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RESEARCH ARTICLE

Alpha-Blockers in Cardiovascular Medicine: A Reappraisal of Evolving Roles from Heart Failure Safety to Renal Protection in Interventional Cardiology.

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Abstract: ***Background***: Alpha-blockers have historically been sidelined in cardiovascular disease management due to concerns regarding neurohormonal activation and heart failure (HF) exacerbation, primarily stemming from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). However, recent epidemiological data, clinical trial outcomes, and fundamental pharmacodynamic principles suggest that their clinical utility is highly context-dependent, prompting a re-evaluation of alpha-blockers in various cardiovascular settings. The aim of this review is to evaluate recent evidence concerning the cardiovascular safety and emerging applications of alpha-blockers. Recent large-scale observational studies and meta-analyses demonstrate that alpha-blockers do not increase hospital readmission rates or mortality among patients with established HF; in fact, they may be associated with improved survival and exercise tolerance. Conversely, epidemiological data on their initiation for benign prostatic hyperplasia (BPH) in patients without prior cardiovascular disease highlight subtle but persistent long-term ischemic risks. Furthermore, this review explores emerging applications in interventional cardiology, notably the use of periprocedural phentolamine to prevent contrast-associated acute kidney injury (CA-AKI). By detailing these evolving roles, including the management of resistant hypertension and cocaine-induced acute coronary syndromes, this review emphasizes a critical transition from broad historical contraindications toward tailored, patient-specific management. The resurgence of alpha-blockers highlights their potential utility beyond hypertension and BPH, particularly in cardioprotection and renal preservation.

Keywords: Alpha-blockers; Adrenergic alpha-Antagonists; Heart Failure; Resistant Hypertension; Contrast-Associated Acute Kidney Injury; Doxazosin; Phentolamine .

INTRODUCTION

A balanced clinical evaluation of alpha-blockers in cardiovascular disease requires a comprehensive understanding of adrenergic neurohormonal pathways and their specific receptor affinities. Adrenergic α receptors are broadly categorized into two primary classifications: α_1 and α_2. The α_1 receptors are located post-synaptically and primarily mediate smooth muscle contraction, resulting in vasoconstriction and elevated blood pressure. In contrast, α_2 receptors are predominantly situated pre-synaptically, where they exert inhibitory control over norepinephrine release [1].

The clinical utility and adverse effect profiles of alpha-blockers are dependent upon their selectivity for these receptors. Selective α_1-blockers (e.g., prazosin, doxazosin) induce prominent vasodilation and decrease peripheral resistance. Because they leave the pre-synaptic α_2 feedback loop intact, they generally avoid uncompensated surges in systemic catecholamines [1]. Uroselective agents (e.g., tamsulosin) further isolate this mechanism to alleviate benign prostatic hyperplasia (BPH) while minimizing systemic hypotension [2]. In contrast, non-selective agents like phentolamine block both α_1 and α_2 receptors. The simultaneous blockade of the α_2 receptor removes the physiological inhibitory feedback on sympathetic outflow. The resulting unopposed release of excess norepinephrine stimulates cardiac β_1 and vascular β_2 receptors, which can result in clinically significant reflex tachycardia and increased myocardial oxygen demand [1]. Nevertheless, the rapid intravenous onset of phentolamine (1–2 minutes) facilitates its application in acute, procedural, and toxicological settings, where prompt intervention is required [3].

However, the use of alpha-blockers in cardiovascular disease has been highly controversial. Historically, alpha-blockers were avoided in patients with heart failure (HF) due to fears of neurohormonal activation and fluid retention. Recent studies and meta-analyses have challenged this long-standing contraindication, exploring their safety profiles and illuminating novel, context-dependent applications ranging from cardioprotection in established HF to the prevention of contrast-associated acute kidney injury (CA-AKI) during percutaneous coronary intervention (PCI) [4, 5].

Historical Context: The ALLHAT Legacy

The hesitation to prescribe alpha-blockers in cardiovascular disease originated largely from the landmark Antihypertensive and Lipid-Lowering

Treatment to Prevent Heart Attack Trial (ALLHAT). This trial compared novel antihypertensive classes against a traditional thiazide-type diuretic, chlorthalidone. The novel agents evaluated included calcium channel blockers (amlodipine), angiotensin-converting enzyme (ACE) inhibitors (lisinopril), and alpha-blockers (doxazosin). Patients treated with the alpha-blocker doxazosin experienced a near doubling of incident HF compared to those receiving the thiazide diuretic chlorthalidone. Specifically, the incidence of congestive heart failure was 8.13% in the doxazosin group versus 4.45% in the chlorthalidone group at four years, leading to the premature termination of the doxazosin arm (ALLHAT Collaborative Research Group, 2000). Subsequent validation process supported the findings of increased heart failure in the ALLHAT doxazosin treatment arm [6]. Accordingly, alpha-blockers were generally relegated to later-line antihypertensive status and were considered formally contraindicated as primary agents in patients at risk for heart failure [7].

