Tolerability of α-Blockade With Doxazosin as a Therapeutic Option for Symptomatic Benign Prostatic Hyperplasia in the Elderly Patient: A Pooled Analysis of Seven Double-Blind, Placebo-Controlled Studies

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**Background.** Benign prostatic hyperplasia (BPH) is a common disorder in males, and its incidence increases with age. Safety results from trials with doxazosin therapy in elderly patients were collated and described.

**Methods.** Safety data were collated from seven completed multicenter, double-blind, placebo-controlled studies of doxazosin in the treatment of BPH in older patients and analyzed according to age group (<65 and >65 years) and blood pressure status.

**Results.** Data for 341 patients aged >65 years (217 normotensive, 124 hypertensive) and 322 patients aged <65 years (207 normotensive, 115 hypertensive) were available. In normotensive subjects a statistically nonsignificant smaller percentage of elderly patients reported adverse events than younger patients in both doxazosin (42% compared with 47%) and placebo (38% compared with 44%) groups. The most common adverse events were fatigue, headache, and dizziness whereas withdrawals due to adverse events were 6% (elderly) and 7% (younger) for doxazosin patients and 9% and 5% for placebo patients, respectively. In hypertensive patients 43% of elderly doxazosin patients reported adverse events compared with 30% of elderly placebo patients, the most common events in both groups being dizziness, headache, fatigue, and dyspnea. Incidence of withdrawal due to adverse events was 11% with doxazosin and 4% with placebo. Very few serious adverse events were reported throughout these trials in any group. Nonsignificant reductions in mean blood pressure were seen in all normotensive patients. Fewer elderly patients had a clinically significant reduction in blood pressure than younger patients (26% vs 30%, respectively).

**Conclusions.** These studies show doxazosin to be equally well tolerated in young and old, normotensive and hypertensive patients with BPH.

SYMPTOMATIC benign prostatic hyperplasia (BPH) is a condition that is familiar to geriatricians because its prevalence increases with age. Histologic BPH is present in some 50% of men aged 60 years (1,2), and 28% of men over 70 years of age have moderate to severe symptoms (3). Urinary symptoms such as frequency, nocturia, urgency, and dribbling have a significant negative impact on the lives of affected patients, obliging many of them to curtail normal daily activities such as traveling and enjoying leisure pursuits (4).

Equally familiar to geriatricians is the existence of multiple pathologies in elderly patients. For example, given that up to 50% of men over the age of 60 years are hypertensive, it is probable that a quarter of men in this age group have concomitant hypertension and BPH (5). Consistent with multiple pathologic conditions is the need to take multiple medications. The risk of adverse drug reactions increases exponentially with the number of drugs being taken by an elderly person, reaching 50% with five drugs and 100% with eight drugs (6). Furthermore, there is a clear association between increasing age and noncompliance with prescribed medications (7). Therefore, it is important that drug therapy for any condition in the elderly is not only effective but also convenient to use and well tolerated.

In terms of the improvement of urinary flow rate, transurethral resection of the prostate (TURP) is still the reference treatment for symptomatic BPH; however, it carries risks of morbidity and mortality that increase with age (8,9). Current treatment guidelines emphasize patient information about treatment options and a joint decision on a case-by-case basis according to patient preference and the judgment of the physician (10,11). Given a choice, most patients with mild to moderate symptoms of BPH prefer an intervention more aggressive than watchful waiting but less aggressive than surgery (12). The main options in this category are 5-α reductase inhibitors and selective α1-adrenoceptor blockers.

The 5-α reductase inhibitors decrease the conversion of testosterone to dihydrotestosterone, which is essential for
prostatic growth, the aim being to cause involution of hyperplastic prostatic tissue and thereby ameliorate symptoms of BPH. This approach has been shown to be effective in some clinical studies (13), although not confirmed in others (14), and has the disadvantage that it may take 6–12 months to achieve its full effect.

Selective \( \alpha_1 \)-blockade has been approved (15,16) as a first-line treatment for high blood pressure, its mechanism being to reduce raised total peripheral resistance by reduction of the vasoconstrictive effect of raised sympathetic tone. In BPH, the same approach reduces the effect of sympathetic tone on prostatic smooth muscle, thereby alleviating a significant element of bladder outflow obstruction in this condition. Long-acting agents such as doxazosin have been shown to be well tolerated and effective in elderly patients with BPH (14,17), and their beneficial effect on BPH symptoms may be expected to occur sooner than with finasteride (within weeks rather than months). In pharmacokinetic terms, the onset of action in both young and elderly patients is gradual (maximum effect on blood pressure at 2–6 h) rather than sudden (18).

Given its dual efficacy in hypertension and BPH, \( \alpha_1 \)-blockade is a rational approach to therapy of BPH in elderly men with BPH, provided that it is well tolerated in this group and that any effect of coexistent hypertension and BPH on its tolerability is properly investigated. Doxazosin is a long-acting selective \( \alpha_1 \)-adrenoceptor blocker whose use in hypertension is well established. This paper presents an analysis of the safety profile of doxazosin in elderly men with BPH, some of whom also had hypertension.

