Patients with Uncontrolled Hypertension or Concomitant Hypertension and Benign Prostatic Hyperplasia

RANDALL ZUSMAN, M.D.
Massachusetts General Hospital, Boston, Massachusetts, USA

Summary: At optimal doses, individual antihypertensive agents lower blood pressure (BP) by an average of 10 mmHg. Many patients with hypertension, including those with stage 3 hypertension, target organ damage, or those at high risk for cardiovascular events and/or adverse effects of high-dose monotherapy, are likely to require combination antihypertensive drug treatment to achieve the recommended systolic/diastolic BP (< 140/90 mmHg). Two studies, a placebo-controlled, double-blind trial (n = 70) and a community-based, open-label trial (n = 491) investigated the antihypertensive efficacy of doxazosin, a long-acting selective α1-adrenoceptor blocker, as add-on therapy for uncontrolled hypertension with other antihypertensive medications and in patients with concomitant benign prostatic hyperplasia (BPH) and treated but inadequately controlled hypertension, respectively. The addition of doxazosin to baseline antihypertensive medication(s) significantly lowered BP and had a significantly positive effect on the serum lipid profile. In patients with concomitant BPH, doxazosin significantly improved all BPH symptom scores, regardless of initial symptom severity. Add-on doxazosin sufficiently reduced systolic/diastolic BP such that many patients whose hypertension was previously uncontrolled by other antihypertensive medications were able to reach goal BP (< 140/90 mmHg). Doxazosin as add-on therapy was well tolerated. In conclusion, doxazosin as add-on therapy improves BP control in hypertensive patients not at goal BP and improves lower urinary tract symptoms in patients with concomitant BPH.

Key words: hypertension, doxazosin, benign prostatic hyperplasia

Introduction

Hypertension affects approximately 60% of white Americans and approximately 71% of black Americans aged > 60 years. Sequelae of hypertension include stroke, heart failure, coronary artery disease (CAD), and end-stage renal disease. The sixth report of the Joint National Committee (JNC VI) defines hypertension as a sustained systolic blood pressure (SBP) of ≥ 140 mmHg and diastolic BP (DBP) of ≥ 90 mmHg. Hypertension is a syndrome of metabolic, end-organ, and cardiovascular changes, including abnormalities in lipid, glucose, and insulin metabolism; decreased renal function; altered left ventricular structure; and altered compliance of proximal and distal arteries. Evaluating patients with hypertension should have three objectives: (1) identifying known causes of high BP; (2) assessing the presence or absence of target organ damage and cardiovascular disease (CVD), the extent of the disease, and response to therapy; and (3) identifying other cardiovascular risk factors or concomitant disorders that may define prognosis and guide treatment. Even mild forms of hypertension are predictive of cardiovascular events. According to the National Blood Pressure Education Program, SBP/DBP as low as 140/90 mmHg are associated with significant increases in risk of cardiovascular events, and there is a near linear correlation between BP and the relative risk of developing cardiovascular events.

The risk reduction for cardiovascular events associated with BP lowering was demonstrated by the results of the Hypertension Optimum Treatment (HOT) study (n = 18,790). Step-up treatment starting with a calcium-channel blocker (CCB; felodipine) followed by the addition of other antihypertensive agents as needed, enabled most (92%) patients with primary hypertension (DBP 100–115 mmHg) at baseline to...
reach a DBP of ≤90 mmHg. The lowest incidence of combined cardiovascular (CV) events was associated with a mean BP level of 138.5/82.6 mmHg. Optimal protection against combined major CV endpoints was observed within the 80 to 85 mmHg range for DBP and the 130 to 140 mmHg range for SBP. Both were lower than the goal BP recommended by JNC VI (< 140/90 mmHg). In a subset of diabetic patients, a decrease in DBP from 90 to 80 mmHg was associated with a 51% reduction in incidence of major CV events. A subanalysis indicated that quality of life (QoL) was linked to the achieved BP: the lower the BP, the better the QoL.

