The management of hypertension in patients with benign prostatic hyperplasia and erectile dysfunction

MICHAEL KIRBY, ROGER KIRBY

Abstract

Lowering elevated blood pressure reduces mortality and the risk of stroke, coronary heart disease and heart failure.

The presence of benign prostatic hyperplasia (BPH) is a compelling indication for the use of an alpha blocker in the treatment of hypertension. Alpha blockers are first-line therapy for men with lower urinary tract symptoms (LUTS) and prostatic hyperplasia. In men with prostates larger than 30 cm³ or prostate-specific antigen > 1.4 ng/ml, 5-alpha reductase inhibitors may also be added. Typically, alpha blockers improve LUTS by 30–40% and maximum urinary flow rates by 16–25%, with clinical improvement within two weeks. The 5-alpha antagonists are only effective in men with a large prostate and may take up to six months to achieve their full effect.

The Medical Treatment of Prostatic Symptoms (MTOPS) study assessed the long-term effects of doxazosin, finasteride and combination treatment on symptom scores, the clinical progression of BPH and the long-term risk of complications. Combination treatment reduced the risk of clinical progression by 66%, a significantly greater reduction than that induced by either agent alone. The improvement in the symptom score was also significantly greater in the combination treatment group.

Erectile dysfunction (ED) may be a marker for other diseases, such as hypertension. ED is both more prevalent and more severe among patients with hypertension than among the general population. The link may be related to nitric oxide/cyclic GMP pathways and endothelial function. Many prescription drugs are associated with ED, including antihypertensive agents.

The alpha blockers and angiotensin receptor blockers are the drugs least likely to cause ED, and may even improve the situation. All currently licensed ED treatments are suitable for managing ED in the cardiovascular patient, when used according to the manufacturer's instructions. PDE5 inhibitors and alpha blockers should be temporally separated, or selective alpha blockers may be preferable, in order to avoid postural hypotension.

Key words: hypertension, antihypertensive agents, benign prostatic hypertrophy, erectile dysfunction, alpha blockers, 5-alpha reductase inhibitors, PDE5 inhibitors.

Br J Cardiol 2005;**12**:107–16

The Nevells Road Surgery, Nevells Road, Letchworth, Herts, SG6 4TS.
Michael Kirby, General Practitioner and Director of HertNet – The Hertfordshire Primary Care Research Network, Visiting Professor, University of Hertfordshire

St George's Hospital, Blackshaw Road, London, SW17 0QT.
Roger Kirby, Visiting Professor in Urology

Correspondence to: Dr M Kirby
(email: kirbym@globalnet.co.uk)

Introduction

The findings of many clinical studies have revealed a consistent message: lowering blood pressure reduces mortality, stroke, coronary heart disease and heart failure.[1] Only about 10% of patients reach goal blood pressure below 140/90 mmHg, however, according to the Health Survey for England. One of the reasons is that many patients receive inadequate treatment: despite the fact that most patients will require multiple antihypertensive agents to reach target, only one third of patients in the UK receive more than one drug, and fewer than 10% receive more than two drugs.[2]

In addition to this, concordance – one of the most important factors affecting the success of hypertension management – is poor. For example, a retrospective analysis of hypertensive patients being treated in general practice found that 50–59% of patients discontinued their treatment after only six months of therapy.[3]

Poor concordance, not only with lifestyle advice but also with medication, may partially account for the high percentage of hypertension patients who are, in theory, being treated and yet who may not achieve control. It is important to identify such patients, and reviewing the frequency of collection of repeat prescriptions is an ideal way to address this problem. It is very important to ensure that the patient understands the reasons for and benefits of treatment.

The recently published British Hypertension Society (BHS) guidelines[4,5] advise that drug therapy should be started in all patients with a sustained systolic blood pressure (SBP) > 160 mmHg or sustained

diastolic blood pressure (DBP) > 100 mmHg despite non-pharmacological measures. For patients with established cardiovascular disease, target organ damage, diabetes mellitus or a 10-year cardiovascular disease risk > 20%, drug treatment is indicated at a lower level of sustained SBP (140–150 mmHg) and sustained DBP (90–99 mmHg).

Several classes of drugs may be used to lower blood pressure effectively – thiazides, beta blockers, calcium channel-acting blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), alpha blockers and centrally acting agents such as moxonidine. It is likely that co-administration of more than one agent will become the preferred first-line approach. Logical combinations of agents, which have the potential to give additive or synergistic effects in lowering blood pressure, include diuretics with beta blockers or ACE inhibitors, and alpha blockers with beta blockers or ACE inhibitors.[6] The combination of rate-limiting calcium antagonists with beta blockers is to be avoided.

Optimal cardiovascular outcome is, in general, linked more closely to the level of blood pressure achieved rather than to the agent used to achieve it. In some cases, however, there are compelling indications (and contra-indications) for specific classes of antihypertensive agent stemming from the co-morbidities of the patient or the other drugs that they are taking. These are summarised in table 1. It is well known that beta blockers should be avoided in patients with asthma: also, the combination of beta blockers and diuretics should be avoided in patients who are at risk of developing type 2 diabetes mellitus. Some drugs may be avoided by the general practitioner but may be used cautiously, under specialist care: examples include ACE inhibitors and ARBs in chronic renal failure.

