Received: 15 May 2022 | Revised: 23 July 2022 | Accepted: 26 July 2022

DOI: 10.1111/jch.14556

REVIEW

WILEY

Role of α1-blockers in the current management of hypertension

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Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 91639203, 81770455, 82070432, 82070435; Shanghai Commission of Science and Technology, Grant/Award Number: 19DZ2340200

Abstract

There is emerging evidence that α1-blockers can be safely used in the treatment of hypertension. These drugs can be used in almost all hypertensive patients for blood pressure control. However, there are several special indications. Benign prostatic hyperplasia is a compelling indication of α1-blockers, because of the dual treatment effect on both high blood pressure and lower urinary tract symptoms. Many patients with resistant hypertension would require α1-blockers as add-on therapy. Primary aldosteronism screen is a rapidly increasing clinical demand in the management of hypertension, where α1-blockers are useful for blood pressure control in the preparation for the measurement of plasma aldosterone and renin. Nonetheless, α1-blockers have to be used under several considerations. Among the currently available agents,

only long-acting α1-blockers, such as doxazosin gastrointestinal therapeutic system 4–8 mg daily and terazosin 2–4 mg daily, should be chosen. Orthostatic hypotension is a concern with the use of α1-blockers especially in the elderly, and requires careful initial bedtime dosing and avoiding overdosing. Fluid retention is potentially also a concern, which may be overcome by combining an α1-blocker with a diuretic.

KEYWORDS
benign prostatic hyperplasia, hypertension, primary aldosteronism screen, resistant hypertension, α1-blocker

1 | INTRODUCTION

Soon after approval for clinical use in the 1970s and 1980s, α1 adrenergic receptor blockers (α1-blockers) became a mainstay of antihypertensive drug treatment.[1–3] Until the end of the 20th century, α1-blockers remained a possible choice for the initiation of antihypertensive therapy in hypertension guidelines.[4,5]

α1-Blockers have several therapeutic advantages in the treatment of hypertension. First, α1-blockers combat adrenergic predominance of the sympathetic nervous system, which plays a pathogenic role in hypertension. Second, α1-blockers are metabolically beneficial, as they show some blood glucose and lipid lowering effects via improving insulin resistance and glucose tolerance. That is why an α1-blocker, doxazosin 2–8 mg daily, together with an angiotensin-converting enzyme inhibitor and a calcium-channel blocker, was put into testing for superiority over a thiazide diuretic in the treatment of hypertension and cardiovascular prevention in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in the 1990s.[6]

ALLHAT involved several comparative groups in a single trial, which substantially limited the choice of add-on antihypertensive therapy for blood pressure control. Patients could only be given either atenolol, reserpine or clonidine as the possible second-line agent and hydralazine as the possible third-line agent.[6] These drugs are not appropriate to be combined with doxazosin, as evidenced by the 2–3 mm Hg higher systolic blood pressure in the doxazosin than chlorthalidone group during the follow-up period of the trial.[7] The ALLHAT trial showed a 104% higher incidence of heart failure in the doxazosin than chlorthalidone group.[7] The observation was astonishing and eventually changed the use of α1-blockers in the management of hypertension.[8] None of the current hypertension guidelines recommend the first-line or general use of α1-blockers in the treatment of hypertension.[9–11]

Current hypertension guidelines continued recommending the use of α1-blockers, because these drugs are also effective in the treatment of symptomatic benign prostatic hyperplasia in addition to their blood pressure lowering effect (Table 1).[9–11] The Prevention And Treatment of Hypertension With Algorithm based Therapy 2 (PATHWAY-2) trial demonstrated that the α1-blocker doxazosin 4–8 mg daily was as efficacious as the β-blocker bisoprolol 5–10 mg daily, though less efficacious than the mineralocorticoid receptor antagonist spironolactone 25–50 mg daily, in the treatment of resistant hypertension.[12] Another therapeutic advantage is that α1-blockers do not have much influence on the renin-angiotensin aldosterone system, and therefore can be used for blood pressure control while screening for primary aldosteronism.[13] Primary aldosteronism is increasingly screened for effective surgical or medical treatment.