**METHODS**

Safety data were collated from seven completed multicenter, double-blind, placebo-controlled studies of doxazosin in the treatment of symptomatic BPH (19–21) and analyzed according to age group and blood pressure status. Results from two of the trials reported by Janknegt et al. (19) have since been published independently (22–24), and results have been supplemented with data on file.

Three of these studies included patients receiving treatment for mild to moderate hypertension (19), whereas two other studies contained only hypertensive patients who were either being treated (19) or uncontrolled (21). The two remaining studies were comprised of normotensive patients.

All studies required that patients had symptomatic BPH but no history of other serious disease (apart from hypertension where stated) such as significant cardiovascular, hepatic, or renal dysfunction. The studies started with a 1-week placebo run-in phase that was followed by randomization to doxazosin or placebo in an overall ratio of approximately two doxazosin to one placebo. In accordance with usual practice for \( \alpha \)-blockers, doxazosin dosage was titrated once every 1–2 weeks from a starting dose of 1 mg/day to the most effective and well-tolerated dose. The duration of maintenance treatment was between 4 and 29 weeks.

Safety was evaluated by considering adverse events as a whole, those requiring discontinuation of treatment, and also blood pressure and heart rate. In the analysis particular attention was paid to hypotensive events.

**RESULTS**

The number of patients included in the analysis is shown in Table 1, categorized by age group and blood pressure status. Patients were defined as normotensive if baseline diastolic blood pressure was \( \leq 90 \) mmHg, irrespective of the use of concomitant hypertensive therapy. The table shows that data are included from 341 patients aged \( \geq 65 \) years who received doxazosin, of whom 217 were normotensive and 124 were hypertensive.

**Adverse Events According to Age in Normotensive Subjects**

Figure 1 shows a comparison of adverse events that occurred in more than 5% of elderly and younger normotensive BPH patients. The figure shows that there is little difference in the overall adverse event profile between younger and older BPH patients. Among those who received doxazosin, the overall incidence of adverse events in the elderly patients was slightly lower (42% compared with 47%; \( p > 0.05 \)); the most common events in both age groups were fatigue, headache, and dizziness. With placebo, adverse event rates were also slightly lower in elderly patients (38% compared with 44%) and had a similar pattern to doxazosin in each age group, except that fatigue and diz-
ziness were less common with placebo than with doxazosin in older patients.

Most events in all groups were not serious. The percentage of patients on doxazosin treatment who withdrew due to adverse events was 6% in elderly normotensive patients and 7% in younger normotensive patients; with placebo it was 9% and 5%, respectively.

**Adverse Events in Hypertensive Elderly Patients**

Figure 2 shows the incidence of adverse events that occurred in more than 5% of hypertensive patients aged ≥65 years. Comparison with Figure 1 shows that the overall incidence of adverse events with doxazosin in hypertensive elderly patients (43%) was similar to that with doxazosin in normotensive elderly patients (42%), and that the most common events in both groups were dizziness, headache, and fatigue, with dyspnea more common in the hypertensive elderly patients (43%) than with doxazosin in normotensive elderly patients (6%) compared with 1%. Overall a greater percentage of hypertensive elderly patients reported adverse events on doxazosin than on placebo (43% compared with 30%). However, in elderly patients receiving placebo, it was observed that there were markedly fewer adverse events reported by the hypertensive group (30%) compared with the normotensive group (38%). The incidence of withdrawal due to adverse events in hypertensive elderly patients was 11% with doxazosin and 4% with placebo (compared with 6% and 9%, respectively, in normotensive elderly patients).

**Relation of Adverse Events to Dose of Doxazosin in Normotensive Elderly Patients**

An analysis of the incidence of the most common adverse events in normotensive patients aged ≥65 years according to the maintenance dose of doxazosin is shown in Figure 3. The data do not suggest any relation between dose and incidence of adverse events in this elderly group. It is noteworthy that although side effects are not dose related, the side effects seen on starting doxazosin tend to diminish with time.

**Changes in Blood Pressure and Heart Rate in Normotensive Patients**

Clinically insignificant mean reductions in blood pressure were recorded in both age groups of normotensives receiving doxazosin: −5/−3 mmHg sitting and −3/−3 mmHg standing for the patients aged <65 years; −5/−3 mmHg sitting and −5/−2 mmHg standing for those aged ≥65 years. The elderly group had a slightly higher mean systolic pressure at baseline, but the changes during treatment were similar in each age group.

The treatment effects of doxazosin and placebo on blood pressure in elderly normotensive patients are compared in Figure 4. The figure shows that doxazosin reduced mean blood pressure slightly more than placebo in this group, but the differences were small and not clinically significant.

Blood pressure changes in normotensive patients were further analyzed in terms of the proportion of patients who experienced a clinically significant reduction during treatment defined as a reduction to <90 mmHg systolic and/or <60 mmHg diastolic or a reduction of ≥20 mmHg systolic and/or ≥10 mmHg diastolic. Among patients treated with doxazosin the proportion of elderly normotensive patients who showed this defined change in blood pressure was similar during placebo (23%) or doxazosin treatment (26%).