It can be seen from table 1 that the presence of benign prostatic hyperplasia (BPH) is considered a compelling indication for the use of alpha blockers in the treatment of hypertension. With age, the prevalence of hypertension, lower urinary tract symptoms (LUTS), erectile dysfunction (ED) and diabetes mellitus are increased. Some 28% of patients with BPH also have hypertension.

ED and hypertension may have common aetiologies such as increased sympathetic activity with endothelial dysfunction and metabolic syndrome. Higher levels of ED are observed in patients with hypertension, and vice versa. Again, there are special therapeutic considerations to be taken into account when treating patients with both conditions.

The links between ED and LUTS were explored by Rosen *et al*. in the Multinational Survey of the Aging Male (MAMS-7).[7] A total of 34,800 surveys were mailed out to men aged between 50 and 80 years in the US and six European countries. Of these, 14,254 were completed and returned, and 12,815 surveys were deemed evaluable and were included in the analysis. Results were consistent from one country to another. Although 90% of men had LUTS, only 19% had sought help for urinary problems and only 11% were medically treated. Twenty-eight per cent of these patients also had hypertension. Sexual activity was reported by 83% of the sample, with 71% reporting at least one episode of sexual activity in the previous four weeks. Sexual disorders and their bothersomeness were strongly related both to age and severity of LUTS (figure 1). The relationship between sexual problems and LUTS was independent of co-morbidities such as diabetes, hypertension, cardiac disease and hypercholesterolaemia.

Table 1. Indications and contra-indications for the use of antihypertensive agents

Class of drug	Compelling indications	Compelling contra-indications
Alpha blockers	Benign prostatic hyperplasia	Urinary incontinence Hypotension
ACE inhibitors	Heart failure Left ventricular dysfunction post-MI Type 1 diabetic nephropathy	Pregnancy Renovascular disease
ARBs	ACE inhibitor intolerance Type 2 diabetic nephropathy Hypertension with LVH	Pregnancy Renovascular disease
Beta blockers	Myocardial infarction Angina	Asthma, COPD
CCB (dihydropyridine)	Elderly patients Isolated systolic hypertension	
CCB (rate-limiting)	Angina	Heart block Heart failure
Thiazides	Elderly patients Isolated systolic hypertension Heart failure	Gout

Key: ACE = angiotensin-converting enzyme; MI = myocardial infarction; ARBs = angiotensin II receptor blockers; LVH = left ventricular hypertrophy; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker

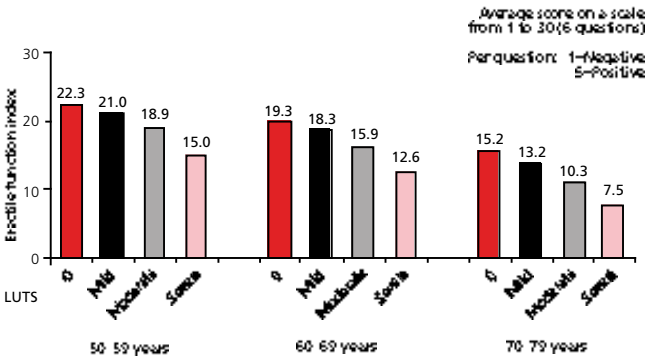
Recommendations taken from Williams B, Poulter NR, Brown MJ *et al*.[4]

The conclusions were that sexual activity is common in a majority of men over the age of 50 years and is an important component of overall quality of life. The presence and severity of LUTS are independent risk factors for sexual dysfunction in older men (figure 1). Results highlighted the clinical importance of evaluating LUTS in patients with sexual dysfunction, and vice versa, and the need to consider sexual issues in the management of patients with BPH.

How ageing leads to smooth muscle dysfunction is, at best, poorly understood. One possible mechanism is chronic ischaemia caused by atherosclerotic occlusive disease. Atherosclerosis-induced arterial insufficiency is a common clinical problem in the elderly, and remains the leading cause of death in the adult population.[8] The abdominal aorta and its branches, especially the bifurcation of the iliac arteries, is often involved earliest and is most severely affected by atherosclerotic lesions.[9] Atherosclerosis of the aorto-iliac bed can potentially compromise the blood supply at the lower genito-urinary tract: for example, atherosclerotic disease of the pudendal and cavernosal arteries has been shown to be a major cause of erectile dysfunction in the elderly patient.[10]

Major risk factors for atherosclerosis, such as hypertension,

Figure 1. MSAM-7 study results, confirming the association between the severity of LUTS and sexual function



Key: MSAM-7 = Multinational Survey of the Aging Male; LUTS = lower urinary tract symptoms

Adapted from Rosen R *et al.*[7]

hypercholesterolaemia, smoking and diabetes, have also been found to be associated with smooth muscle dysfunction. In animal models, atherosclerosis-induced pelvic ischaemia can produce functional and structural alterations in detrusor and corpora cavernosal smooth muscle which parallel the age-related changes in bladder and cavernosal smooth muscle in humans.[11] Therefore, there has been increasing interest in the possible role of atherosclerosis-induced ischaemia in LUTS and erectile dysfunction of the elderly. Table 2 summarises the key pathophysiological changes that can lead to LUTS.

