

Q: Should alpha-blockers ever be used as antihypertensive drugs?

GIACOMO ROSSITTO, MD

Department of Clinical and Experimental Medicine, University of Padua School of Medicine, Padua, Italy

GANESH KAMATH, MD

Department of Medicine, St. Luke's-Roosevelt Hospital Center, New York, NY

FRANZ H. MESSERLI, MD

Director, Hypertension Program, Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons; Division of Cardiology, St. Luke's-Roosevelt Hospital Center, New York, NY

A: Alpha-blockers should not be used as first-line therapy for hypertension. However, an alpha-blocker can be considered as a second-line or third-line add-on in a patient whose blood pressure is not under control despite treatment with other drugs.

In addition, alpha-blockers are useful in relieving lower urinary tract symptoms in patients with benign prostatic hypertrophy. However, even in a patient who has both hypertension and benign prostatic hypertrophy, we advise physicians to use alpha-blockers primarily to relieve the urinary symptoms, and we recommend lowering the blood pressure with a drug of a class shown to reduce rates of illness and death.

■ NOT FIRST-LINE THERAPY

All antihypertensive drugs, including alpha-blockers, lower blood pressure. Alpha-blockers have been approved by the US Food and Drug Administration for treating high blood pressure, and they are just as effective as other antihypertensive drugs—if efficacy is defined as a decrease in millimeters of mercury.

doi:10.3949/ccjm.77a.10058

However, lowering the blood pressure is not the main goal of antihypertensive therapy. What we want to achieve when prescribing antihypertensive drugs is to reduce the rates of heart attacks, strokes, and other adverse cardiovascular adverse outcomes, including death.

Unfortunately, alpha-blockers fall short in this regard. In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) trial,^{1,2} doxazosin (Cardura) was found to carry a higher risk of combined cardiovascular disease (relative risk 1.19, $P = .04$), mostly stroke. Alarming, the incidence of symptomatic heart failure in patients on doxazosin was twice that in patients on chlorthalidone (relative risk 2.04, $P < .001$). Doxazosin was minimally more effective in lowering blood pressure than chlorthalidone, but the small difference in blood pressure was unlikely to have accounted for the significant difference in the risk of heart failure.³

This experience with doxazosin illustrates a key drawback to surrogate end points: a treatment may produce a favorable outcome in the surrogate end point (blood pressure) but produce little or no benefit in terms of the real end point (stroke, myocardial infarction, and heart failure).⁴

Based on the ALLHAT data as well as on a Veterans Administration study in patients with chronic heart failure in which survival with prazosin (Minipress) was no better than with placebo,⁵ it seems reasonable to no longer use alpha-blockers as initial therapy for hypertension. This view is reflected by current European⁶ and American⁷ guidelines.

Lowering blood pressure is not the main goal of antihypertensive therapy

■ ALPHA-BLOCKERS AS PART OF COMBINATION THERAPY

In several clinical trials, alpha-blockers were allowed⁸ or were specified^{9,10} as add-on therapy if other drugs failed to control the blood pressure, but they were not used in a randomized fashion. Thus, we cannot judge their effect on cardiovascular outcomes such as heart attack and stroke.

The choice of drugs for combination therapy very often is still empirical and based on personal preference. Doxazosin as add-on therapy, in general, has been shown to be safe and well tolerated.¹¹ But even if it is acceptable, it is not a preferred combination.

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),⁹ patients received extended-release doxazosin as a third drug if they did not reach their goal blood pressure with either the combination of amlodipine (Norvasc) plus perindopril (Aceon) or atenolol (Tenormin) plus bendroflumethiazide. Extended-release doxazosin was an effective add-on, and there was no apparent excess rate of heart failure in doxazosin users.

In other studies, in patients with uncontrolled hypertension, adding doxazosin as a second- or third-line agent to a gold-standard drug—calcium channel blocker, diuretic, beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or combinations of these—allowed significantly more participants to achieve their blood pressure goal.¹¹

Personally, we consider doxazosin in patients whose blood pressure is not controlled with triple therapy with a renin-angiotensin system blocker, a diuretic, and a calcium channel antagonist in full doses. In patients with stage 3 or stage 4 kidney disease who can no longer tolerate renin-angiotensin system blockers, doxazosin may also be a useful adjunct. Whether the metabolic effects of alpha-blockers, such as a reduction in insulin resistance and a decrease in total and low-density lipoprotein cholesterol, will result in lower rates of morbidity and death has not been conclusively determined.

A point of view somewhat more favorable to the use of alpha-blockers has recently been put forward by Chapman et al.¹²

■ ALPHA-BLOCKERS ALLEVIATE SYMPTOMS OF BENIGN PROSTATIC HYPERTROPHY

Doxazosin and other alpha-blockers are commonly used to alleviate lower urinary tract symptoms in patients with benign prostatic hypertrophy.