The JNC VI–recommended goal BP of < 140/90 mmHg may be achieved by lifestyle modification alone or by pharmacologic intervention. They identified seven different classes of antihypertensive drugs as first-line therapy for hypertension: diuretics, beta blockers, CCBs, angiotensin-converting enzyme (ACE) inhibitors, \( \alpha_1 \)-blockers, combined alpha and beta blockers, and angiotensin II receptor blockers (ARBs). The JNC VI also recommended that in the selection of initial therapy for hypertension management, concomitant diseases that may be positively or adversely affected by antihypertensive medication should be considered, and that selection of an antihypertensive agent that also treats a concomitant disease simplifies therapeutic regimens and reduces costs. For the initial treatment of mild uncomplicated hypertension, a step-up approach is recommended, beginning with a single drug, increasing the dose according to response, and adding a second (and third) agent when high doses of the initial drug fail to achieve the goal BP.

For patients at high risk of clinical CV events (including patients with stage 3 hypertension; target organ damage or clinical CVD and/or diabetes; or patients at increased risk for a coronary event or stroke), it is often necessary to add a second or third agent shortly after initiation of single-agent therapy if control is not achieved. Only 50% of patients with hypertension treated with single-drug therapy achieve goal BP (140/90 mmHg). It has been demonstrated that antihypertensive agents in combination increase control rates to 75 to 85%. Therefore, JNC VI recommends combination therapy.

Hypertensive patients with underlying diabetes represent a special patient population in whom intensive antihypertensive therapy is beneficial, as demonstrated by the UK Prospective Diabetes Study. This 20-year study (more than 5,000 patients with type 2 diabetes) was designed to evaluate various treatments for controlling hyperglycemia. Early in the study it became apparent that high BP was a strong risk factor for the development of diabetes-related complications. As a result, evaluation of the effect of BP-lowering treatments was added to the protocol. The results showed that reduction in either blood glucose levels or BP reduced the risk of diabetes-related ophthalmic disease by 25%, serious deterioration of vision by 50%, and early kidney damage, stroke, and death from diabetes-related causes by 33%. The targets of blood glucose and BP control were often achieved only after combination therapy was instituted (up to five drugs in some cases), and the best results were observed in individuals in whom treatment of hyperglycemia and hypertension was intensified. Each incremental reduction in blood glucose level or arterial pressure was accompanied by a nearly linear diminution in the incidence of diabetic complications. The choice of pharmacologic agent appeared to be less important than the overall improvements in blood glucose and BP control.

Rationale for Combination Therapy

The rationale for combination therapy is to improve BP control without increasing the incidence of adverse events (AEs). Combination therapy addresses two major limitations incurred with monotherapy: a high incidence and severity of AEs at drug doses required to achieve adequate BP control and the inability to reduce BP to the target level.

The adverse effects of antihypertensive drugs are often dose related, as they are extensions of their pharmacologic properties. By using a combination of two or more drugs from different classes, the goal BP may be achieved at lower doses of each drug, thereby reducing the risk of dose-related AEs. Furthermore, the pharmacologic action of one drug of the combination may attenuate an AE of the other. Reduced frequency and severity of AEs may contribute to improved patient compliance, resulting in a greater number of patients at goal BP and subsequently reducing mortality and morbidity.

Only one half of monotherapy-treated patients achieve goal BP; it cannot be predicted who will respond to a given drug. Patients may not fully respond to a single agent for several reasons: (1) monotherapy addresses only one of several physiologic mechanisms that contribute to high BP; (2) monotherapy may induce compensatory changes in other blood pressure–elevating mechanisms (e.g., diuretic-induced activation of the renin-angiotensin system); (3) physicians fail to increase or modify the initially prescribed single-drug therapy despite ineffective BP control, possibly because of AEs; and (4) patient noncompliance.

