Review Article

Beyond Blood Pressure: A Systematic Review of the Effects of Antihypertensive Drug Classes on Endothelial-Related Outcomes and Arterial Stiffness in Adults with Hypertension

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Abstract

Hypertension remains a leading cause of cardiovascular morbidity and mortality worldwide, and residual vascular risk may persist despite treatment. Endothelial dysfunction and arterial stiffness are clinically relevant but distinct vascular domains and should not be regarded as interchangeable constructs.

The aim of this review was to systematically evaluate whether major antihypertensive drug classes exhibit differential effects across two predefined vascular domains (endothelial-related outcomes and arterial stiffness/central hemodynamic outcomes) in adults with hypertension.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. PubMed/MEDLINE, Embase, CENTRAL, and LILACS were searched from inception through April 2025. Original studies involving human participants and reporting direct vascular outcomes were eligible for the primary synthesis. Endothelial-related outcomes were analyzed separately from arterial stiffness and central hemodynamic outcomes. Because of substantial clinical and methodological heterogeneity, the findings were synthesized narratively, first by vascular domain and then by drug class. Protocol was retrospectively registered with the Open Science Framework under DOI 10.17605/OSF.IO/CWA5X.

The primary synthesis included 40 original studies involving human participants. Across the available evidence, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) yielded the most consistently favorable findings for pulse wave velocity (PWV). Selected calcium channel blocker regimens and specific beta-blocker strategies also demonstrated potentially favorable vascular effects in certain settings, although certainty and consistency of evidence varied across vascular domains and study designs. Findings for augmentation index (AIx), peripheral arterial tonometry (PAT), and circulating biomarkers were more heterogeneous and warrant cautious interpretation.

Available evidence most consistently supports favorable PWV findings with ACE inhibitors and ARBs, whereas evidence regarding AIx, PAT, circulating biomarkers, and combination therapies remains less consistent. Endothelial-related outcomes and arterial stiffness indices should therefore be interpreted as distinct vascular domains, and the current evidence does not support a definitive ranking of antihypertensive drug classes.

Keywords

Vascular Endothelium; Vascular Stiffness; Antihypertensive Agents; Pulse Wave Analysis; Systematic Review

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Introduction

Hypertension affects more than 1.28 billion adults worldwide and remains the leading modifiable risk factor for cardiovascular disease, accounting for a substantial proportion of premature deaths and disability.[1-4] Despite the well-established benefits of blood pressure (BP) reduction, a substantial proportion of treated patients continue to experience cardiovascular events even after achieving guideline-recommended BP targets, a phenomenon commonly referred to as residual cardiovascular risk.[4-10] This persistent risk has prompted growing interest in vascular phenotypes that are not fully captured by office brachial BP measurements.

Emerging evidence suggests that vascular damage associated with endothelial dysfunction and arterial stiffening contributes to residual cardiovascular risk; however, these domains should be conceptually distinguished. Endothelial dysfunction is characterized by impaired nitric oxide bioavailability, endothelial activation, inflammatory signaling, and reduced vasodilatory responsiveness.[11,12] By contrast, arterial stiffness reflects cumulative structural and hemodynamic changes in the arterial wall and is commonly assessed using aortic pulse wave velocity (PWV) and the augmentation index (AIx).[13-25] Although both domains are clinically relevant, they are not interchangeable measures of the same pathophysiological construct (Figure 1).

Different antihypertensive drug classes may exhibit distinct vascular effects beyond office BP reduction through anti-inflammatory, antioxidant, endothelial, and hemodynamic mechanisms.[8,9,26] However, whether these effects are consistent across predefined vascular domains remains uncertain. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have been associated with vascular protection in multiple settings, whereas

Central Illustration: Beyond Blood Pressure: A Systematic Review of the Effects of Antihypertensive Drug Classes on Endothelial-Related Outcomes and Arterial Stiffness in Adults with Hypertension