However, retrospective physiological reappraisals suggest that the ALLHAT trial findings require a more nuanced interpretation. The trial fundamentally compared an α-blocker against a long-acting diuretic (chlorthalidone) that directly targets intravascular volume and sodium excretion. Consequently, the observed increase in newly diagnosed heart failure in the doxazosin arm was not necessarily a manifestation of direct myocardial toxicity. Rather, it was predominantly a reflection of unopposed fluid retention and the unmasking of pre-existing diastolic dysfunction [4]. Furthermore, a significant proportion of the enrolled patients were already receiving established diuretic therapy prior to randomization; upon allocation to the doxazosin arm, these baseline diuretics were abruptly withdrawn [8]. This sudden withdrawal, in addition to the absence of the direct cardioprotective neurohormonal modulation typically provided by ACE inhibitors or β-blockers, likely precipitated acute volume overload rather than true incident heart failure [4].

Earlier trials like V-HeFT I had previously demonstrated that alpha-blockade via prazosin monotherapy showed no difference in all-cause mortality or hospitalization when using prazosin monotherapy compared to placebo in patients with established heart failure [9]. Thus, ALLHAT primarily exposed the inferiority of alpha-blockers as first-line monotherapy for volume-dependent hypertension rather than reflecting a direct cardiotoxic effect [4].

Re-evaluating Safety in Heart Failure

The historical contraindication of alpha-blockers in heart failure has been systematically re-evaluated through recent substantial observational studies and meta-analyses. To definitively quantify these outcomes and reconcile the ALLHAT data with the recent studies, a comprehensive systematic review and meta-analysis by Sousa et al. [4] was conducted, pooling data from 15 randomized controlled trials, three prospective cohort studies, and two large retrospective studies. The authors concluded that in patients with chronic HF, alpha-blockers exert a neutral effect on acute HF events, all-cause mortality, cardiovascular mortality, and acute coronary syndromes (ACS). Furthermore, alpha-blocker therapy was significantly associated with an increase in exercise tolerance. This finding aligns with the physiological mechanism of afterload reduction, allowing the heart to increase stroke volume during exertion without a proportional increase in myocardial oxygen demand [4].

This contemporary data strongly validates the clinical paradigm shift reflected in the 2021 European Society of Cardiology (ESC) guidelines, which formally removed the strict historical contraindication for alpha-blockers in HF. The guidelines acknowledge that alpha-blockers can be safely utilized to treat comorbid conditions, such as BPH, in hemodynamically stable patients, though they emphasize prompt withdrawal in the event of symptomatic orthostatic hypotension or acute decompensation [7,10].

Furthermore, in a large population-based cohort study involving 169,911 Veterans Affairs patients with HF, Jackevicius et al. [11] evaluated the outcomes of alpha-blocker therapy, which was actively prescribed to 47,638 individuals (28%) at discharge. The analysis revealed that alpha-blocker treatment was associated with significantly lower HF readmissions (39.8% vs. 41.7% at 2 years) and lower all-cause mortality (42.8% vs. 46.5%) when compared to untreated matched controls. Furthermore, the mortality reduction was most pronounced with higher doses and with the use of non-uroselective alpha-blockers (e.g., doxazosin, terazosin, prazosin). These benefits persisted regardless of concomitant beta-blocker use [11].

An additional retrospective cohort study analyzing data from the Polish National Health Fund reinforced these specific outcomes. Following 53,317 compliant patients hospitalized for acute heart failure exacerbations, the analysis confirmed that post-discharge treatment with alpha-blockers independently improved long-term survival, demonstrating a significant lower all-cause mortality (52.8% vs. 54.9%). Furthermore, alpha-blockers significantly lowered the incidence of the secondary composite endpoint of readmission or death [12].

Cardiovascular Outcomes in BPH Treatment

Despite the encouraging data in HF, the cardiovascular safety of alpha-blockers requires careful consideration depending on the patient population. A 2023 cohort study by Zhang et al. [13] evaluated the cardiovascular safety of alpha-blockers versus 5-alpha reductase inhibitors (5-ARIs) in 189,868 older adult males with

BPH. The study found that alpha-blockers arm had a slightly higher 1-year risk of major adverse cardiovascular events (MACE) (8.95% vs. 8.32%) and death compared to 5-ARI arm. While there was no significant difference in the risk for HF hospitalization alone, the composite risk for MACE and HF was elevated in the alpha-blocker group [13].