In spite of the clinical usefulness, α1-blockers have not been properly and sufficiently used in the management of hypertension, because of the safety concerns on heart failure[7] and other possible side effects such as orthostatic hypotension.[9–11] However, there is emerging evidence that α1-blockers can be safely used with long-acting agents,[14–16] especially in the era with several classes of new agents with both blood pressure lowering and heart failure treatment effects, such as angiotensin-receptor and neprilysin inhibitors and sodium-glucose cotransporter 2 inhibitors.[17] Indeed, a post-hoc analysis of the Anglo-Scandinavian Outcome Trial (ASCOT) proved that the α1-blocker doxazosin gastrointestinal therapeutic system (GITS, 4–8 mg daily) was as an add-on antihypertensive therapy efficacious in blood pressure lowering and did not increase the risk of incident heart failure.[14] A recent large cohort study showed that in treated patients with heart failure the use of α1-blockers was associated with a lower rate of heart failure admission and death.[15] Another large cohort study showed that in patients with chronic kidney disease the use of α1-blockers was associated with a lower rate of cardiac events and death, albeit with a higher risk of kidney disease progression.[16] The present review paper intends to revisit and review the clinical use of α1-blockers in hypertension with concomitant benign prostatic hyperplasia, in resistant hypertension, and in blood pressure control during primary aldosteronism screen, while taking into account the recently emerged evidence on their safety profile.

2 | PATIENTS WITH HYPERTENSION AND CONCOMITANT BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia is a major cause of lower urinary tract symptoms, such as urinary frequency, urgency, and nocturia. According to the 2011 China Health and Retirement Longitudinal Study (CHARLS) in 5888 men aged 50 years or older, the prevalence of

TABLE 1 Role of α1-blockers in the current management of hypertension

Indication	Epidemiology	Mechanism of action	Treatment effect
Benign prostatic hypertrophy	Up to 25% of hypertensive patients older than 60 years of age	Inhibition of prostatic smooth muscle tone and relaxation of the prostate	Blood pressure lowering and alleviation of lower urinary tract symptoms
Resistant hypertension	13.7% treated hypertension[34]	Add-on therapy	Blood pressure lowering and control
Primary aldosteronism screen	6%–8% in primary care[39,40]; 15% in resistant hypertension[41]	No or little effect on plasma aldosterone-to-renin ratio	Blood pressure control

self-reported lower urinary tract symptoms suggestive of benign prostatic hyperplasia was 10.7%. The prevalence increased with age, to 14.7% in men aged 70 years or older.[18] The prevalence for the self-reported recognized cases in the United States was 16.5% in 4492 men (≥40 years of age) enrolled in the 2001–2008 National Health and Nutrition Examination Surveys (NHANES), much higher than in the China study. In addition, there was an additional 9.6% prevalence of the so-called unrecognized cases.[19] Although benign prostatic hyperplasia and hypertension do not necessarily share common pathophysiological mechanisms, these two disorders often occur concomitantly, because of the high prevalence of both diseases in the elderly. The prevalence of hypertension in those older than 60 years of age is as high as 40%–50%.[20,21] The estimation therefore is that benign prostatic hyperplasia and hypertension may be jointly present in 15%–25% of male hypertensive patients over 60 years of age.

The mechanism of action for the therapeutic effect of α1-blockers on lower urinary tract symptoms is well understood. α1-Blockers reduce the tone of the prostate smooth muscle, and brings about relaxation of the prostate. There is evidence that α1-blockers relieve both obstructive and irritative symptoms in patients with benign prostatic hyperplasia.[22] After further subtyping of α1-adrenergic receptors into α1A, α1B, and α1D, uroselective α1 adrenergic receptor (α1A or α1A/1D) antagonists, such as tamsulosin and silodosin, had been developed for the treatment of benign prostatic hyperplasia.[23] These drugs have less blood pressure lowering effect, and hence cannot be used for the treatment of hypertension. However, both selective and non-selective α1A subtype blockers are recommended for the symptomatic relief of benign prostatic hypertrophy.[24–26]

The efficacy and safety of α1-blockers have been well-established for the treatment of hypertension and benign prostatic hyperplasia, especially with the use of long-acting agents, such as doxazosin GITS[27] or terazosin. In an early study in 232 patients with benign prostatic hyperplasia, doxazosin 1–4 mg daily, compared with placebo, significantly reduced blood pressure in patients with hypertension from 162/99 mm Hg at baseline to 143/89 mm Hg after 12-week treatment, but not as much in normotensive participants (from 139/82 to 134/78 mm Hg).[28] In a multicenter longer-term study of up to 4 years follow-up in patients with benign prostatic hyperplasia, systolic/diastolic blood pressure reductions with doxazosin 1–4 mg daily were 8/11 mm Hg in 178 hypertensive patients and only 4/2 mm Hg in 272 normotensive participants.[29] In this long-term study, doxazosin 1–4 mg daily treatment significantly increased from baseline the maximum and average urinary flow rates by 1.9 and 1.0 ml/s, respectively.[29] There is apparently no safety concern on incident hypotension in either normotensive patients or treated hypertensive patients with a blood pressure in the normal range, when they are treated with an α1-blocker for benign prostatic hyperplasia.[30]