Distinct but interrelated vascular domains

Antihypertensive drug classes	Endothelial-related outcomes FMD | PAT | Circulating biomarkers	Arterial stiffness and central hemodynamic outcomes PWV | AIx | Central BP
1. ACE inhibitors	Favorable findings in selected studies	Most consistently favorable findings for PWV
2. ARBs	Variable findings; favorable effects reported in selected studies	Most consistently favorable findings for PWV
3. CCBs	Favorable findings in selected studies	Favorable pattern in selected studies
4. Beta-blockers	Heterogeneous findings across individual agents	Class-level heterogeneity; newer agents may have distinct effects
5. MRAs	Potential benefits in selected high-risk populations	Potential benefits in selected populations
6. Thiazide and thiazide-like diuretics	Neutral or inconsistent findings	Overall neutral or inconsistent findings
7. RAAS inhibitor plus CCB combinations	Promising findings in selected studies	Promising profile; limited standardization across studies
	Overall: heterogeneous findings across outcomes and drug classes	**PWV: most consistently favorable signal AIx and central hemodynamic measures: less consistent findings**

Narrative synthesis of 40 original studies involving human participants

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Endothelial-related outcomes and arterial stiffness/central hemodynamic outcomes represent distinct but interrelated vascular domains in hypertension. Central Illustration summarizes the structured narrative synthesis of 40 original studies involving human participants. Endothelial-related outcomes encompass endothelial responsiveness, microvascular reactivity, and circulating biomarkers, whereas arterial stiffness and central hemodynamic outcomes encompass pulsatile arterial load, wave reflection, central BP, and vascular aging. The most consistently favorable findings involved PWV among patients treated with ACE inhibitors or ARBs. Findings for other drug classes and vascular outcomes were more heterogeneous. Because these domains are not interchangeable, the vascular effects of antihypertensive drug classes should be interpreted separately by domain, and the available evidence does not support a definitive class ranking. ACE: angiotensin-converting enzyme; AIx: augmentation index; ARB: angiotensin II receptor blocker; BP: blood pressure; CCB: calcium channel blocker; FMD: flow-mediated dilation; MRA: mineralocorticoid receptor antagonist; PAT: peripheral arterial tonometry; PWV: pulse wave velocity; RAAS: renin-angiotensin-aldosterone system.

calcium channel blockers (CCBs), mineralocorticoid receptor antagonists (MRAs), beta-blockers, and different diuretic subclasses appear to have distinct vascular profiles.[8,9,27-43]

Accordingly, this systematic review aimed not to establish a universal hierarchy of antihypertensive efficacy but to determine whether major antihypertensive drug classes exhibit differential patterns across predefined vascular domains — namely, endothelial-related outcomes and arterial stiffness/central hemodynamic outcomes — in adults with hypertension.

Methods

Study design and registration

The review used a structured and methodologically transparent approach aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[44] Protocol was retrospectively registered with the Open Science Framework under DOI 10.17605/OSF.IO/CWA5X.

Eligibility criteria

Eligible studies included adults (≥18 years) with hypertension and evaluated treatment with an established class of antihypertensive drugs, including ACE inhibitors, ARBs, CCBs, beta-blockers, diuretics, and MRAs, administered as monotherapy or combination therapy. Eligible comparators included placebo, active treatment, usual care, or clearly described before-and-after assessments, provided that direct vascular outcomes were measured and the study context allowed meaningful within-study interpretation.

In order to address conceptual concerns and enhance methodological clarity, vascular outcomes were classified

