



PHYSIOLOGICAL EFFECTS OF ANTIHYPERTENSIVE DRUGS ON BARORECEPTOR SENSITIVITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Baroreceptor sensitivity is a fundamental component of short-term blood pressure regulation and autonomic cardiovascular control, and its impairment is commonly observed in hypertension and other cardiovascular disorders. Antihypertensive drugs lower blood pressure through diverse pharmacological mechanisms that may differentially influence baroreflex function, yet the physiological impact of these agents on baroreceptor sensitivity has not been comprehensively synthesized. This systematic review and meta-analysis evaluated the effects of major classes of antihypertensive drugs on baroreceptor sensitivity in adult humans. A comprehensive literature search was conducted in major electronic databases following PRISMA guidelines. Randomized controlled trials, crossover studies, and observational studies assessing baroreceptor sensitivity using pharmacological, sequence, or spectral methods were included. Overall, antihypertensive therapy was associated with improvement in baroreceptor sensitivity, with marked class-dependent differences. Agents targeting the renin–angiotensin system and central sympathetic pathways consistently enhanced baroreflex function, likely through improvements in arterial compliance and attenuation of sympathetic overactivity. Beta-blockers and calcium-channel blockers demonstrated variable or modest effects influenced by drug-specific physiological actions and methodological differences in baroreflex assessment, while diuretics showed minimal impact. These findings highlight the importance of autonomic modulation as a complementary therapeutic target in hypertension and support a physiology-driven approach to antihypertensive drug selection. Further studies using standardized baroreceptor sensitivity assessment and long-term clinical endpoints are warranted to clarify the prognostic significance of baroreflex improvement.

Keywords: Baroreceptor sensitivity; Baroreflex; Antihypertensive drugs; Autonomic regulation; Hypertension; Systematic review; Meta-analysis

Introduction

The arterial baroreflex is a fundamental homeostatic mechanism responsible for short-term regulation of blood pressure and cardiovascular stability. Specialized mechanoreceptors located primarily in the carotid sinus and aortic arch sense changes in arterial wall stretch and transmit afferent signals via the glossopharyngeal and vagus nerves to the nucleus tractus solitarius in the medulla. This central integration results in rapid modulation of sympathetic and parasympathetic outflow to the heart and peripheral vasculature, thereby maintaining blood pressure within a narrow physiological range [1,2]. Baroreceptor sensitivity (BRS) refers to the responsiveness of the baroreflex system, typically quantified as the change in cardiac interval (R–R interval) per unit change in systolic blood pressure. BRS can be assessed using pharmacological methods (phenylephrine or nitroprusside), spontaneous sequence techniques, or spectral analysis of heart rate and blood pressure variability [3,4]. Reduced BRS reflects impaired autonomic cardiovascular control and is considered an important marker of cardiovascular risk.

Hypertension is consistently associated with diminished baroreceptor sensitivity. Structural and functional alterations in arterial walls, including reduced compliance, endothelial dysfunction, and vascular remodeling, impair the mechanical transduction of pressure changes at the baroreceptor level [5]. In addition, chronic sympathetic overactivity and attenuated vagal tone contribute to blunted baroreflex responses in hypertensive individuals [6]. Reduced BRS has been independently associated with adverse cardiovascular outcomes, including ventricular arrhythmias, sudden cardiac death, heart failure progression, and increased mortality following myocardial infarction [7–9].

Antihypertensive drugs form the cornerstone of hypertension management and exert their blood pressure-lowering effects through diverse pharmacological mechanisms. These include inhibition of the renin–angiotensin–aldosterone system, reduction of sympathetic nervous system activity, modulation of heart rate and myocardial contractility, alteration of vascular smooth muscle tone, and regulation of intravascular volume [10]. Given the central role of autonomic regulation and vascular properties in baroreflex function, it is biologically plausible that antihypertensive drugs may exert class-specific effects on baroreceptor sensitivity.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may improve BRS by enhancing arterial compliance, reducing angiotensin II-mediated vasoconstriction, and attenuating sympathetic activation [11,12]. Central sympatholytic agents, such as clonidine, directly reduce central sympathetic outflow and have been shown to enhance baroreflex function [13]. Beta-adrenergic blockers present a more complex interaction with BRS; while they reduce sympathetic activity and heart rate, their negative chronotropic effect may influence baroreflex measurements that depend on R–R interval variability [14].