3 | TREATMENT OF RESISTANT HYPERTENSION

Resistant hypertension is defined as uncontrolled blood pressure with the concurrent use of at least three antihypertensive agents of different classes (including a diuretic) or as controlled blood pressure with four or more antihypertensive drugs.[31] The definition of resistant hypertension is primarily based on the number of antihypertensive drugs. Many patients with uncontrolled blood pressure take only one or two antihypertensive drugs and have never taken three antihypertensive drugs or more. The prevalence of resistant hypertension is therefore difficult to precisely determine on the population level. Nonetheless, because of the low control rate of hypertension in almost all populations, resistant hypertension must be very common. According to an analysis of the NHANES 2003–2008, the prevalence of resistant hypertension was 12.8% in treated hypertensive patients.[32] A study in primary care clinics in Asia showed that the prevalence of resistant hypertension was 8.8% in treated hypertensive patients (n = 1217).[33] An estimation in a recent meta-analysis of 24 studies (n = 961,035) was that about 13.7% of treated hypertensive patients might fulfill the diagnostic criteria of resistant hypertension, which would equate to more than 100 million people globally.[34]

Current hypertension guidelines recommend the combination of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, calcium-channel blocker, and thiazide diuretic, when three drugs are required for blood pressure control.[9–11] The fourth drug can therefore be considered for the treatment of resistant hypertension. Although some guidelines do recommend the preferential use of mineralocorticoid receptor antagonists, α1-blockers are also among several other classes of antihypertensive drugs. In fact, because α1-blockers have a better safety profile and tolerability, these drugs have been often used in the treatment of resistant hypertension.

PATHWAY-2 specifically investigated the blood pressure lowering efficacy of several guideline-recommended antihypertensive drugs including an α1-blocker doxazosin GITS for the treatment of resistant hypertension.[12] In this double-blind, placebo-controlled, crossover trial, 335 patients with resistant hypertension were randomly assigned to receive spironolactone (25–50 mg), bisoprolol (5–10 mg), doxazosin GITS (4–8 mg), and placebo. The average reduction in home systolic blood pressure by doxazosin was -4.0 mm Hg (95% confidence

interval -5.0 to -3.0 mm Hg; $P < .0001$); it was similar to that by bisoprolol (-4.5 mm Hg, 95% confidence interval -5.5 to -3.5 mm Hg) but smaller than that by spironolactone (-8.7 mm Hg, 95% confidence interval -9.7 to -7.7 mm Hg).[12]

4 | BLOOD PRESSURE CONTROL IN PRIMARY ALDOSTERONISM SCREEN

Primary aldosteronism is characterized by aldosterone hypersecretion independent of plasma renin. With the use of plasma aldosterone-to-renin ratio for primary aldosteronism screen, the prevalence of primary aldosteronism is high, being 6%–8% in patients with hypertension in primary care[35,36] and up to 15% in patients with resistant hypertension[37] or patients with both hypertension and diabetes mellitus.[38] Patients with primary aldosteronism have more severe target organ damage[39–43] and higher risks of stroke, atrial fibrillation, acute myocardial infarction and heart failure than patients with primary hypertension matched for blood pressure.[44] The current endocrine[13] and hypertension[9–11] guidelines strongly advocate screening for primary aldosteronism in various groups of hypertensive patients, such as those with moderate or severe hypertension, treatment-resistant hypertension, spontaneous or diuretic-induced hypokalemia, adrenal incidentaloma, atrial fibrillation, obstructive sleep apnea syndrome, or a family history of early (< 40 years of age) onset hypertension or cerebrovascular accident, and the first-degree relatives of patients with primary aldosteronism.[13,45]

Primary aldosteronism screen requires accurate measurement of plasma renin and aldosterone for the calculation of the aldosterone-to-renin ratio. In treated hypertension, almost all antihypertensive drug classes interfere with the renin angiotensin-aldosterone system and therefore with the accurate measurement of plasma renin and aldosterone.[46,47] However, for safety reasons, many hypertensive patients cannot discontinue their antihypertensive drug treatment. Current guidelines recommend several classes of antihypertensive drugs that have the least influence on the renin-angiotensin aldosterone system, such as non-dihydropyridine calcium-channel blockers, α1-blockers, and direct vasodilators, as possible alternative choices of antihypertensive therapy after withdrawal of drugs that may interfere with the renin-angiotensin aldosterone system, while screening for primary aldosteronism.[13]