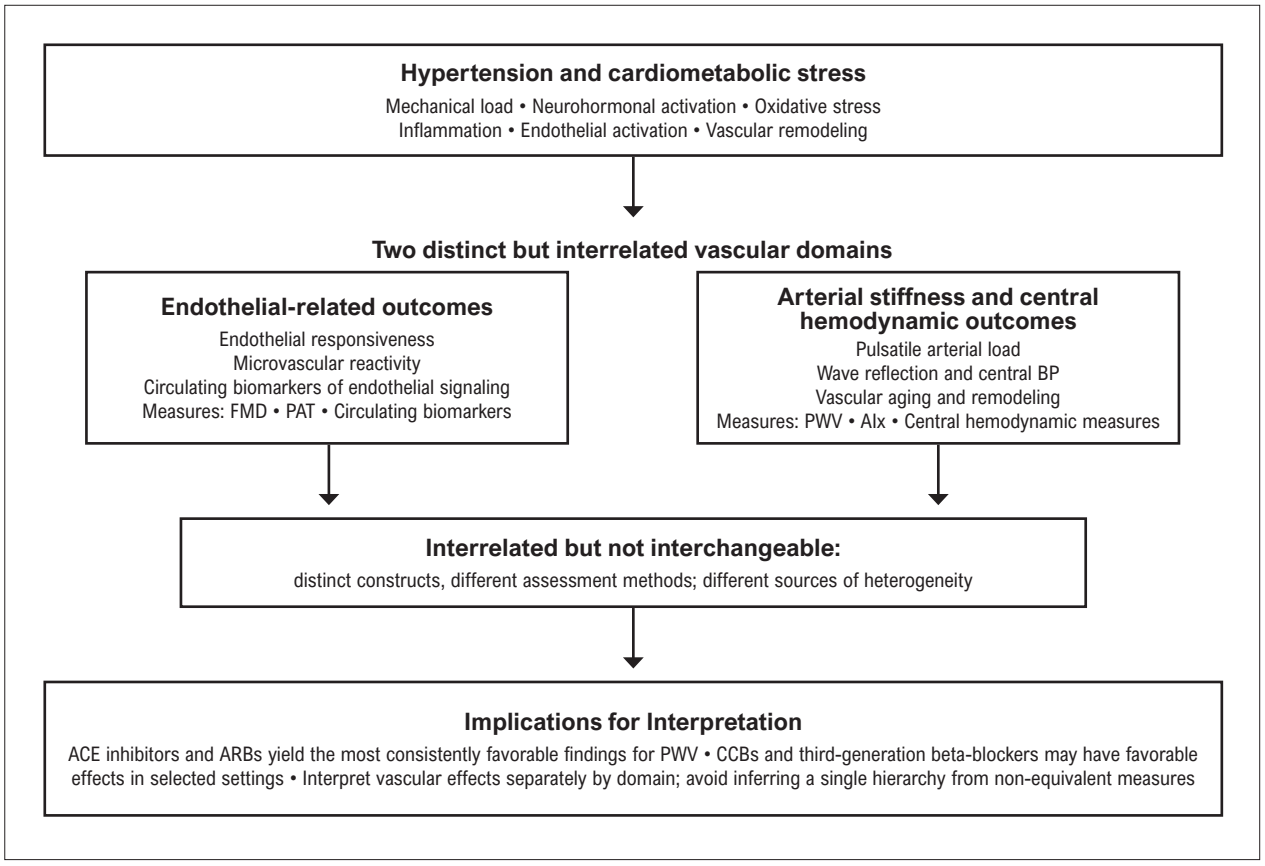

Figure 1 – *Conceptual framework for distinct vascular domains in hypertension. Hypertension-related vascular injury can be understood in terms of two distinct but interrelated domains: endothelial-related outcomes and arterial stiffness/central hemodynamic outcomes. Endothelial-related outcomes encompass endothelial responsiveness, microvascular reactivity, and biomarker-based signaling pathways and are commonly assessed using FMD, PAT, and circulating biomarkers. Arterial stiffness and central hemodynamic outcomes encompass pulsatile arterial load, wave reflection, central BP, and vascular aging and are commonly assessed using PWV, AIx, and other central hemodynamic measures. These domains are related but not interchangeable. Accordingly, vascular effects of antihypertensive therapy should be interpreted within each domain rather than combined into a single inferred hierarchy. ACE: angiotensin-converting enzyme; AIx: augmentation index; BP: blood pressure; CCB: calcium-channel blocker; FMD: flow-mediated dilation; PAT: peripheral arterial tonometry; PWV: pulse wave velocity; RAAS: renin-angiotensin-aldosterone system.*

a priori into two distinct domains. Endothelial-related outcomes included flow-mediated dilation (FMD), peripheral arterial tonometry (PAT), and circulating biomarkers of inflammation, oxidative stress, nitric oxide/L-arginine signaling, or endothelial activation and injury. Arterial stiffness and central hemodynamic outcomes included PWV, the AIx, central BP, and related measures of pulsatile arterial load. These domains were analyzed separately and were not considered interchangeable.