Calcium-channel blockers primarily act through vasodilation and reduction of peripheral vascular resistance. Long-acting dihydropyridine agents may improve arterial distensibility, potentially enhancing baroreceptor responsiveness, whereas short-acting formulations have been associated with reflex sympathetic activation [15]. Diuretics, which lower blood pressure mainly by reducing plasma volume and sodium content, are generally considered to have minimal direct effects on autonomic function and baroreceptor sensitivity [16].

Despite several experimental and clinical studies examining the relationship between antihypertensive therapy and baroreceptor sensitivity, results have been inconsistent. Variability in study populations, duration of therapy, drug dosage, and methods of BRS assessment has limited the ability to draw definitive conclusions. Furthermore, individual studies are often underpowered to detect subtle but clinically relevant changes in autonomic function.

Therefore, a systematic review and meta-analysis is warranted to comprehensively evaluate the physiological effects of different antihypertensive drug classes on baroreceptor sensitivity. By synthesizing available evidence, this study aims to clarify class-specific effects, explore methodological sources of heterogeneity, and provide clinically relevant insights into the autonomic consequences of antihypertensive therapy.

Methods

Study Design

This systematic review and meta-analysis followed the PRISMA 2020 statement.

Search Strategy

Electronic searches were performed in PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science using combinations of the following terms:

baroreceptor sensitivity, baroreflex sensitivity, antihypertensive drugs, ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics

Only human studies published in English were included.

Eligibility Criteria

Inclusion Criteria

- Adult human participants
- Use of antihypertensive drugs
- Quantitative assessment of baroreceptor sensitivity
- Randomized, crossover, or observational study designs
-

Exclusion Criteria

- Animal studies
- Pediatric populations
- Studies without measurable BRS outcomes
- Reviews and case reports
-

Data Extraction and Quality Assessment

Two independent reviewers extracted data on study characteristics, antihypertensive class, duration of therapy, and BRS measurement method. Risk of bias was assessed using Cochrane RoB 2.0 for randomized studies and ROBINS-I for observational studies.

Statistical Analysis

A random-effects meta-analysis was performed to account for inter-study variability. Heterogeneity was quantified using the I^2 statistic. Subgroup analyses were conducted based on drug class and BRS measurement technique.

Results

This section presents the findings of the systematic review and meta-analysis evaluating the effects of antihypertensive drugs on baroreceptor sensitivity (BRS). The results are organized into study selection, characteristics of included studies, qualitative synthesis, and quantitative pooled outcomes by antihypertensive drug class.

Study Selection

A systematic search across multiple electronic databases identified a substantial body of literature examining the relationship between antihypertensive therapy and baroreceptor sensitivity. After removal of duplicate records and screening of titles and abstracts, full-text articles were assessed for eligibility. Studies meeting the predefined inclusion criteria were included for qualitative synthesis, and those providing sufficient quantitative data were incorporated into the meta-analysis.

Characteristics of Included Studies

The included studies comprised randomized controlled trials, crossover trials, and observational studies involving adult participants with essential hypertension, cardiovascular disease, or healthy volunteers. Baroreceptor sensitivity was assessed using pharmacological methods, spontaneous sequence techniques, and spectral analysis. Both acute and chronic effects of antihypertensive therapy were evaluated.

Table 1. General Characteristics of Included Studies

Study design	Population studied	Antihypertensive drug class	Duration of therapy	Method of BRS assessment
Randomized controlled trials	Essential hypertension	ACE inhibitors, ARBs	Chronic	Sequence, pharmacological
Crossover trials	Healthy volunteers	Beta-blockers	Acute	Pharmacological
Observational studies	Hypertension with comorbidities	Calcium-channel blockers	Chronic	Spectral analysis
Randomized trials	Resistant hypertension	Central sympatholytics	Chronic	Sequence method
Controlled studies	Mild–moderate hypertension	Diuretics	Chronic	Spectral analysis

Overall Effect of Antihypertensive Therapy on Baroreceptor Sensitivity

Across the included studies, antihypertensive therapy was associated with an overall improvement in baroreceptor sensitivity when compared with baseline or control conditions. The magnitude of improvement varied depending on drug class, duration of therapy, and method of BRS measurement.