Interestingly, alpha blockers such as doxazosin appear to reduce blood pressure in hypertensive individuals, but only have minimal effect on blood pressure in normotensive patients. In those 20–30% of patients with BPH who are also hypertensive, alpha blocker therapy may therefore have dual efficacy and be very cost-effective.[12]

Lifestyle measures such as maintenance of normal body weight and reduction of salt intake are important to prevent the development of overt hypertension in people with high-normal blood pressures. Effective lifestyle modification can lower blood pressure as much as a single blood pressure-lowering drug in people with established hypertension: such measures may reduce the number of antihypertensive agents needed and may improve LUTS and erectile dysfunction, especially if bladder retraining and pelvic floor exercises are included. In addition, to reduce the overall cardiovascular disease risk, patients should stop smoking and increase their consumption of monounsaturated fats and oily fish.

Benign prostatic hyperplasia

BPH is almost universal in ageing men: post-mortem evidence reveals that more than 90% of men aged 70 years or more have this condition (figure 2). The pathogenesis seems to have three

Table 2. Causes of lower urinary tract symptoms (LUTS)

- Atherosclerosis-induced arterial insufficiency
- Bladder outlet obstruction
- Raised intravesical pressure
- Decreased bladder blood flow
- Chronic bladder ischaemia and hypoxia
- Structural changes, such as fibrosis
- Functional changes, such as non-compliance, hyperactivity and impaired contractility

strands: conversion of testosterone to dihydrotestosterone (DHT) in the prostate, which promotes prostatic growth; rising oestradiol levels with age, which acts in synergy with DHT; and activation of alpha$_1$ adrenoreceptors in the bladder neck and smooth muscle tissue. In addition to this, there are ageing and ischaemia-related changes of the bladder.

Patients suffer from obstructive symptoms such as hesitancy and poor stream, and also from irritative symptoms such as dysuria, nocturia, frequency and urgency. Complications include acute urinary retention and recurrent urinary tract infections. Table 3 shows the International Prostate Symptom Score (IPSS) used to assess prostatic symptoms.

Management, traditionally, is a selection of one of four options. Watchful waiting is safe for those with mild-to-moderate symptoms (though annual monitoring is required). Lifestyle measures for the patient include avoiding substances with a known diuretic effect such as cola drinks, tea and coffee. Double voiding, especially at bedtime, can be helpful when there is impaired bladder emptying and in those patients who have a significant urinary residual volume. Alpha blockers have been considered first-line therapy because of their rapid onset of action. In the new British Association of Urological Surgeons (BAUS) guideline for the management of male LUTS,[13] patients who cannot be managed with lifestyle advice alone are split into two groups according to their risk factors for progression. Those with bothersome LUTS but a prostate smaller than 30 cm^3 and a Prostate-specific antigen (PSA) below 1.4 ng/ml are recommended to receive an alpha blocker and review at six to 12 weeks. Those with an enlarged prostate or high PSA should also receive a 5-alpha reductase inhibitor and be reviewed at three to six months. Finally, there is invasive treatment such as surgery.

In the IPSS, there is an additional question on the patient's quality of life due to urinary symptoms. "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" The question is graded from 0 (delighted) to 6 (terrible).

Alpha blockers in BPH

Alpha blockers are used in the treatment of BPH because alpha-adrenergic mediated innervation of smooth muscle at the bladder neck controls tension at the bladder outlet. The early alpha antagonists such as phenoxybenzamine and phentolamine are

Figure 2. Benign prostatic hyperplasia showing progressive enlargement of the central zone which causes increasing bladder outflow obstruction

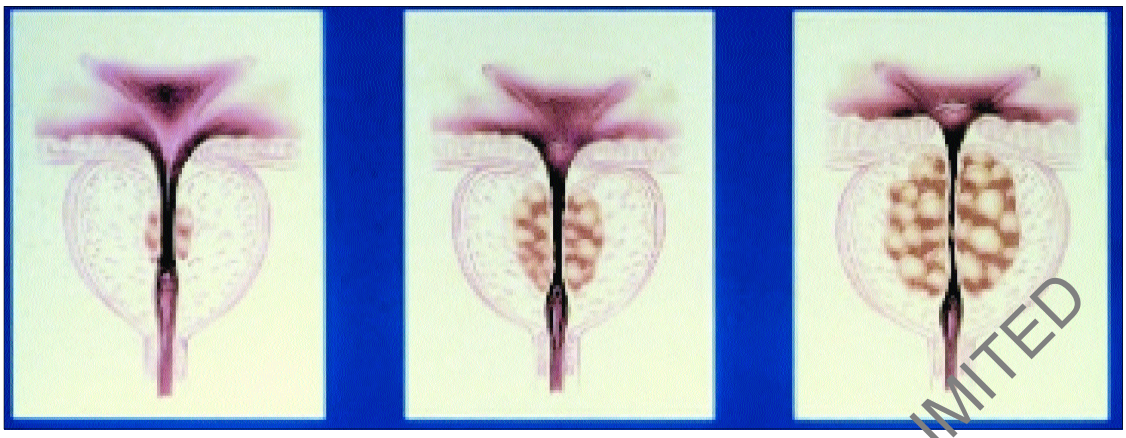


Table 3. The International Prostate Symptom Score (IPSS), used in the assessment of prostatic symptoms

- Over the past month, how often have you had the sensation of not emptying your bladder completely after you finished urinating?
- How often have you had to urinate again in less than two hours?
- How often have you found that you stopped and started several times when you urinated?
- How often have you found it difficult to postpone urination?
- How often have you had a weak urinary stream?
- How often have you had to push or strain to begin urination?
- How many times did you get up to urinate between the time you went to bed and the time you got up in the morning?