Only original studies involving human participants and reporting direct vascular outcomes were included in the primary synthesis. Editorials, narrative reviews, conference abstracts with insufficient data, case reports, methodological or guideline documents, non-human studies, and reports that did not address the vascular outcomes of interest were excluded from the primary evidence base. Prior systematic reviews and meta-analyses were screened to provide context and identify additional eligible studies but were not included in the primary synthesis, thereby avoiding duplication of evidence.

Information sources and search strategy

Comprehensive literature searches were conducted in PubMed/MEDLINE, Embase, CENTRAL, and LILACS from database inception through April 2025. Searches combined controlled vocabulary terms and free-text terms related to hypertension, antihypertensive therapy, endothelial function, arterial stiffness, PWV, AIx, FMD, and PAT. Boolean operators and search syntax were adapted to the requirements of each database. Complete database-specific search strategies are provided in Supplementary Appendix 1. Reference lists of eligible reports and relevant review articles were also manually screened to identify potentially eligible studies not retrieved through the database searches.

Study selection

All retrieved records were imported into Rayyan for deduplication and screening. Two review authors independently performed study selection in two sequential stages: i) title and abstract screening, followed by ii) full-text assessment of potentially eligible reports. Decisions at the full-text stage were based on the final eligibility criteria for original studies involving human participants and reporting direct vascular outcomes. Disagreements were resolved through consensus or, when necessary, consultation with a third review author. Reasons for exclusion following full-text assessment were recorded and are presented in a PRISMA flow diagram.

Data extraction

Two review authors independently extracted data using a standardized form developed in accordance with Cochrane guidance. Extracted variables included first author, year of publication, study design, sample size, population characteristics, intervention, comparator, treatment duration, vascular outcome definitions, and principal vascular findings. In order to facilitate interpretation of heterogeneous vascular assessments, technical and methodological variables were extracted whenever available, including device type, vascular territory, arterial segment, acquisition protocol, operator dependence, pretest conditions, and heart rate (HR) correction for AIx. Data on circulating biomarkers were extracted and synthesized according to the underlying biological pathway rather than being grouped into a single, undifferentiated endothelial category.

Assessment of risk of bias

Two review authors independently assessed risk of bias according to study design. Randomized controlled trials (RCTs) were evaluated using Revised Cochrane Risk-of-Bias Tool for Randomized Trials, whereas observational studies were assessed using the Newcastle-Ottawa Scale. Because the primary synthesis was restricted to original studies involving human participants, non-human experimental studies were not included in the main evidence synthesis.

Data synthesis and certainty of evidence

Because of substantial clinical and methodological heterogeneity — such as differences in study design, patient populations, drug regimens, treatment duration, vascular territories, acquisition methods, outcome definitions, and reporting formats — a de novo quantitative synthesis of the overall dataset was considered inappropriate. Accordingly, a structured narrative synthesis was performed. The synthesis was organized first by vascular domain and then by antihypertensive drug class, with emphasis on the consistency, interpretive coherence, and clinical relevance of the reported vascular effects rather than on an indirect quantitative ranking of heterogeneous outcome measures.

When pooled estimates from previously published meta-analyses were cited, they were explicitly identified as secondary evidence used solely to contextualize the consistency or inconsistency of findings across literature and not as estimates generated by the present review. Certainty of evidence for key vascular outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and classified as high, moderate, low, or very low.

Results

Search results and study selection

Database searches identified a total of 2,760 records: 1,284 from PubMed/MEDLINE, 892 from Embase, 421 from CENTRAL, and 163 from LILACS. After removing 802 duplicates, 1,958 records were screened by title and abstract, of which 287 full-text reports were assessed for eligibility. Applying the final eligibility criteria for the primary synthesis, 40 original studies involving human participants were included (Figure 2). Exclusions were most often due to the absence of directly measured vascular outcomes, a secondary or contextual study design, or failure to meet the final eligibility criteria for primary synthesis.

