involvement. This will increase interest in the use of specialist GPs and nurses to manage most patients with BPH and reduce hospital referrals. The NICE guideline includes criteria for referral for specialist assessment that should be incorporated into shared-care agreements (Table 3) [5].

TABLE 1 Risk factors for BPH complications (acute urinary retention and BPH-related surgery)

Baseline variables [17–23]	Dynamic variables [24–26]
Old age	Worsening LUTS [24,25]
Severe LUTS	Persistence of bothersome symptoms during treatment [24]
Low peak flow rate	
Increased post-void residual urine volume (PVR)	Increasing PVR, regardless of treatment
Enlarged prostate	
High serum PSA level	

TABLE 2 BPH treatment allocation by risk stratification [5]

Risk category	Recommended treatment
Moderate to severe LUTS	α-blocker
LUTS *and* Prostate >30 g or a PSA level of >1.4 ng/mL *and* Considered to be at high risk of progression (e.g. older men)	5ARI
Bothersome moderate to severe LUTS *and* Prostate >30 g or a PSA level of >1.4 ng/mL	α-blocker + 5ARI

TABLE 3 Criteria for referral for specialist assessment [5]

Criteria
• Bothersome LUTS failing to respond to initial drug therapy
• Acute or chronic urinary retention
• LUTS complicated by persistent or recurrent UTI
• Suspected urological cancer (e.g. haematuria, raised age-specific PSA level)
• LUTS and renal impairment suspected to be related to their LUTS (i.e. not including men with established stable renal impairment

DISCUSSION

MTOPS and CombAT have shown the value of using risk factors to identify patients whose BPH is most likely to progress and targeting appropriate treatment. Primary and secondary care will need to share resources and expertise more effectively if the management of BPH and LUTS in men is to be moved away from its focus on symptom control for all, towards a policy of risk stratification and tailored treatment embracing reductions in both symptoms and the long-term consequences of BPH.

Implementing the policy of risk-assessment up-front has been recommended by the most recent clinical practice guidelines [5]. To what extent can the transition to this approach be realised? The study populations in our main sources of evidence (MTOPS and CombAT) were broadly representative of the men we see in urology clinics. Case selection, targeting treatment and regular review should mean that fewer patients will stop their treatment due to adverse effects or lack of effectiveness. Measurement of most baseline and dynamic risk factors is feasible in primary care, although ultrasonography is not routinely available. Further research is needed to determine whether DRE is sufficiently accurate to estimate prostate size as a risk factor for disease progression.

The combination of drug treatment with self-management techniques, in particular supported by group management, may offer important benefits and requires investigation; access to resources and cost may be an obstacle. In MTOPS and CombAT, combined therapy was associated with a higher incidence of adverse effects on sexual function than monotherapy but information about their impact on adherence is lacking. More research is needed to clarify the risks and benefits so that men are able to make an informed choice about treatment. There is evidence that α-blockers can be discontinued after ≈1 year with no deterioration in symptoms [29] but this has not been tested in a prospective trial.

CONCLUSION

The management of LUTS associated with BPH should now focus on risk stratification as a means of identifying men who will benefit most from treatment to reduce the risk of long-term complications. Management will

increasingly be delivered in primary care. There is evidence to suggest that this approach can deliver better treatment of BPH and, it is hoped, better adherence. If this strategy is to succeed, primary care will need health professionals with the right competencies and skills, with access to the technology necessary for diagnosis and follow-up. Further research is needed into how best to implement this approach by integrating resources from primary and secondary care, and to identify determinants of adherence and, in particular, strategies for appropriately discontinuing treatment.

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CONFLICT OF INTEREST

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Abbreviations: **5ARI**, 5α-reductase inhibitor; **MTOPS**, Medical Therapy of Prostate Symptoms study; **CombAT**, Combination therapy of Avodart (dutasteride) and Tamsulosin study; **NICE**, National Institute for Health and Clinical Excellence.