α1-Blockers are among the very few classes of antihypertensive drugs that have no or little influence on the renin-angiotensin aldosterone system.[48] In a randomized controlled parallel-group comparison trial in 230 patients with suspected primary aldosteronism, Mulatero and colleagues compared 2 months monotherapy with five classes of antihypertensive drugs (in alphabetical order, amlodipine 10 mg, atenolol 100 mg, doxazosin 8 mg, fosinopril 20 mg, and irbesartan 300 mg) in their effect on the plasma aldosterone-to-renin ratio and the diagnostic accuracy after a 3–4 weeks washout period. The relative change in percentage from baseline in plasma aldosterone-to-renin ratio in ascending order was -43%, -30%, -17%, -5%, and 62% in the irbesartan, fosinopril, amlodipine, doxazosin and atenolol groups, respectively. Doxazosin had the least effect on plasma aldosterone-to-renin ratio. Only in the doxazosin and fosinopril groups, none of the patients displayed a false-negative or false-positive plasma aldosterone-to-renin ratio.[49]

5 | HEART FAILURE AND OTHER SAFETY CONCERNS

Although α1-blockers are clinically useful in the treatment of hypertension, safety concerns have been a determining factor for the non-use of this class of drugs. However, there is emerging evidence that these drugs can be safely used in various clinical situations.

Doxazosin GITS was used as a third-line antihypertensive agent for the ASCOT study participants whose blood pressure was not controlled to the target (< 140/90 mm Hg and < 130/80 mm Hg in diabetes mellitus) with the first/second line antihypertensive drugs (amlodipine 5–10 mg/perindopril 4–8 mg or atenolol 50–100 mg/bendroflumethiazide 1.25-2.5 mg).[14] Doxazosin was initiated after 8 months (median) of randomization, and the mean starting and final doses were 4.1 and 7.0 mg, respectively. During a median of 12 months of uninterrupted doxazosin treatment, systolic/diastolic blood pressure fell 11.7/6.9 mm Hg from 158.7/89.2 mm Hg. During the entire ASCOT follow-up period (median 5.5 years), heart failure occurred in 178 of 11 768 participants (1.51%) who received doxazosin at any point and 115 of 7489 participants (1.54%) who never received doxazosin. The incidence rate of heart failure was 2.97 per 1000 person-years during doxazosin treatment, and 3.34 per 1000 person-years during or after discontinuation of doxazosin treatment; it was not different from the 2.85 per 1000 person-years rate among those who never received doxazosin ($P \geq .20$).[14]

The results of several recent studies in patients with heart failure further cleared the doubts about the safety concerns of worsening heart failure with the use of an α1-blocker. In a cohort study in 388 patients with heart failure, patients treated with α1-blockers had similar risks of heart failure readmission and total mortality as those without use of α1-blockers.[50] In a large propensity score-matched cohort study in patients with a primary diagnosis of heart failure and ascertained α1-blockers use at discharge, 35,713 patients treated with an α1-blocker had a lower risk of recurrent heart failure and all-cause mortality than the matched control patients not on α1-blocker treatment.[15] The lower rate of mortality was observed in those patients treated with α1-blockers that have vasoactive properties (doxazosin, prazosin, and terazosin) but not in those treated with the selective α1A receptor blockers, such as tamsulosin and alfuzosin. In addition, patients treated with a higher dose of α1-blockers had a lower risk of mortality than those treated with lower doses, with no increase in heart failure readmissions.[15]

Chronic kidney disease, which is a major comorbidity of resistant hypertension,[51] and is often considered an indication for α1-blockers in the presence of hyperkalemia, is also a concern. In a 1:1 matched analysis, Hundemer and coworkers investigated the use of α1-blockers in patients with various stages of chronic kidney disease ($n = 16{,}088$).[16]

During a maximum of 3 years follow-up, initiation of α1-blockers was associated with a lower risk of cardiovascular events (hazard ratio .92, 95% confidence interval .89–.95) and total mortality (hazard ratio .89, 95% confidence interval .84–.94), but with a higher risk of ≥30% decline in estimated glomerular filtration rate (hazard ratio 1.14, 95% confident interval 1.08–1.21) and kidney failure requiring replacement therapy (hazard ratio 1.28, 95% confidence interval 1.13–1.44). The associations for both the lower risk of total mortality and higher risk of kidney function decline were only evident in patients with an estimated glomerular filtration rate < 60 ml/min/1.73 m^2 (43% of the total study population). The association for kidney function decline might have been confounded by the competing risks of total mortality in those patients with a worse kidney function and higher mortality.[16] This large study also reported the incidence rate of the possible drug-related side effects; it was significantly higher in users than non-users of α1-blockers for syncope (19.5 *vs.* 15.9 events/1000 person-years; hazard ratio 1.23, 95% confidence interval 1.11–1.37), but not for hypotension, falls and fractures.