The characteristics of the 40 original studies involving human participants included in the final primary synthesis are summarized in Table 1 and detailed at the study level in Supplementary Table S1.

The risk-of-bias assessment indicated that most RCTs raised some concerns, whereas the observational studies were predominantly of moderate-to-good methodological quality (Table 2).

Angiotensin-converting enzyme inhibitors

ACE inhibitors yielded the most consistently favorable findings for PWV across the final body of human evidence, whereas findings for the AIx and endothelial-related outcomes were less consistent.[27,29,45] In PERTINENT,[27] a substudy of EUROPA trial,[28] perindopril improved endothelial-related measures and was associated with increased nitric oxide bioavailability and lower levels of endothelial activation markers. Quinapril also improved endothelial vasomotor dysfunction in patients with coronary artery disease in TREND study.[29] Overall, the most consistent findings associated with ACE inhibitors involved arterial stiffness outcomes rather than endothelial-related outcomes considered collectively.

Mineralocorticoid receptor antagonists

MRAs, such as spironolactone, eplerenone, and finerenone, were associated with favorable vascular findings in patients with resistant hypertension, primary aldosteronism, heart failure with preserved ejection fraction, or diabetic kidney disease.[30-33,46-49] However, the evidence base was smaller and more heterogeneous than that available for ACE inhibitors or ARBs, and the reported outcomes varied across endothelial-related measures and arterial stiffness parameters. These findings should therefore be interpreted as population- and context-specific rather than as evidence of a uniform class-wide vascular benefit.