Because individual antihypertensive agents at optimal doses lower BP by about 10 mmHg on average, patients with excessively high BP or concomitant exacerbating conditions are likely to require therapy with at least two agents. An ideal combination is one where two agents with different side effect profiles act synergistically to lower BP. Brown and Dickerson demonstrated the benefit of such a combination using enalapril (ACE inhibitor) and doxazosin (\( \alpha_1 \) blocker). This combination produced a decrease in BP that was not only greater than the decrease produced by each drug alone, but one that was significantly greater (\( p < 0.002 \)) than predicted by adding the monotherapy-induced decreases in BP (Fig. 1). This greater decrease in BP was achieved at minimum median doses (doxazosin, 1 mg/day; enalapril, 5 mg/day), in contrast to the much higher median doses from monotherapy (doxazosin, 4 mg/day; enalapril, 20 mg/day).

Alpha1 Blockers in Combination Therapy

\( \alpha_1 \) blockers inhibit \( \alpha_1 \) adrenoceptors in peripheral vasculature, thereby inducing peripheral vasodilation and decreasing total peripheral resistance and subsequently a reduc-
Doxazosin as Combination Therapy

Several studies have demonstrated significant reductions in standing and/or sitting BP with doxazosin in combination with beta blockers, diuretics, CCBs, ACE inhibitors, and ARBs in hypertension previously uncontrolled by monotherapy. Recent studies have demonstrated an additive antihypertensive effect of combination therapy with doxazosin and amiodipine (at reduced doses) that allowed 94% of patients with essential hypertension at baseline to reach a target sitting BP of $\leq 140/90$ mmHg, compared with 78% of patients treated with either drug alone at higher doses.

Doxazosin also provides lipid and glucose benefits when used as combination therapy, as demonstrated in an 8-month, randomized, crossover study in 31 patients with mild to moderate uncontrolled hypertension on losartan monotherapy. This study showed that while the addition of either doxazosin or a diuretic (hydrochlorothiazide) to ongoing losartan therapy produced similar decreases in BP, doxazosin/losartan therapy also produced statistically significant improvements in serum lipid profiles and glycemia. Furthermore, the cardiovascular risk in patients treated with doxazosin/losartan decreased significantly, compared with patients treated with losartan/hydrochlorothiazide.

The recently published results of a placebo-controlled double-blind study and a community-based multicenter open-label study highlight the efficacy of add-on doxazosin therapy in (1) patients with hypertension uncontrolled by other antihypertensive treatments, and (2) patients with concomitant symptomatic BPH and hypertension untreated or uncontrolled despite treatment with one or two antihypertensive agents.

Doxazosin as add-on therapy in uncontrolled primary hypertension: In the first study, 70 patients with uncontrolled hypertension (up to two antihypertensive agents) were randomized to receive double-blind treatment with either doxazosin or placebo. The majority of patients (73%) were receiving either a CCB or an ACE inhibitor as their primary antihypertensive agent, and 90% of all patients were receiving moderate to high doses. An additional 31% were receiving treatment with a second antihypertensive. The dose of study drug was titrated over 4 weeks until the target sitting DBP ($< 90$ mmHg) was achieved. Patients who achieved target DBP were maintained for 4 weeks on their baseline antihypertensive plus the optimum dose of study drug determined during the titration phase. The primary efficacy measure was the change from baseline in sitting and standing SBP and DBP at the end of the 4-week add-on maintenance phase. Changes in lipid profile and HR were also assessed.

The efficacy analysis included data from 56 patients (34 receiving doxazosin and 22 receiving placebo) who received add-on maintenance therapy. Clinically and statistically significant reductions in sitting and standing SBP and DBP were achieved in the doxazosin group during add-on therapy ($p < 0.001$) (Table I). At the end of the add-on maintenance phase, the mean sitting SBP/DBP had decreased from 156/100 mmHg at baseline to 136/88 mmHg following doxazosin add-on. Similarly, mean standing SBP/DBP had decreased from 154/101 mmHg at baseline to 133/88 mmHg in the add-on doxazosin treatment group at the end of this phase. The target reduction in sitting DBP was achieved during add-on therapy by significantly ($p < 0.05$) more patients receiving doxazosin (21 of 38; 55%) than placebo (10 of 32; 31%). The mean daily dose of doxazosin in patients reaching goal DBP was 7.8 mg/day (range 1–16 mg/day).