6 | CONCLUSIONS AND PERSPECTIVES

There is emerging evidence that α1-blockers can be safely used in the treatment of hypertension. These drugs can be used monotherapy or in combination with other classes of antihypertensive drugs in almost all hypertensive patients for blood pressure control.[52,53] However, there are some special indications. Benign prostatic hyperplasia is a compelling indication, because of the dual treatment effect on both high blood pressure and lower urinary tract symptoms. Many patients with resistant hypertension would require α1-blockers as add-on therapy, especially those with chronic kidney disease. Primary aldosteronism screen is increasing rapidly in clinical practice and herein α1-blockers are useful for blood pressure control in the preparation for the measurement of plasma aldosterone and renin.

Although α1-blockers are clinically useful in the treatment of hypertension, these drugs have to be used with several considerations (Table 2). First, among the currently available agents, only long-acting drugs with appropriate dosages, such as doxazosin GITS 4–8 mg daily and terazosin 2–4 mg daily, should be chosen. Orthostatic hypotension and first-dose hypotension are major concerns with the use of α1-blockers. Bedtime dosing and low-dose initial dosing are effective in the prevention of orthostatic hypotension and first-dose hypotension. Bedtime dosing is also effective for the treatment of morning hypertension and orthostatic hypertension.[54,55] The GITS formulation of doxazosin substantially reduces or even eliminates the need for dose titration and the potential risk of overdosing, and therefore the risk of orthostatic hypotension. Fluid retention is potentially a concern for the use of α1-blockers.[56] In resistant hypertension, diuretics have often been used, which may exert counter-regulatory effect on fluid retention possibly associated with the use of α1-blockers. In primary aldosteronism screen, α1-blockers are only used for a short period of time, and hence may have been discontinued before fluid retention develops. Intraoperative Floppy Iris Syndrome is an emerging concern with the use of α1-blockers, especially tamsulosin.[57] Although the relationship has not yet sufficiently well defined, it would be important that patients be educated with regard to this possible side effect particularly when cataract surgery is considered.

TABLE 2 Key points in the use of α1-blockers in the current management of hypertension

Key point	Therapeutic suggestion
Choice of agents	Long acting agents, for example, doxazosin gastrointestinal therapeutic system or terazosin
Prevention of orthostatic hypotension	Careful initial dosing and no overdosing
Fluid retention	Combination with a diuretic
Intraoperative Floppy Iris Syndrome[57]	Patients should be educated with regard to this possible side effect particularly when cataract surgery is considered

ACKNOWLEDGMENTS

The study investigators were financially supported by grants from the National Natural Science Foundation of China (91639203, 81770455, 82070432 and 82070435), Beijing and from the Shanghai Commission of Science and Technology (19DZ2340200), Shanghai, China.

CONFLICT OF INTEREST

Yook-Chin Chia has received unrestricted educational grants from Omron and Viatris and from Medtronic for activities of the Malaysian Society for World Action on Salt, Sugar and Health (MyWASSH), and speaker honoraria from Astra-Zeneca, Medtronic, Omron and Xepa-Sol. Kazuomi Kario reports research grants from Otsuka Pharmaceutical, Sanwa Kagaku Kenkyusho, Daiichi Sankyo, MSD, Astellas Pharma, Eisai, Taisho Pharmaceutical, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Teijin Pharma, Boehringer Ingelheim Japan, Bristol-Myers Squibb, and Mochida Pharmaceutical; Consulting fees from Kyowa Kirin, Sanwa Kagaku Kenkyusho, and Mochida Pharmaceutical; Honoraria from Otsuka Pharmaceuticals, Daiichi Sankyo, Novartis Pharma, and Mylan EPD; Participation in Advisory Board of Daiichi Sankyo, and Novartis Pharma. Ji-Guang Wang reports having received lecture and consulting fees from Novartis, Omron, Servier and Viatris. The other authors declare noconflict of interest.

AUTHOR CONTRIBUTIONS

Ji-Guang Wang contributed to the conception and design, and, together with Hua Li and Ting-Yan Xu, prepared the first draft of the manuscript. All authors critically commented and revised the manuscript and gave the final approval.

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How to cite this article: Li H, Xu T-Y, Li Y, et al. Role of α1-blockers in the current management of hypertension. *J Clin Hypertens*. 2022;24:1180–1186.
https://doi.org/10.1111/jch.14556