Score: 0 = not at all; 1 = less than one time in five; 2 = less than half the time; 3 = about half the time; 4 = more than half the time; 5 = almost always

Grading: 0–7 = mild symptoms; 8–19 = moderate symptoms; 20–35 = severe symptoms

In addition, there is a question on the patient's quality of life due to urinary symptoms. "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" The question is graded from 0 (delighted) to 6 (terrible)

non-selective blockers of the alpha$_1$ and alpha$_2$ receptors, and they cause significant cardiovascular side effects, including postural hypotension (mediated predominantly by alpha$_2$ antagonism).

The selective alpha$_1$-receptor antagonists, such as prazosin, doxazosin, terazosin, tamsulosin and alfuzosin, have few side effects and are considered first-line drugs. Typically, placebo-controlled trials have shown that these agents improve lower urinary tract symptoms by 30–40% and maximum urinary flow rates by 16–25%. Most men treated with these agents sense clinical improvement within two weeks, and the full effects are usually obtained by four to six weeks.

Most evidence to date has shown that the alpha$_1$ antagonists are of similar effectiveness, though there have been few head-to-head studies. A recent paper by Kirby *et al*. suggested that doxazosin was superior to tamsulosin in the management of BPH.[14] The paper consists of two post-hoc analyses of a study in which 52 men with BPH were randomised to treatment with either doxazosin-GITS (gastrointestinal therapeutic system) 4–8 mg/day or tamsulosin 0.4–0.8 mg/day. BPH was defined as a total International Prostate Symptom Score (IPSS) of 12 or more, a maximum urinary flow rate > 5 and < 15 ml/s for a total voided volume of > 150 ml, and prostate enlargement on digital rectal examination.

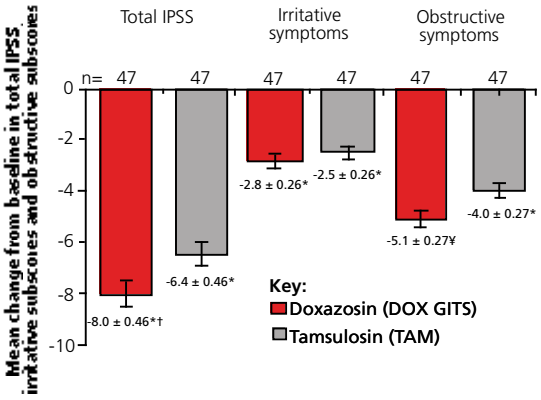
After the first eight weeks of treatment, both doxazosin and tamsulosin provided a significant ($p<0.001$) improvement from baseline in total IPSS and obstructive and irritative subscores. There was a significant difference in favour of doxazosin both for total IPSS ($p=0.019$) and for the irritative subscore ($p=0.001$) (figure 3).

The difference between the two agents' effectiveness may be explained by their chemistry. Doxazosin is a quinazolone whereas tamsulosin is a sulphonamide-based non-quinazolone. These differences may affect how the two compounds react with alpha receptors in prostatic smooth muscle, and perhaps other receptors. Alfuzosin and tamsulosin do not lower blood pressure, whereas doxazosin and terazosin can be used to treat both hypertension and BPH simultaneously, and this may be cost-effective.

5-alpha reductase inhibitors

Men born with an inherited defect of 5-alpha reductase have small prostates and never develop BPH. DHT is the primary prostatic androgen: it is derived from testosterone by the action of 5-alpha reductase. Clinical trials have shown that the 5-alpha reductase inhibitor, finasteride, reduced circulating DHT levels by 80%, prostatic size by 20% and American Urological Association (AUA) symptom scores by three points.

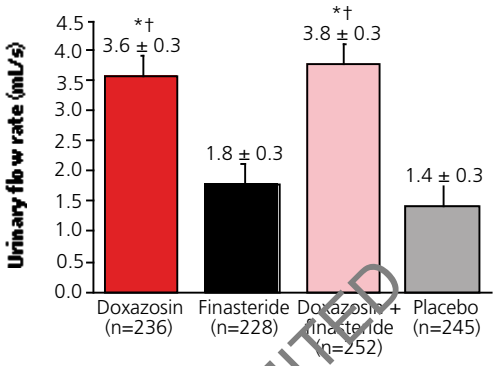
Figure 3. A comparison of doxazosin and tamsulosin in the treatment of benign prostatic hypertension



Key: IPSS = International Prostate Symptom Score; *p=0.001 *vs.* baseline; †p=0.019 DOX GITS *vs.* TAM; ¥p=0.004 DOX GITS *vs.* TAM

Data from Kirby RS *et al.*[14]

Figure 4. Results of the PREDICT study



Values are least-squares adjusted mean change from baseline

* p≤0.0001 *vs.* placebo; † p≤0.0001 *vs.* finasteride alone

Adapted from Kirby RS *et al.*[16]

Dutasteride, which suppresses both isoforms of 5-alpha reductase, was launched in the UK about a year ago. It has been shown to reduce serum DHT levels further than finasteride, but efficacy and tolerability seem similar for both.