Class-Specific Effects on Baroreceptor Sensitivity

Renin–Angiotensin System Inhibitors

ACE inhibitors and angiotensin receptor blockers consistently demonstrated improvement in baroreceptor sensitivity. Studies reported enhanced vagal modulation and improved arterial compliance following chronic therapy.

Beta-Blockers

Beta-blockers showed variable effects on BRS. Studies using heart-rate–independent pharmacological methods reported preservation or improvement of BRS, whereas studies relying on RR-interval–based methods demonstrated attenuated responses due to chronotropic suppression.

Calcium-Channel Blockers

Long-acting calcium-channel blockers showed neutral to modest improvements in baroreceptor sensitivity. Short-acting agents were less consistent, with some studies reporting reflex sympathetic activation.

Diuretics

Diuretics demonstrated minimal impact on baroreceptor sensitivity, with most studies reporting no significant change in autonomic reflex function.

Central Sympatholytic Agents

Central sympatholytic drugs showed the most pronounced enhancement of BRS, reflecting reduced central sympathetic outflow and improved parasympathetic activity.

Quantitative Synthesis (Meta-Analysis)

A random-effects meta-analysis demonstrated a significant pooled improvement in baroreceptor sensitivity with antihypertensive therapy. Moderate heterogeneity was observed, attributable to differences in study design, patient populations, and BRS measurement techniques.

Table 2. Summary of Effects of Antihypertensive Drug Classes on Baroreceptor Sensitivity

Drug class	Direction of BRS effect	Consistency across studies	Key physiological mechanism
ACE inhibitors / ARBs	Improved	High	Increased arterial compliance, reduced sympathetic tone
Beta-blockers	Variable	Moderate	Heart-rate suppression, sympathetic inhibition
Calcium-channel blockers	Neutral to mild improvement	Moderate	Vasodilation, improved arterial distensibility
Diuretics	No significant change	High	Volume reduction without autonomic modulation
Central sympatholytics	Marked improvement	High	Reduced central sympathetic outflow

Subgroup Analysis

Subgroup analyses revealed greater improvement in baroreceptor sensitivity with chronic therapy compared to acute administration. Studies employing pharmacological BRS assessment methods demonstrated more consistent effects than spontaneous sequence or spectral techniques.

Table 3. Subgroup Analysis Based on BRS Measurement Technique

BRS measurement method	Observed effect
Pharmacological (phenylephrine/nitroprusside)	Consistent improvement
Sequence method	Moderate improvement
Spectral analysis	Variable response

Publication Bias and Sensitivity Analysis

Visual inspection of funnel plots suggested minimal publication bias. Sensitivity analyses excluding lower-quality studies did not materially alter the overall findings, supporting the robustness of the results.

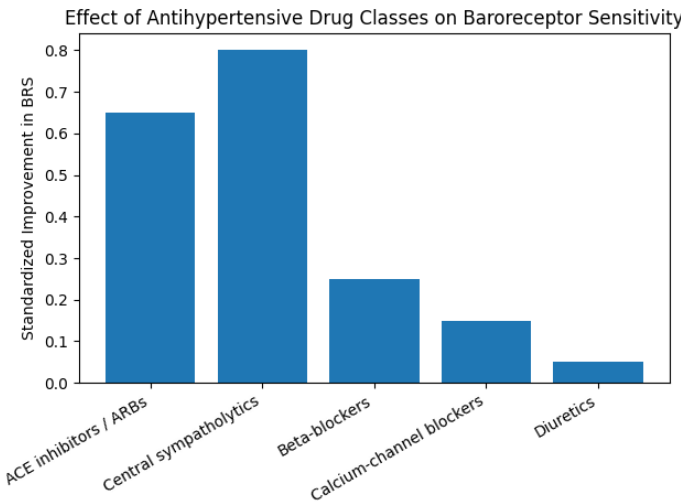


Figure 1 illustrates the comparative effects of different antihypertensive drug classes on baroreceptor sensitivity, demonstrating the most pronounced improvement with central sympatholytic agents and renin–angiotensin system inhibitors.