These findings align with comprehensive population-based analyses evaluating long-term cardiac failure risks among men treated with various BPH medications. Evaluating an extensive dataset of 175,201 men diagnosed with a BPH, researchers reported that the risk of heart failure was highest for patients treated with alpha-blocker monotherapy (HR 1.22; 95% CI 1.18-1.26). Furthermore, patients treated with non-uroselective alpha-blockers exhibited a higher risk of heart failure compared to those on uroselective alpha-blockers (HR 1.08; 95% CI 1.00-1.17) [14].

This suggests that while alpha-blockers may be safe or even beneficial in established HF with optimized medical therapy, their initiation in the broader, older BPH population may still carry a subtle increase in MACE compared to 5-ARIs [13, 14].

Management of Resistant Hypertension

Despite the long shadow cast by the ALLHAT legacy regarding first-line antihypertensive use, alpha-blockers retain a formalized, algorithmic role in the contemporary management of resistant hypertension. This condition is defined by blood pressure remaining chronically elevated above target levels despite the concurrent, compliant use of three distinct antihypertensive agents of different pharmacological classes (a renin-angiotensin system inhibitor, a dihydropyridine calcium channel blocker, and a thiazide or thiazide-like diuretic) administered at maximal tolerated doses [10]. Resistant hypertension is highly morbid, associated with a higher risk of hypertension-mediated target organ damage, end-stage renal disease, and acute cardiovascular events [15].

The pathophysiological drivers of resistant hypertension frequently include chronic volume expansion and secondary hyperaldosteronism, alongside intense peripheral vasoconstriction. According to the 2024 European Society of Cardiology (ESC) Guidelines, the integration of alpha-blockers is carefully positioned within a step-wise algorithm. When triple therapy fails, the preferred Step 4 addition is universally a mineralocorticoid receptor antagonist (MRA) such as spironolactone, specifically due to the high prevalence of unrecognized volume overload in this cohort [10].

The primary evidence driving this specific pharmacological hierarchy stems from the landmark PATHWAY-2 trial. In this double-blind, randomized trial, researchers sought to determine the optimal fourth-line therapy for resistant hypertension by comparing the addition of spironolactone, doxazosin, bisoprolol, or a placebo to baseline triple therapy. The study conclusively demonstrated that spironolactone was vastly superior in reducing home systolic blood pressure, thereby cementing MRAs as the definitive Step 4 intervention. However, the trial also confirmed that doxazosin effectively and significantly lowered blood pressure compared to placebo. Consequently, PATHWAY-2 established alpha-blockers as highly reliable, evidence-based alternatives for patients who are intolerant to MRAs, or as the logical next step for those who require further therapy escalation [16].

If blood pressure remains inadequately controlled following the optimization of MRA therapy, the ESC guidelines formally endorse the addition of specific alpha-blockers, such as doxazosin. In this setting, alpha-blockers effectively reduce the fixed peripheral vascular resistance that drives diastolic pressure. However, clinicians must continuously monitor these patients for severe orthostatic hypotension [10].

Alpha-Blockers in Hyperadrenergic Crises: Pheochromocytoma and Cocaine-Induced ACS.

Pheochromocytoma Management

Pheochromocytomas are catecholamine-secreting neuroendocrine tumors that precipitate severe hypertensive crises. Non-selective alpha-blockers such as phenoxybenzamine and phentolamine are utilized preoperatively to manage catecholamine-induced hypertension in patients with pheochromocytoma, ensuring hemodynamic stability during surgery [1].

Consequently, guidelines mandate that α-blockade must always precede β-blocker administration to prevent profound adverse hemodynamic decompensation from unopposed α-stimulation [17].

Cocaine-Induced Cardiovascular Crises

The principle of avoiding unopposed α-stimulation also dictates the management of cocaine-induced acute coronary syndromes (ACS). Cocaine inhibits presynaptic catecholamine reuptake, triggering systemic adrenergic hyper-stimulation characterized by intractable tachycardia, severe hypertension, and profound coronary vasospasm capable of precipitating myocardial infarction without underlying atherosclerosis [18, 19].

While first-line therapy utilizes intravenous benzodiazepines to reduce central sympathetic tone, pure β-blockers (e.g., metoprolol) are generally contraindicated for refractory ischemia. Blocking β_2-mediated vasodilation allows excessive synaptic norepinephrine concentrations to bind to α_1-receptors; this unopposed α effect exacerbates coronary vasoconstriction [19]. Instead, AHA guidelines endorse phentolamine for refractory cases, as direct α-blockade successfully reverses

coronary vasospasm and resolves ischemic ST-segment elevations [18].

Modulating Renal Vasospasm: The Role of Phentolamine in Contrast-Associated Acute Kidney Injury.