Treatment with doxazosin had a small but significant effect on serum lipid profiles (Table II). At the end of the add-on maintenance therapy phase, patients receiving doxazosin showed statistically significant mean reductions from baseline in total cholesterol (−18.0 mg/dl; $p = 0.013$) and LDL cholesterol (−12.8 mg/dl; $p = 0.003$). The reduction in HDL cholesterol seen with doxazosin was significantly greater than that with placebo ($p < 0.05$). There was no change from baseline in HDL cholesterol in either the doxazosin or placebo group.

![Figure 1: Mean changes in systolic and diastolic blood pressure (BP) in patients receiving doxazosin (median dose 4 mg/day), enalapril (median dose 20 mg/day), or combination therapy (doxazosin 1 mg/day; enalapril 5 mg/day). Results are recorded for supine and erect BP measurements. Significance of changes from baseline: *$p<0.02$. DBP = diastolic blood pressure, SBP = systolic blood pressure, S = supine, E = erect.](image-url)
The AE profile of doxazosin was similar to that observed for placebo. The only statistically significant differences between doxazosin and placebo were a higher incidence of fatigue for doxazosin (24 vs. 3% with placebo; p = 0.017) and a higher incidence of headache for placebo (44 vs. 11% with doxazosin; p = 0.002). This study demonstrated that doxazosin was safe and effective as add-on therapy in patients whose hypertension is inadequately controlled by other antihypertensive medications.

Doxazosin add-on therapy in concomitant hypertension and symptomatic benign prostatic hyperplasia: Because concomitant hypertension and BPH is prevalent among older men, $\alpha_1$-blocker therapy is a rational choice based on its efficacy against both conditions. The Hypertension and BPH Intervention Trial (HABIT), a multicenter study conducted in community practices, investigated the efficacy and safety of doxazosin in concomitant BPH and hypertension. Because it was conducted in community practices, the results are particularly relevant to everyday clinical practice.

In this study, doxazosin was added to current antihypertensive therapy (if treated) in 500 outpatients with symptomatic BPH (mean baseline American Urological Association [AUA] symptom score, 18.2) and mild to moderate essential hypertension. Elderly men ($\geq$ 65 years) comprised 48% of the enrolled patients. At baseline, the patients were allocated to one of four observation groups according to BP control (DBP < 90 mmHg) and whether they received antihypertensive medication before study entry. The four groups were: treated/well controlled, treated/poorly controlled, untreated/hypertensive, and untreated/normotensive. The latter group had a history of hypertension but was normotensive at baseline. During dose titration ($\leq$ 5 weeks), optimal doxazosin doses for maintaining

### Table I  Blood pressure measurements after 4 weeks of add-on maintenance therapy$^{a,32}$

<table>
<thead>
<tr>
<th></th>
<th>Doxazosin (n=34)</th>
<th>Placebo (n=22)</th>
<th>Doxazosin vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline, mmHg</td>
<td>End of treatment (adjusted mean change), mmHg</td>
<td>p Value vs. baseline $^b$</td>
</tr>
<tr>
<td>Sitting SBP</td>
<td>155.7 (150.9)</td>
<td>136.1 (129.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sitting DBP</td>
<td>100.2 (95.5)</td>
<td>87.7 (81.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Standing SBP</td>
<td>154.4 (149.5)</td>
<td>134.3 (128.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Standing DBP</td>
<td>100.9 (96.1)</td>
<td>87.8 (81.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

$^a$Data for BP presented as mean values.
$^b$p value for mean change from baseline from analysis of variance test.
$^c$p value for difference in adjusted mean from analysis of variance test.