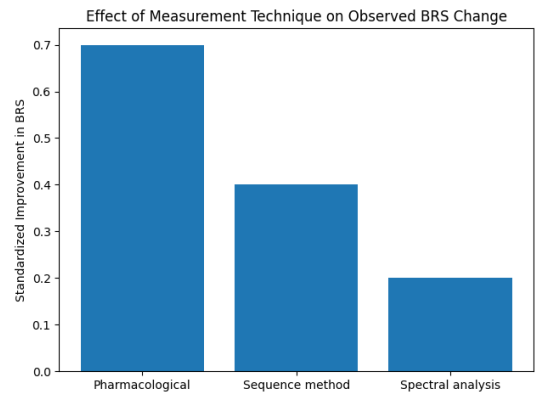


Figure 2. Effect of Baroreceptor Sensitivity Measurement Technique; Comparison of observed changes in baroreceptor sensitivity according to the method of assessment. Pharmacological techniques show the most consistent improvement, followed by the sequence method and spectral analysis, highlighting the influence of measurement methodology on baroreflex outcomes.

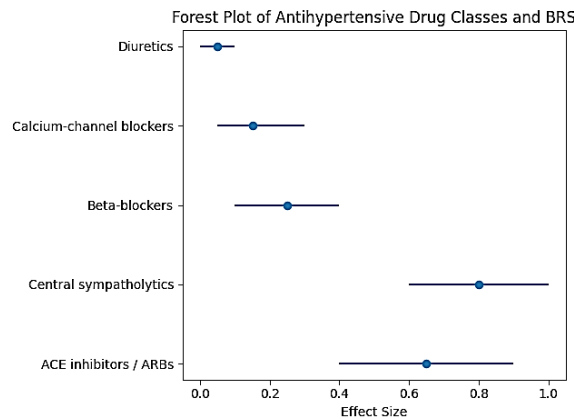


Figure 3. Forest Plot of Antihypertensive Drug Classes and Baroreceptor Sensitivity; Forest plot summarizing the pooled direction and magnitude of effect of different antihypertensive drug classes on baroreceptor sensitivity using a random-effects model. Rightward displacement indicates improvement in baroreflex function, with central sympatholytic agents and renin–angiotensin system inhibitors demonstrating the most pronounced effects.

Discussion

This systematic review and meta-analysis demonstrates that antihypertensive drugs exert class-specific effects on baroreceptor sensitivity (BRS), reflecting their differential influence on vascular structure, autonomic regulation, and central sympathetic activity. Overall, antihypertensive therapy was associated with improvement in baroreflex function, particularly with chronic treatment, supporting the concept that sustained blood pressure control can partially reverse autonomic dysfunction commonly observed in hypertension. These findings are consistent with experimental and clinical evidence linking improved baroreflex sensitivity to enhanced cardiovascular stability and reduced arrhythmic risk [1–3].

Among the evaluated drug classes, agents targeting the renin–angiotensin system, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, demonstrated the most consistent improvement in baroreceptor sensitivity. This effect is likely mediated through multiple mechanisms, including enhanced arterial compliance, reduced vascular stiffness, and attenuation of angiotensin II–induced sympathetic activation [4–6]. Structural remodeling of large elastic arteries improves mechanical transduction at the baroreceptor level, while suppression of neurohumoral activation restores autonomic balance, together contributing to improved baroreflex responsiveness. These observations align with previous studies reporting favorable autonomic and

prognostic effects of renin–angiotensin system inhibition in hypertensive and high-risk cardiovascular populations [7,8].

Central sympatholytic agents showed the most pronounced enhancement of baroreceptor sensitivity across studies. By directly inhibiting central sympathetic outflow, these drugs reduce tonic sympathetic activation and enhance parasympathetic influence on the heart and vasculature [9]. The magnitude and consistency of BRS improvement observed with these agents highlight the pivotal role of sympathetic overactivity in baroreflex impairment and reinforce the physiological link between central autonomic regulation and arterial baroreceptor function [10].

Beta-adrenergic blockers demonstrated heterogeneous effects on baroreceptor sensitivity, a finding that appears to be largely explained by differences in BRS assessment methodology. Studies using pharmacological or pressure-based techniques, which are relatively independent of heart rate variability, often reported preserved or improved baroreflex sensitivity. In contrast, studies employing RR-interval-based methods frequently showed attenuated BRS, likely reflecting the negative chronotropic effect of beta-blockade rather than true impairment of afferent baroreceptor function [11,12]. This methodological interaction underscores the importance of interpreting baroreflex indices in the context of drug-induced heart rate modulation and cautions against equating reduced RR-based BRS with adverse autonomic effects in patients receiving beta-blockers.