Both high blood pressure and benign prostatic hypertrophy become more common with advancing age, and it has been estimated that both are present in more than 25% of men over age 60.¹³ Indeed, two trials documented that a significant reduction in symptoms of benign prostatic hypertrophy and in systolic and diastolic blood pressure can be achieved with an alpha-blocker.^{13,14}

This raises the question whether such a “twofer” (treating two disease states with one drug) should be used in clinical practice. We have to consider that the principle of the twofer has never been tested and agree with Davis et al,³ who, in a further analysis of the ALLHAT data, stated that, “In older men with benign prostatic hypertrophy in whom an [alpha]-adrenergic blocker seems like the best treatment for the uropathy, coexisting hypertension should be treated with another antihypertensive drug as well.”¹³

Again, this would clearly relegate doxazosin to second-line or third-line status, even in patients with benign prostatic hypertrophy, in whom it has been shown to be indicated.

■ ADVERSE EFFECTS OF ALPHA-BLOCKERS

Dizziness, fatigue, and somnolence are occasionally reported but appear to be well tolerated. Postural hypotension is much less common with proper titration of standard doxazosin or with the use of controlled-release formulations.⁹⁻¹⁵ However, in patients with impaired autonomic function, even long-acting alpha-blockers can cause postural hypotension and syncope.

Patients using phosphodiesterase type 5 inhibitors—sildenafil (Viagra), vardenafil (Levitra), or tadalafil (Cialis)—for erectile dysfunction should avoid alpha-blockers because the blood-pressure-lowering effects of the two drug classes may be additive. ■

Even in men with benign prostatic hypertrophy, alpha-blockers are second-line or third-line antihypertensive drugs

REFERENCES

1. Messerli FH. Implications of discontinuation of doxazosin arm of ALLHAT. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (commentary). *Lancet* 2000; 355:863–864.
2. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA* 2000; 283:1967–1975.
3. Davis BR, Cutler JA, Furberg CD, et al; ALLHAT Collaborative Research Group. Relationship of antihypertensive treatment regimens and change in blood pressure to risk for heart failure in hypertensive patients randomly assigned to doxazosin or chlorthalidone: further analyses from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial. *Ann Intern Med* 2002; 137:313–320.
4. Messerli FH. Doxazosin and congestive heart failure (viewpoint). *J Am Coll Cardiol* 2001; 38:1295–1296.
5. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; 314:1547–1552.
6. Mancia G, De Backer G, Dominiczak A, et al; ESH-ESC Task Force on the Management of Arterial Hypertension. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* 2007; 25:1751–1762.
7. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003; 289:2560–2572.
8. Jamerson K, Weber MA, Bakris GL, et al, for the ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; 359:2417–2428.
9. Chapman N, Chang CL, Dahlöf B, Sever PS, Wedel H, Poulter NR; ASCOT Investigators. Effect of doxazosin gastrointestinal therapeutic system as third-line antihypertensive therapy on blood pressure and lipids in the Anglo-Scandinavian Cardiac Outcomes Trial. *Circulation* 2008; 118:42–48.
10. de Alvaro F, Hernandez-Presa MA; ASOCIA Study. Effect of doxazosin gastrointestinal therapeutic system on patients with uncontrolled hypertension: the ASOCIA Study. *J Cardiovasc Pharmacol* 2006; 47:271–276.
11. Black HR. Doxazosin as combination therapy for patients with stage 1 and stage 2 hypertension. *J Cardiovasc Pharmacol* 2003; 41:866–869.
12. Chapman N, Chen C-Y, Fujita T, et al. Time to re-appraise the role of alpha-1 adrenoceptor antagonists in the management of hypertension? *J Hypertens* 2010; 28:1796–1803.
13. Steers WD, Kirby RS. Clinical ease of using doxazosin in BPH patients with and without hypertension. *Prostate Cancer Prostatic Dis* 2005; 8:152–157.
14. Guthrie RM, Siegel RL. A multicenter, community-based study of doxazosin in the treatment of concomitant hypertension and symptomatic benign prostatic hyperplasia: the Hypertension and BPH Intervention Trial (HABIT). *Clin Ther* 1999; 21:1732–1748.
15. MacDonald R, Wilt TJ, Howe RW. Doxazosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. *BJU Int* 2004; 94:1263–1270.

ADDRESS: Franz H. Messerli, MD, Hypertension Program, Division of Cardiology, St. Luke's-Roosevelt Hospital Center, 1000 Tenth Avenue, New York, NY 10019; e-mail Fmessengerli@chpnet.org.