**Abbreviations:** DBP = diastolic blood pressure, SBP = systolic blood pressure, NS = not significant.

### Table II  Lipid profile after 4 weeks of add-on maintenance therapy$^{a,32}$

<table>
<thead>
<tr>
<th></th>
<th>Doxazosin</th>
<th>Placebo</th>
<th>Doxazosin vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Baseline</td>
<td>Adjusted mean change</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>26</td>
<td>221.8</td>
<td>−18.0</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>23</td>
<td>131.2</td>
<td>−12.8</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>26</td>
<td>49.3</td>
<td>−0.6</td>
</tr>
<tr>
<td>Cholesterol/HDL cholesterol ratio</td>
<td>26</td>
<td>4.4</td>
<td>−0.3</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>27</td>
<td>173.8</td>
<td>−9.7</td>
</tr>
</tbody>
</table>

$^a$Data are presented as mean values.
$^b$p value for mean change from baseline from analysis of variance test.
$^c$p value for difference in adjusted mean from analysis of variance tests.

**Abbreviations:** HDL = high-density lipoprotein, LDL = low-density lipoprotein, n = number of patients, NS = not significant.
a target SBP within 100–140 mmHg and DBP within 70–90 mmHg and alleviating BPH symptoms were established. During the maintenance phase, patients were maintained on optimal doxazosin doses (up to 16 mg/day) for 8 weeks. Patients completed questionnaires to assess BPH symptoms at baseline and again after 4 and 8 weeks of maintenance. The primary efficacy outcome was the change in BPH symptom score; secondary efficacy outcomes included changes in BP.

**Effect on benign prostatic hyperplasia symptoms:** Mean AUA symptom scores were significantly reduced from baseline in all patient groups, by 56% in patients with moderate BPH symptoms, and by 65% in patients with severe BPH symptoms (p < 0.001 vs. baseline). Doxazosin also significantly improved the AUA bothersomeness scores (p < 0.001), with mean decreases from baseline of 62 to 69% at the end of the 8-week treatment period. After treatment with doxazosin, BPH-specific health status index mean scores significantly improved by 55 to 62% (p < 0.001), and BPH interference with activities index scores significantly improved by 34 to 36% (p < 0.001), compared with mean baseline scores. Doxazosin significantly improved BPH symptoms (p < 0.001) in both older (≥ 65 years) patients (by 54–65% from mean baseline scores) and in younger (45–64 years) patients (by 64–66% from mean baseline scores).

**Effect on blood pressure:** Eight weeks of doxazosin resulted in statistically significant mean reductions from baseline in DBP and SBP in all groups (p < 0.001; Table III). Mean changes from baseline in standing and sitting DBPs and SBPs after treatment with doxazosin were similar in all four groups. Mean changes from baseline in standing BP (Fig. 2) and sitting BP were generally similar between older and younger patients.

At the end of 8 weeks of maintenance treatment, mean daily doses of doxazosin were 7.2 mg (treated/well controlled), 9.2 mg (treated/poorly controlled), 8.0 mg (untreated/hypertensive), and 7.6 mg (untreated/normotensive). The magnitude of BP lowering by doxazosin differed markedly according to hypertensive status at baseline. In the treated/well controlled and untreated/normotensive patients

![Table III](https://example.com/table3.png)