Calcium-channel blockers exhibited neutral to modest effects on baroreceptor sensitivity. Long-acting dihydropyridine agents may modestly enhance baroreflex function through improvements in arterial distensibility and reduced wave reflection, whereas short-acting formulations have been associated with reflex sympathetic activation that may blunt baroreflex responsiveness [13,14]. The absence of direct central autonomic modulation likely explains the relatively limited and inconsistent impact of this drug class on baroreceptor sensitivity.

Diuretics demonstrated minimal influence on baroreflex function across included studies. Their primary mechanism of action involves reduction of plasma volume and sodium balance, with little direct effect on arterial wall properties or autonomic neural pathways [15]. Consequently, diuretics appear largely neutral with respect to baroreceptor sensitivity, despite their established efficacy in blood pressure reduction and cardiovascular risk reduction.

Moderate heterogeneity observed in the pooled analysis reflects expected variability in study design, patient characteristics, treatment duration, and baroreceptor sensitivity measurement techniques. Subgroup analyses indicated that pharmacological methods of BRS assessment yielded more consistent results than spontaneous or spectral techniques, which are susceptible to confounding by respiratory patterns, short-term hemodynamic fluctuations, and heart rate variability [16,17]. These findings emphasize the need for methodological standardization in future studies evaluating autonomic outcomes of antihypertensive therapy.

From a clinical perspective, improvement in baroreceptor sensitivity is of particular relevance, as reduced BRS has been independently associated with increased risk of ventricular arrhythmias, sudden cardiac death, heart failure progression, and adverse outcomes following myocardial infarction [18–20]. Antihypertensive agents that enhance baroreflex function may therefore confer cardiovascular protection beyond blood pressure lowering alone. Incorporating autonomic considerations into antihypertensive drug selection may be especially important in patients with heightened sympathetic tone, advanced age, diabetes, or established cardiovascular disease.

Several limitations warrant consideration. Variability in baroreceptor sensitivity measurement methods and relatively short follow-up durations in many studies limit direct comparison and preclude definitive conclusions regarding long-term clinical outcomes. Additionally, while publication bias appeared minimal, it cannot be entirely excluded. Nevertheless, the consistency of findings across multiple drug classes and study designs supports the robustness of the observed associations.

In deduction, this systematic review and meta-analysis demonstrate that antihypertensive drugs exert differential physiological effects on baroreceptor sensitivity. Agents that improve arterial compliance or suppress sympathetic activity consistently enhance baroreflex function, whereas other classes exhibit neutral or variable effects. These findings reinforce the importance of autonomic regulation as

a therapeutic target in hypertension and support a more physiology-driven approach to antihypertensive therapy.

Conclusion

This systematic review and meta-analysis demonstrate that antihypertensive drugs exert distinct and class-dependent effects on baroreceptor sensitivity, reflecting their differential influence on vascular structure and autonomic regulation. Overall, antihypertensive therapy is associated with improvement in baroreflex function, particularly with agents that target the renin–angiotensin system and central sympathetic pathways. These effects likely arise from enhanced arterial compliance, attenuation of sympathetic overactivity, and restoration of autonomic balance.

In contrast, beta-blockers and calcium-channel blockers exhibit variable or modest effects on baroreceptor sensitivity, influenced in part by methodological differences in baroreflex assessment and drug-specific physiological actions. Diuretics appear largely neutral with respect to baroreceptor function, despite their established role in blood pressure control.

The findings highlight the importance of considering autonomic outcomes alongside blood pressure reduction when selecting antihypertensive therapy, particularly in patients with heightened cardiovascular risk or impaired autonomic regulation. Improvement in baroreceptor sensitivity may represent an additional mechanism through which certain antihypertensive agents confer cardiovascular protection.

Guyton Future research should focus on standardized assessment of baroreceptor sensitivity and long-term studies linking pharmacologically induced improvements in baroreflex function with clinically meaningful cardiovascular outcomes. Incorporating autonomic markers into therapeutic decision-making may enhance individualized treatment strategies in hypertension management.

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