Although alpha blockers are effective at reducing prostatic symptoms in most men with prostatic enlargement (> 30 cm³ or prostate-specific antigen > 1.4 ng/ml as a surrogate marker for prostate size), finasteride and dutasteride are only effective in men with larger prostates (and take several months to achieve full effect). Since alpha blockers and 5-alpha antagonists act at completely different sites of action, combination therapy might be expected to give superior results compared to either agent alone, especially with medium- to long-term treatment, and might be synergistic. This theory has been investigated in several clinical trials.

Trials of combination therapy in BPH

A number of trials have investigated the effects of combination therapy with an alpha blocker and a 5-alpha reductase inhibitor in BPH. Early trials of combination therapy were confounded because patients did not have significant prostatic enlargement, and therefore finasteride was unlikely to be efficacious. An example is the Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group which compared the safety and efficacy of placebo, the alpha-blocker terazosin 10 mg daily, the 5-alpha reductase inhibitor finasteride 5 mg daily, and the combination of both, in 1,229 men with BPH.[15]

The mean changes from baseline to one year in the AUA symptom scores were 2.6 points for placebo treatment, 3.2 points for finasteride, 6.1 points for terazosin and 6.2 points for the combination (p<0.001 for terazosin and combination groups compared with finasteride alone and placebo). Mean changes in peak urinary flow rates were increases of 1.4 ml per second for the placebo group, 1.6 ml for finasteride, 2.7 ml for terazosin and 3.2 ml for the combination (again p<0.001, as before).

The authors of this study concluded that terazosin was effective treatment in men with BPH, and that the combination of terazosin with finasteride was no more effective than terazosin treatment alone.

Prostate size was a confounding issue in the Prospective European Doxazosin and Combination Therapy (PREDICT) trial which evaluated the efficacy and tolerability of doxazosin and finasteride, alone or in combination, for the symptomatic treatment of BPH.[16] In this placebo-controlled trial, 1,095 men aged 50 to 80 were randomised to treatment for 52 weeks with finasteride 5 mg/day, doxazosin, both or placebo. Doxazosin was started at a dose of 1 mg/day and titrated up to a maximum of 8 mg/day according to the response of the maximal urinary flow rate (Qmax) and the IPSS.

Results of an intention-to-treat analysis of 1,007 men showed that doxazosin and combination therapy produced statistically significant improvements in IPSS and Qmax compared with placebo and finasteride alone (p<0.05). The authors stated that doxazosin was useful treatment for BPH, but added that finasteride did not give additional benefit (figure 4).

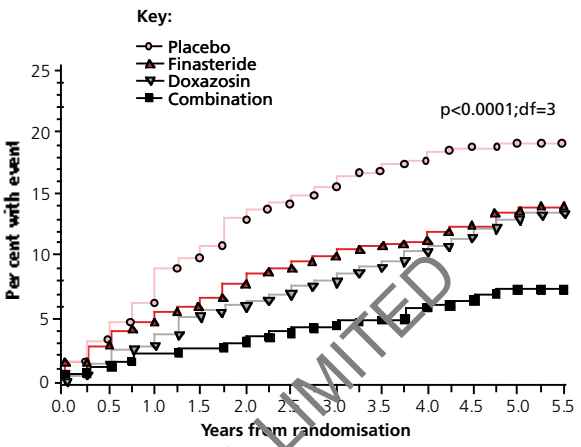
McConnell *et al.*, for the Medical Treatment of Prostatic Symptoms (MTOPS) study group, published results from a study which assessed the long-term effects of doxazosin, finasteride and combination therapy not only on symptom scores but on the clinical progression of BPH and the long-term reduction in risk of associated complications.[17] The trial included 3,047 men, who were followed up for a mean of 4.5 years. The mean prostate volume was 36.3 +/- 20.1 ml and the median prostate volume was 31 ml, measured by transrectal ultrasonography. There were no significant differences between the groups assigned to the different treatments.

Table 4. Clinical progression of BPH in the McConnell study[17]

Event	Placebo n=737 Rate	Doxazosin n=756 Rate, RR	Finasteride n=768 Rate, RR	Combination n=786 Rate, RR
Clinical* progression	4.5	2.7 (39)	2.9 (34)	1.5 (66)
>4 pt AUA	3.6	1.9 (45)	2.5 (30)	1.3 (64)
Retention	0.6	0.4 (35)	0.2 (68)	0.1 (81)
Incontinence	0.3	0.3 (-32)	0.3 (9)	0.1 (65)
UTI/sepsis	0.1	0.1 (insuff)	0.0 (insuff)	<0.1 (insuff)
Need for invasive therapy	1.3	1.3 (3)	0.5 (64)	0.4 (67)

Key: BPH = benign prostatic hyperplasia; *clinical progression as described in the text, or a rise in serum creatinine; AUA = American Urological Association; UTI = urinary tract infection

Figure 5. Results of the MTOPS study, showing cumulative incidence of BPH progression



Key: MTOPS = Medical Treatment of Prostatic Symptoms

Adapted from McConnell JD *et al.*[17]

Men aged 50 years or more with an AUA score of eight to 30 and with a maximal urinary flow rate of 4–15 ml per second were enrolled between 1993 and 1998. Men were randomly assigned in a double-blind fashion to receive placebo, doxazosin 4 mg or 8 mg, finasteride 5 mg or combination therapy. The primary outcome was the first occurrence of an increase from baseline of at least four points in the AUA symptom score, acute urinary retention, renal insufficiency, recurrent urinary tract infections or urinary incontinence.