No clinically significant changes in heart rate were seen in any of the normotensive treatment groups.

**Electrocardiograms**

Baseline and final visit electrocardiograms (ECGs) were available for 138 younger (110 doxazosin, 28 placebo) and 183 elderly (121 doxazosin, 62 placebo) normotensive patients. ECG abnormalities arising following treatment were seen at a slightly higher rate in the younger than in the elderly normotensive patients (26% and 20%, respectively). The rates in the younger and elderly patients treated with placebo, however, were similar (23% and 21%). The most common abnormality was sinus bradycardia, which occurred with similar frequency in doxazosin-treated younger and elderly normotensive patients (16% and 14%, respectively) and with a similar incidence to that with placebo in each group (14% and 18%, respectively).

**DISCUSSION**

The data presented here demonstrate that doxazosin is well tolerated by elderly patients with symptomatic BPH whether they are normotensive or hypertensive. Among normotensive patients, the young and the elderly showed similar patterns of adverse events with either doxazosin or placebo. Neither age nor hypertension would therefore seem to be a disadvantage in terms of the ability to tolerate this treatment for BPH.

The dose of doxazosin has to be titrated against efficacy and tolerability. The data show no evidence to suggest that patients who required a higher maintenance dose tolerated treatment any less well. Postural effects on blood pressure, assumed by many to be typical of α-blockers, were avoided by careful dose titration. This is consistent with the previ-
Figure 3. Relation between dose of doxazosin and incidence of most common adverse events in normotensive patients aged >65 years.

![Figure 3](image)

Figure 4. Changes in mean blood pressure in elderly normotensive patients being treated for BPH: doxazosin compared with placebo.

![Figure 4](image)

ous observation that, whereas doxazosin reduces blood pressure significantly (and therapeutically) in hypertensive patients, in normotensive patients (of any age) it produces only a small, clinically insignificant reduction (21,25).

Therefore, doxazosin may be given to normotensive elderly patients for BPH without concern that there may be a clinically significant drop in blood pressure.

Although 26% of elderly normotensive patients who received doxazosin in the present analysis did experience a defined clinically significant reduction in blood pressure, so did a similar proportion (23%) who received placebo. Orthostatic fluctuations in blood pressure of a similar magnitude to those found in the present analysis occurred in some 15% of men and women aged over 65 years included in the Cardiovascular Health Cohort Study (26). However, the incidence of such changes in the present analysis was no higher in elderly than in younger normotensive patients who received doxazosin (26% and 30%, respectively).

There were no significant changes in heart rate with doxazosin therapy in the present analysis; this is consistent with previous observations of the use of this agent (25).

The safety data from the present analysis in elderly patients with BPH are consistent with the extensive published experience of the use of doxazosin in elderly hypertensive patients (27,28) in showing that the incidence and pattern of adverse events in elderly patients are similar to those in the population as a whole. This is a reflection of the observation that its pharmacokinetic characteristics are also similar in older and younger volunteers (29,30).

Long-term tolerability and compliance are important in the drug treatment of chronic conditions such as BPH and hypertension. Ongoing studies with doxazosin have demonstrated good tolerability for follow-up periods currently extending to as much as 4 years (23,31–33). The half-life of doxazosin permits once-daily dosing, and this is an important consideration for elderly patients where compliance is concerned. Compliance with once-daily regimens is significantly higher than with regimens requiring three or four drug intakes per day (34). Moreover, doxazosin may be
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taken either in the morning or in the evening (35), a factor that may further aid compliance.

In the management of BPH generally, there is a trend away from TURP toward pharmaceutical treatments. There has been a reduction of about one third in the number of TURPs performed under the U.S. Medicare Program from 1987 to 1993, and a recent survey commissioned by the American Urological Association to assess urologists’ practice patterns found that the most frequently recommended treatment for BPH of any grade is now α-blockade (36); a similar change in the pattern of clinical practice has been noted in Europe (37). α-Blockade is supported by the International Consensus Committee recommendations as an appropriate treatment option in patients with a confirmed diagnosis of BPH with bothersome symptoms but no serious complications (11). The movement away from surgery also has implication in reducing costs of health care. Economic analysis suggests that for a typical 70-year-old male with a 10-year life expectancy, medical management of BPH saved some $1500 per case in 1994 (38); therefore effective treatment in the large elderly population with BPH offers substantial cost savings.

Selection for the choice of treatments available for symptomatic BPH should be a joint process in which both the patient and the physician participate (10). The present analysis has shown that α-blockade using doxazosin in elderly patients with BPH is well tolerated and may be of additional benefit to the estimated 25% of elderly men who also have concomitant hypertension. Providing a once-daily therapy that not only gives improvements in BPH symptoms but may also have positive effects on cardiovascular risk factors such as hypertension may be of significant benefit to elderly patients.

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REFERENCES


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