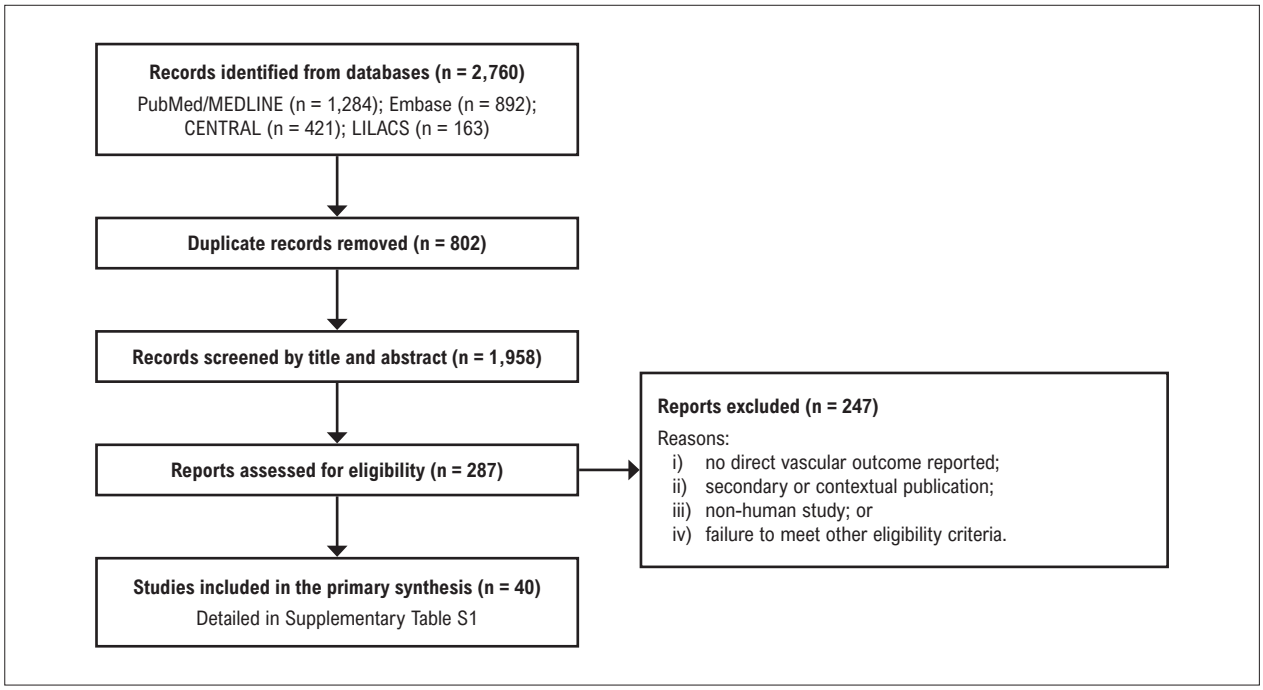

Figure 2 – *Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram of study selection. The flow diagram summarizes the identification, screening, eligibility assessment, and final inclusion of studies in the primary synthesis. The 40 included original studies involving human participants are detailed in Supplementary Table S1.*

Diuretics

Conventional thiazide diuretics, particularly hydrochlorothiazide, generally had neutral vascular effects in the available studies.[34,35,50] Thiazide-like diuretic regimens yielded more favorable findings in some studies, particularly when combined with inhibition of the renin-angiotensin-aldosterone system (RAAS). However, the evidence remained limited, regimen-dependent, and less consistent than that available for ACE inhibitors or ARBs.

Beta-blockers

The evidence for beta-blockers was more limited and heterogeneous than that for RAAS-based therapies. Comparative evidence derived primarily from atenolol-based regimens in LIFE,[40] ASCOT,[41] and CAFE[42] studies suggested less favorable central hemodynamic profiles. However, the available data did not support firm class-wide conclusions regarding newer agents. These findings underscore the need for caution when generalizing vascular effects across the beta-blocker class. As context, conventional beta-blockers have been associated, in meta-analyses, with a higher risk of diabetes,[51] and their clinical benefits remain well-established in specific settings, such as the post-myocardial infarction phase[52] and heart failure,[53] although the role of this drug class following a myocardial infarction—in patients without a reduced ejection fraction or heart failure—is currently being re-evaluated.[54] This underscores the need for caution when generalizing vascular effects to the entire class of beta-blockers.

Calcium channel blockers

Dihydropyridine CCBs, particularly amlodipine, were associated with favorable effects on central hemodynamics, PWV, and some endothelial-related measures in several clinical studies.[38,41,42,55] Data from CAFE[42] and ASCOT[41] support the relevance of central BP and arterial stiffness outcomes when comparing amlodipine-based strategies with conventional beta-blocker regimens. Nevertheless, the magnitude and consistency of these benefits varied according to the vascular outcome assessed. The most consistent signal associated with CCBs involved central hemodynamic and arterial stiffness measures rather than endothelial-related outcomes considered broadly.

Angiotensin II receptor blockers

Findings for ARBs were broadly comparable to those for ACE inhibitors with respect to PWV, representing the most consistently favorable pattern among non-ACE inhibitors drug classes in the final synthesis.[36,40,43] Secondary evidence used for contextual purposes suggested potentially favorable effects on AIx. However, these estimates were not generated by the present review and should not be assigned greater weight than the included primary human evidence.[56]

Combination therapy

Combination regimens comprising a RAAS inhibitor and a CCB were associated with favorable vascular patterns in several of included studies.[38,41-43] However, available evidence was insufficiently standardized and too limited to

Table 1 – Characteristics of the studies included in the final primary synthesis of human evidence, by antihypertensive drug class