Results are shown in table 4. As compared with placebo, doxazosin reduced the risk of progression of BPH by 39% (p<0.001) and finasteride reduced it by 34% (p=0.002). Combination treatment reduced the risk of clinical progression by 66% (p<0.001), a significantly greater reduction than that induced by either drug alone.

The four-year mean reduction in symptom score was 4.9 in the placebo group, 6.6 in the doxazosin group, 5.6 in the finasteride group and 7.4 in the combination therapy group. Again, the improvement in the symptom score was significantly greater in the combination group than in patients taking either agent singly. This outcome has clinical importance because, among men with BPH, invasive surgery is most commonly performed for worsening symptoms. The impact of the four treatment arms on BPH progression is shown in figure 5.

Prostate volume in the 1,148 men who were receiving placebo or doxazosin increased by a median of 24% after an average follow-up period of 4.5 years. Among the 427 men who were receiving finasteride or combination therapy and who had a large prostatic volume at baseline, the prostatic volume decreased by a median of 19%. The reduction in the risk of acute urinary retention and in the need for invasive surgery observed in the finasteride and combination groups may be attributed to a decrease in prostate size.

Incidence rates of the typical adverse events seen with doxazosin and finasteride therapy were similar to those reported in previous studies. The findings from these studies are reflected in the 2004 BAUS guidelines.[13]

Erectile dysfunction

Erectile dysfunction (ED) is common: the Massachusetts Male Aging Study[18] estimated that about 50% of men aged between 40 and 70 years were persistently unable to attain and maintain an erection. The prevalence of ED increases with age, with a 39% prevalence among 40-year-olds and a 67% prevalence among 70-year-olds. It is not easy to obtain accurate figures, partly because men are reticent in seeking advice and partly because physicians omit to enquire about their patients' sexual function.

ED may be a marker for other diseases.[19] Patients who present with ED should be assessed for previously undiagnosed conditions such as diabetes, hyperlipidaemia, hypertension, ischaemic heart disease and benign prostatic hypertrophy. The identification of ED and knowledge of the link between ED and other cardiovascular diseases is an opportunity to address risk factors; the Joint Societies' cardiovascular disease risk calculator can be applied to assess the need for therapies such as antihypertensive agents, aspirin and lipid-lowering agents to reduce the risk of cardiovascular disease. (Nevertheless, 80% of ED patients are at low cardiovascular risk and can be managed effectively in primary care.)

ED is not only more prevalent among patients with hypertension than among the general population – it is also more severe. For instance, in a study by Burchardt *et al.*[20] the International Index of Erectile Function questionnaire was sent to male patients of the out-patient Hypertension Center of Columbia Presbyterian Medical Center. Of the 104 respondents, with a mean age of 62.2 years (age range 34 to 75 years),

84.8% were sexually active and 68.3% had various degrees of ED. This was mild in 7.7%, moderate in 15.4% and severe in 45.2%. Although correlation with antihypertensive medication did not reach statistical significance, there was a clear trend: patients treated with diuretics and beta blockers had the highest incidence, and those treated with alpha blockers had the lowest incidence, of ED.

The nature of the link between ED and hypertension is likely to be related to nitric oxide/cyclic GMP pathways and endothelial function.

Many prescription drugs are associated with ED, including antihypertensive thiazide diuretics, beta blockers and ACE inhibitors.[21] It must be remembered, of course, that these drugs may also be treating conditions that in themselves cause ED. Reports have indicated an incidence range of 5–43% for propranolol and 4–32% for thiazide diuretics. A strong relationship between the start of the drug therapy and the onset of ED may indicate an iatrogenic problem. There is little good-quality evidence to confirm reversal of ED on changing suspect drug therapy. Any improvements in ED that do occur are likely to take place within two to four weeks.

Alpha blockers and ARBs are the drugs least likely to cause ED, and may well improve the situation. In one study, patients with BPH were treated with doxazosin for up to eight weeks and assessed at weeks four and eight using a sexual function questionnaire.[22] Results showed that doxazosin significantly improved overall sexual function, in particular, the ability to gain and keep an erection, compared with baseline values. A 10% improvement in overall sexual function was noted at week 4 ($p=0.002$) and a 15% improvement at week 8 ($p<0.001$). A more recent study[23] reported 237 patients with concomitant BPH and ED treated with doxazosin. Significant improvement in ED occurred, with the range of improvement ranging from 13–41%.