<table>
<thead>
<tr>
<th>Mean BP, mmHg</th>
<th>Patient groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated/well controlled</td>
</tr>
<tr>
<td>Sitting DBP</td>
<td></td>
</tr>
<tr>
<td>Baseline ± SD (n)</td>
<td>81±6 (122)</td>
</tr>
<tr>
<td>Treatment ± SD (change) a, b</td>
<td>78±10 (−3)</td>
</tr>
<tr>
<td>Sitting SBP</td>
<td></td>
</tr>
<tr>
<td>Baseline ± SD (n)</td>
<td>137±14 (122)</td>
</tr>
<tr>
<td>Treatment ± SD (change) a, b</td>
<td>132±16 (−6)</td>
</tr>
<tr>
<td>Standing DBP</td>
<td></td>
</tr>
<tr>
<td>Baseline ± SD (n)</td>
<td>82±7 (121)</td>
</tr>
<tr>
<td>Treatment ± SD (change) a, b</td>
<td>78±9 (−4)</td>
</tr>
<tr>
<td>Standing SBP</td>
<td></td>
</tr>
<tr>
<td>Baseline ± SD (n)</td>
<td>136±15 (121)</td>
</tr>
<tr>
<td>Treatment ± SD (change) a, b</td>
<td>130±17 (−6)</td>
</tr>
</tbody>
</table>

a Values are mean change from baseline.
b All changes from baseline were statistically significant (p<0.001).

**Abbreviation:** SD = standard deviation. Other abbreviations as in Tables I and II.
chlorthalidone in preventing heart failure symptoms.37 As compared with chlorthalidone confirm the potency of symptomatic heart failure in the other study arms of ALLHAT. Finding is not surprising. Significantly higher relative rates of chlorthalidone is a diuretic as well as an antihypertensive, this rate of symptomatic heart failure (p <0.001). Because zosin arm was principally driven by a two-fold increase in the 0.56). The higher incidence of combined CVD in the doxazosin arm (p <0.001). Although doxazosin was not superior to chlorthalidone in the primary endpoint, neither was it inferior to chlorthalidone in preventing heart failure symptoms. The ALLHAT study did demonstrate that multiple drugs are often required to achieve goal blood pressure. Because doxazosin is not commonly used as first-line antihypertensive therapy and is not indicated in the treatment of heart failure, ALLHAT results neither directly apply to nor conflict with the safety and efficacy of doxazosin in combination antihypertensive therapy.

Conclusions

Treating high BP reduces the risk of cardiovascular mortality and morbidity, including strokes, coronary events, and renal disease. Although some patients respond to monotherapy, many require the addition of a second or third agent to achieve the recommended goal blood pressure of <140/90 mmHg. In addition to enhancing reduction of BP, combination therapy using drugs from different classes at reduced doses is likely to improve tolerability and, with thoughtful selection of agent, also ameliorate coexisting diseases.1

The α₁-blocker doxazosin, as a component of combination therapy, has been shown to enhance BP control safely and, in addition, provide positive changes in associated cardiovascular risk factors, such as serum lipid abnormalities and insulin resistance, as well as provide relief of urinary symptoms in concomitant symptomatic BPH. In many patients with hypertension uncontrolled by other antihypertensive medications, the addition of doxazosin to existing regimens can safely lower BP to recommended target levels.