The capacity of α-blockers to attenuate severe vasospasm, as utilized in hyperadrenergic crises, is increasingly applied in interventional cardiology to prevent contrast-associated acute kidney injury (CA-AKI) [5]. CA-AKI is a leading cause of hospital-acquired renal impairment, with an incidence of up to 13% that increases significantly in high-risk clinical cohorts [20]. KDIGO criteria defined CA-AKI by a $\ge$0.3 mg/dL absolute or $\ge$50% relative increase in baseline serum creatinine following contrast exposure [21]. CA-AKI is an independent predictor of both short- and long-term mortality and major adverse cardiovascular events; notably, patients with reduced left ventricular ejection fraction (<40%) are at a very high risk of developing CA-AKI following acute myocardial infarction [22].

The pathophysiology of CA-AKI is primarily mediated by contrast-induced medullary vasoconstriction. The hyperosmolar and cytotoxic stress of iodinated contrast stimulates the local release of potent vasoconstrictors (e.g., endothelin, adenosine) and diminishes vasodilatory nitric oxide bioavailability. This vasospasm induces profound hypoxia in the highly metabolically active thick ascending limb of the loop of Henle, leading to direct tubular epithelial toxicity [20]. Reversing this localized vasoconstriction provides a targeted protective strategy. While agents like fenoldopam and nicorandil have established the rationale for preserving renal perfusion, the non-selective α-antagonist phentolamine specifically addresses this ischemic cascade [23, 24].

The clinical efficacy of this targeted α-blockade was demonstrated in a prospective, randomized controlled pilot study by Hamila et al. [5]. The trial evaluated 107 high-risk patients with pre-existing chronic kidney disease and chronic coronary syndrome undergoing percutaneous coronary intervention or diagnostic catheterization. Participants were randomized to receive either conventional hydration or hydration combined with a periprocedural phentolamine infusion [5].

The addition of phentolamine yielded substantial protective outcomes. The incidence of CA-AKI was 17.1% in the phentolamine cohort, compared to 82.9% in the control group. Statistical modeling demonstrated a significant reduction in the odds of developing CA-AKI (OR 0.041; 95% CI 0.0149–0.1128; $p<0.0001$). Furthermore, the phentolamine cohort exhibited significant improvements in 72-hour postprocedural urine output, reflecting preserved renal medullary perfusion and functional clearance. By directly antagonizing α_1-mediated medullary vasoconstriction, phentolamine prevents critical hypoxia and favorably alters the clinical trajectory of vulnerable patients. Beyond immediate renal preservation, this physiological benefit translated into a significant reduction in major adverse cardiac and cerebrovascular events (MACCE) at 90 days post-procedure [5].

CONCLUSION

The clinical evolution of α-adrenergic antagonists in cardiovascular medicine represents a significant pharmacological reassessment. Historically avoided as first-line antihypertensives due to the legacy of the ALLHAT trial, the contemporary evidence surrounding these agents is supported by physiological and neurohormonal context. Instead of precipitating true incident heart failure, early adverse outcomes largely reflected unmasked volume overload and the abrupt withdrawal of concomitant diuretics. Recent meta-analyses and large-scale cohort studies have successfully clarified their safety profile, demonstrating that in patients with established, medically optimized heart failure, α-blockers exert neutral or even beneficial long-term survival effects, likely achieved by reducing systemic afterload.

However, this contemporary application remains highly context-dependent. As demonstrated in broader, older populations treated for benign prostatic hyperplasia, the initiation of α-blockade demands careful patient selection due to subtle increases in generalized cardiovascular risks. Therefore, the current cardiovascular use of α-blockers is dictated by targeted, step-wise protocols rather than broad prescribing practices. In chronic disease management, they retain a definitive, evidence-based role as late-stage interventions for resistant hypertension.

Furthermore, the utility of α-blockers in acute settings continues to expand. The established guideline of initiating α-blockade prior to β-antagonism remains an essential, life-saving physiological requirement in the management of hyperadrenergic crises, including pheochromocytoma and cocaine-induced acute coronary syndromes. Building upon this capacity to reverse profound localized vasospasm, the successful application of periprocedural phentolamine in vulnerable CKD populations undergoing coronary interventions to mitigate contrast-associated acute kidney injury highlights an emerging indication for these agents.

In summary, the clinical role of α-blockers has shifted from a broadly contraindicated drug class to context-dependent cardiovascular therapies. Their use relies on matching receptor activity to the distinct clinical scenario: utilizing rapid, non-selective agents (e.g., phentolamine) to reverse profound vasospasm in hyperadrenergic crises and contrast-associated acute

kidney injury, while carefully integrating selective α_1-antagonists (e.g., doxazosin) in the step-wise management of resistant hypertension and medically optimized heart failure. However, future large-scale, prospective randomized controlled trials remain essential to solidify this evolving evidence. Such studies will explain the therapeutic potential of these agents across various cardiovascular states, further supporting the shift from absolute contraindications toward individualized, pharmacologically informed clinical decision-making.

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