In a study by Fogari and colleagues,[24] the effects of valsartan 80–160 mg daily and atenolol 50–100 mg daily on sexual activity and plasma testosterone were compared in men with newly diagnosed essential hypertension. Clinical evaluation was performed after eight weeks and 16 weeks of treatment. It included measurement of blood pressure and plasma testosterone and completion of a questionnaire about sexual activity. The two agents gave similar reductions in blood pressure. However, atenolol reduced sexual activity from 6.0 to 4.2 episodes per month whereas valsartan increased it from 5.8 to 7.4 episodes per month ($p<0.05$ compared with atenolol). Testosterone was reduced by atenolol from 18.2 to 13.8 nmol/L, $p<0.01$ compared to baseline. The testosterone level rose very slightly with valsartan, from 17.6 to 18.3 nmol/L.

Any modifications to drug treatments for cardiovascular disease should keep the patient's entire clinical picture in mind. For example, alpha blockers or ARBs could be considered as an alternative treatment for patients with both hypertension and ED. However, since beta blockers confer prognostic benefit post-MI and in patients with heart failure, the alternative might not be in the patient's best interests.[21]

All patients with ED should undergo a thorough medical assessment, though laboratory tests can be kept to a minimum (glucose, lipid profile, liver function tests and testosterone). Management of ED will depend on the patient's cardiovascular risk profile. Patients with controlled hypertension (plus those with mild stable angina, New York Heart Association class I heart failure, post-revascularisation, mild valvular disease and with a maximum of cardiovascular risk factors) can be managed within the primary care setting. Others, including those with left ventricular dysfunction or uncontrolled hypertension, require specialised evaluation such as exercise testing and echocardiography before their management can be decided.

Treatment of ED

All currently licensed ED treatments are suitable for managing ED in the cardiovascular patient, when used according to the manufacturer's instructions.[21] There is the possibility of a drug interaction, causing postural hypotension, between a phosphodiesterase type 5 (PDE5) inhibitor and an alpha blocker. Thus, either a temporal separation should be observed or a selective alpha blocker might be used in order to avoid a potentially disadvantageous drop in blood pressure. The PDE5 inhibitors such as sildenafil, vardenafil and tadalafil are currently the treatment of first choice for ED.[25] When nitric oxide is released through stimulation of non-adrenergic, non-cholinergic cavernosal nerves, it activates guanylate cyclase to allow the production of cyclic GMP. In turn, cyclic GMP causes smooth muscle relaxation by decreasing intracellular calcium, leading to penile erection. PDE5 is the enzyme that breaks down cyclic GMP, leading to smooth muscle contraction and detumescence. Because PDE5 is present widely in the vasculature, its inhibition has potential in the treatment of conditions such as systemic and pulmonary hypertension.[26]

The most comprehensive safety and efficacy data relate to sildenafil. Prior to its approval, sildenafil was evaluated in 5,000 subjects: the main adverse events of note were headache (16%), flushing (10%), dyspepsia (7%) and nasal congestion (4%).[27] A prescription event monitoring study[28] followed 5,601 men who were prescribed sildenafil for five months, and compared their mortality figures with those of the general male population of England. No difference in mortality was found between the two populations, and there was no evidence of a higher incidence of fatal myocardial infarction or ischaemic heart disease. An evaluation of the available data from spontaneous reports, clinical trials and one observational study shows that the number of events that have occurred within this high-risk population of patients with ED is compatible with the number that would be expected to occur, based on available incidence data.[29]

The safety database for tadalafil includes more than 4,000 patients from 60 clinical studies. Only six myocardial infarctions were reported in the total patient population, giving an incidence rate of 0.39 per 100 patient-years in tadalafil-treated patients, compared with 1.1 per 100 patient-years in patients who received placebo. The cardiac mortality in tadalafil-treated patients was similar to, if not lower than, the cardiac mortality in an age-standardised population of British men.[30]

Key messages

- In men with hypertension, the presence of benign prostatic hyperplasia (BPH) is a compelling indication for use of an alpha blocker
- Results from the MTOPS study showed that combination treatment of BPH with both doxazosin and finasteride significantly improved the symptom score and reduced clinical progression
- The alpha blockers and angiotensin II receptor blockers are the antihypertensive agents least likely to cause erectile dysfunction (ED)
- Higher levels of ED are observed in patients with hypertension, and vice versa; they may have aetiologies in common

As regards vardenafil, the incidence rates of cardiovascular adverse events were similar to placebo in one review of five placebo-controlled trials.[31]

Thus, PDE5 inhibitors may be used safely in most patients with cardiovascular disease. There is also the possibility that PDE5 inhibitor treatment could be used to treat both hypertension and ED. One study used sildenafil 50 mg in eight hypertensive patients. With placebo, the drop in blood pressure was 6/3 mmHg; by comparison, with sildenafil treatment, the drop was 24/8 mmHg.[32] Here, a longer-acting formulation of sildenafil or a long-acting drug such as tadalafil might have advantages. It is certainly an area that deserves further investigation.

Conflict of interest

MK and RK have received sponsorship to attend international conferences and advisory boards from companies that manufacture alpha blockers and 5-alpha reductase inhibitors.