References

1. The sixth report of the Joint National Committee (JNC-VI) on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997;157:2413–2446
13. Brown MJ, Dickerson JE: Synergism between alpha 1-blockade and angio-
tensin converting enzyme inhibition in essential hypertension. J Hypertens
1991;7(suppl):S362–S363
87:25–115
15. Fulton B, Wagstaff A, Sorkin E: Doxazosin:- An update of its clinical phar-
cmacology and therapeutic applications in hypertension and benign prostatic
16. Grimm RJ Jr, Flack JM, Grandits GA, Elmer PJ, Neaton JD, Cutler JA,
Lewis C, McDonald R, Schoenberger J, Stamler J, for the Treatment of Mild
Hypertension Study (TOMHS) Research Group: Long-term effects on pla-
tma lipids of diet and drugs to treat hypertension. J Am Med Assoc 1996;
275:1549–1556
17. Fawzy A, Braun K, Lewis GP, Gaffney M, Ice K, Dias N: Doxazosin in the
treatment of benign prostatic hyperplasia in normotensive patients: A multi-
18. Gillenwater JY, Conn RL, Chrysant SG, Roy J, Gaffney M, Ice K, Dias N,
for the Multicenter Study Group: Doxazosin for the treatment of benign pro-
static hyperplasia in patients with mild to moderate essential hypertension:
A double-blind, placebo-controlled, dose-response multicenter study. J Urol
1995;154:110–115
19. Donnelly R, Elliott HL, Meredith PA, Howie CA, Reid JL: Combination of
nifedipine and doxazosin in essential hypertension. J Cardiovasc Phar-
cmacol 1992;19:479–486
20. Lindner UK, von Manteuffel GE, Stafusky M: The addition of doxazosin
to the treatment regimen of hypertensive patients not responsive to nifedip-
(suppl)6:3562–3636
22. Engler RG, Barlage U: The addition of doxazosin to the treatment regimen
of patients with hypertension not adequately controlled by beta-blockers.
Am Heart J 1991;121:311–316
23. Searle M, Dathan R, Dean S, Christensen CC, Westheim A: Doxazosin in
combination with atenolol in essential hypertension: A double-blind place-
JF: Comparative and combined efficacy of doxazosin and enalapril in hy-
25. Englert RG, Mauersberger H: A single-blind study of doxazosin in the treat-
ment of essential hypertension when added to nonresponders to angiotensin-
Tonolo G, Pupita G, Gliorioso N, Gitti M, Rappelli A: Efficacy and tolerabil-
ity of doxazosin alone or in combination with chlorthalidone in essential hy-
27. Marti-Canales JC, Ceballos R, Puerta-Jimenez LM, Gil-Extremena B, Sanz-
Burgos V: Comparative study of doxazosin and hydrochlorothiazide when
added to nonresponders to ARBII losartan therapy. Am J Hypertens 2001;
14(4[suppl]):A177
28. Naibangtij S, Naibangtij I, Onder R: Clinically additive effect between dox-
azosin and amiodipine in the treatment of essential hypertension. Am J Hy-
pertens 2000;13:921–926
29. Hunter Hypertension Research Group: Combined effect of doxazosin and
pindolol on blood pressure control and lipid concentrations in patients with
essential hypertension selected from general practice. J Hum Hypertens
1992;6:181–184
30. Brown M, Dickerson J: Alpha-blockade and calcium antagonism: An effect-
tive and well-tolerated combination for the treatment of resistant hyperten-
pha-adrenergic blocker, and ACE inhibitor and hydrochlorothiazide on
blood pressure and on renal function in type 2 diabetic patients with hyper-
tension and albuminuria. A randomized cross-over study. Nephron 1998;
80:175–182
32. Black HR, Sollins JS, Garofalo JL: The addition of doxazosin to the thera-
petic regimen of hypertensive patients inadequately controlled with other
antihypertensive medications: A randomized, placebo-controlled study. Am
33. Guthrie RM, Siegel RL: A multicenter, community-based study of doxa-
zosin in the treatment of concomitant hypertension and symptomatic benign
prostatic hyperplasia: The Hypertension and BPH Intervention Trial
34. Boyle P, Napalkov P: The epidemiology of benign prostatic hyperplasia and
observations on concomitant hypertension. Scand J Urol Nephrol 1995;
(suppl)168:7–12
35. Guthrie R: Terazosin in the treatment of hypertension and symptomatic
benign prostatic hyperplasia: A primary care trial. J Fam Pract 1994;39:
129–133
36. ALLHAT Collaborative Research Group: Major cardiovascular events in
hypertensive patients randomized to doxazosin vs. chlorthalidone: The anti-
hypertensive and lipid-lowering treatment to prevent heart attack trial
(ALL-
37. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart
Attack Trial (ALLHAT) Collaborative Research Group: Major outcomes in
moderately hypercholesterolemic, hypertensive patients randomized to prav-
avastatin vs. usual care: The Antihypertensive and Lipid-Lowering Treat-
ment to Prevent Heart Attack Trial (ALLHAT-LLT). J Am Med Assoc
2002;288(23):2998–3007