References

1. Collaboration of Blood Pressure Lowering Treatment Trialists. Effects of angiotensin converting enzyme inhibitors, calcium antagonists and other blood pressure-lowering drugs on mortality and major cardiovascular morbidity. *Lancet* 2000;**355**:1955-64.
2. Williams B. Drug treatment of hypertension—the future is combination therapy. *Br J Cardiol* 2003;**10**(suppl 3):S1-S2.
3. Ramsay LE, Johnston GD, MacGregor GA *et al*. Guidelines for the management of hypertension: Report of the third working party of the British Hypertension Society. *J Hum Hypertens* 1999;**13**:569-92.
4. Williams B, Poulter NR, Brown MJ *et al*. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society—BHS IV. *J Hum Hypertens* 2004;**18**:139-85.
5. Williams B, Poulter NR, Brown MJ *et al*. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004;**328**:634-40.
6. Poulter NR, Thom S, Kirby M. Shared care for hypertension. London: Taylor & Francis, 2000.
7. Rosen R, Altwein P, Boyle P *et al*. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *Eur Urol* 2003;**44**:637-49.
8. Rose G. Epidemiology of atherosclerosis. *BMJ* 1991;**303**:1537-9.
9. Bierman BL. Atherosclerosis and other forms of atherosclerosis. In: Wilson JD, Braunwald E, Isselbacher KG *et al. Harrison's principles of internal medicine, 12th edition, volume 1*. New York: McGraw-Hill, 1991;992-1001.
10. Krane RJ, Goldstein I, Saenz de Tejada I. Impotence. *N Engl J Med* 1989;**321**:1648-59.
11. Azadzoy KM, Siroky MB, Goldstein I. Study of aetiologic relationship of arterial atherosclerosis to corporeal veno-occlusive dysfunction in the rabbit. *J Urol* 1996;**155**:1795-800.
12. Kirby RS, Chappell CR, Christmas TJ. Doxazosin: minimal blood pressure effects in normotensive BPH patients. *J Urol* 1993;**149**:434.
13. Speakman MJ, Kirby RS, Joyce A, Abrams P, Pocock R. Guideline for the primary care management of male lower urinary tract symptoms. *B J U Intl* 2004;**93**:985-90.
14. Kirby RS, Quinn S, Mallen S, Jensen D. Doxazosin controlled release vs tamsulosin in the management of benign prostatic hyperplasia: an efficacy analysis. *Int J Clin Pract* 2004;**58**:6-10.
15. Lepor H, Williford WO, Barry MJ *et al*. The efficacy of terazosin, finasteride, or both in benign prostatic hypertrophy. *N Engl J Med* 1996;**335**:533-40.
16. Kirby RS, Roehrborn S, Boyle P *et al*. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hypertrophy: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology* 2003;**61**:119-26.
17. McConnell JD, Roehrborn CG, Bautista OM *et al*. for the Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hypertrophy. *N Engl J Med* 2003;**349**:2387-98.
18. Feldman HA, Goldstein I, Hatzichristou DG *et al*. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;**151**:54-61.
19. Kirby M, Jackson G, Betteridge J, Friedli K. Is erectile dysfunction a marker for cardiovascular disease? *Int J Clin Pract* 2001;**55**:614-18.
20. Burchardt M, Burchardt T, Baer L *et al*. Hypertension is associated with severe erectile dysfunction. *J Urol* 2000;**164**:1188-91.
21. Jackson G, Betteridge J, Dean J *et al*. A systematic approach to erectile dysfunction in the cardiovascular patient: a consensus statement—update 2002. *Int J Clin Pract* 2002;**56**:663-71.
22. Gratzke P, Kirby RS. Doxazosin GITS und herkömmliches Doxazosin zur Behandlung der benignen Prostatahyperplasie. *MMW Fortschritte Medizin* 2000;**118**:83-92.
23. Kirby RS, O'Leary MP, Carson C, Efficacy of extended-release doxazosin and doxazosin standard in patients with concomitant benign prostatic hyperplasia and sexual dysfunction. *BJU Int* 2005;**95**:103-09.
24. Fogari R, Preti P, Derosa G *et al*. Effect of antihypertensive treatment with valsartan or atenolol on sexual activity and plasma testosterone in hypertensive men. *Eur J Clin Pharmacol* 2002;**58**:177-80.
25. Kirby M. Management of erectile dysfunction in men with cardiovascular conditions. *Br J Cardiol* 2003;**10**:305-07.
26. Jackson G. Phosphodiesterase type 5 inhibition: effects on the coronary vasculature. *Int J Clin Pract* 2001;**55**:183-8.
27. Sadovsky R, Miller T, Moskowitz M, Hackett G. Three-year update of sildenafil citrate (Viagra®) efficacy and safety. *Int J Clin Pract* 2001;**55**:115-28.
28. Shakir SAW, Wilton LV, Bashier A, Layton D, Heeley E. Cardiovascular events in users of sildenafil: results from first phase of prescription event monitoring in England. *BMJ* 2001;**322**:651-2.
29. Lewis M. The safety of sildenafil. *Br J Cardiol* 2005 (in press).
30. Emmick JT, Stuett SR, Mitchell M. Overview of the cardiovascular events of tadalafil. *Eur Heart J* 2002;**4**(suppl 4):32-47.
31. Kloner RA *et al*. Poster presentation at the European Society for Sexual and Impotence Research (ESSIR), Hamburg, Germany, 1st-4th December 2002.
32. Jackson G, Alexander W, Evans M *et al*. Phosphodiesterase type 5 (PDE5) inhibitors: looking beyond erectile dysfunction. *Br J Cardiol* 2003;**10** (suppl 4):S1-S8.