Drug class	Predominant evidence base	Main clinical settings/ populations	Principal vascular outcomes reported	Overall pattern in the revised synthesis
ACE inhibitors	RCTs and observational studies	Essential hypertension, coronary artery disease, and mixed populations at high cardiovascular risk	PWV, AIx, FMD, and markers of endothelial activation	Most consistently favorable pattern for PWV; endothelial-related findings were generally favorable but more heterogeneous
ARBs	RCTs and observational studies	Essential hypertension, hypertension in individuals with overweight or obesity, and populations with metabolic or inflammatory risk profiles	PWV, AIx, FMD, and inflammatory and endothelial biomarkers	Most consistently favorable pattern for PWV among non-ACE inhibitors classes; favorable contextual findings for AIx; endothelial-related effects varied across assessment methods
CCBs	RCTs and comparative clinical studies	Essential hypertension, studies assessing central hemodynamics, and cohorts receiving combination therapy	PWV, central blood pressure, AIx, and FMD	Favorable pattern for arterial stiffness and central hemodynamics in selected studies; endothelial-related benefits were reported in some trials but were not consistent across all outcomes
Beta-blockers (conventional and third-generation agents)	RCTs and observational studies	Essential hypertension and comparative trials of beta-blocker regimens versus amlodipine- or RAAS-based regimens	Central hemodynamics, PWV, and endothelial-related vasodilatory responses	Findings varied within the class; third-generation beta-blockers yielded more favorable endothelial-related and hemodynamic findings than conventional agents
MRAs	Small randomized and observational studies	Resistant hypertension, primary aldosteronism, diabetic kidney disease, and heart failure with preserved ejection fraction	PAT, PWV, and endothelial-related outcomes	Potentially favorable vascular effects in selected high-risk populations; however, the evidence base was smaller and more heterogeneous
Diuretics (conventional thiazides)	Comparative clinical and observational studies	Essential hypertension and background combination therapy	PWV and endothelial-related measures	Generally neutral or inconsistent vascular effects when evaluated as an isolated class effect
Diuretics (thiazide-like agents)	Small clinical studies, often evaluating combination regimens	Essential hypertension and combination-therapy regimens	PWV and endothelial-related measures	More favorable findings than those for conventional thiazides in some regimens, particularly when combined with RAAS inhibition; however, the evidence remained limited
Combination therapy (RAAS inhibitor plus CCB)	Comparative clinical studies	Hypertension with moderate-to-high cardiovascular risk, hypertension in individuals with overweight or obesity, and cohorts with angina or vascular dysfunction	PWV, AIx, and endothelial-related outcomes	Most favorable combination-therapy pattern in several studies, particularly for arterial stiffness outcomes; however, direct standardized comparative evidence remained limited

Table summarizes the final primary synthesis of human evidence, in which endothelial-related outcomes and arterial stiffness/central hemodynamic outcomes were interpreted as distinct vascular domains. ACE: angiotensin-converting enzyme; AIx: augmentation index; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; FMD: flow-mediated dilation; MRA: mineralocorticoid receptor antagonist; PAT: peripheral arterial tonometry; PWV: pulse wave velocity; RAAS: renin-angiotensin-aldosterone system; RCT: randomized controlled trial.

Table 2 – Summary of assessment of risk of bias for studies included in the final primary synthesis of human evidence

Study design	Risk of bias assessment tool	Overall judgment pattern	Main recurring limitations	Implications for interpretation
RCTs	RoB 2	A minority of studies were judged to be at low risk of bias; most raised some concerns, and a small proportion were judged to be at high risk	Incomplete reporting of allocation concealment, limited information on blinding, short follow-up periods in some trials, and heterogeneity in outcome-specific reporting	Evidence from RCT supports several favorable vascular signals, particularly for PWV; however, certainty of evidence varies across outcome domains, and direct comparability among studies is limited
Observational studies	NOS	Studies were predominantly of moderate-to-good methodological quality	Residual confounding, selection bias, nonuniform comparator groups, and inconsistent outcome acquisition and reporting	Observational findings are clinically informative and hypothesis-generating but should not be considered equivalent to evidence from randomized comparative studies

Table excludes animal studies and secondary evidence from the main risk of bias display, in accordance with the final primary synthesis restricted to original human studies. Supplementary Table S1 provides a detailed study-level breakdown of final evidence base. NOS: Newcastle-Ottawa Scale; PWV: pulse wave velocity; RCT: randomized controlled trial; RoB 2: Revised Cochrane Risk-of-Bias Tool for Randomized Trials.

support firm comparative conclusions across combination strategies.

Overall pattern of evidence

Overall, the final synthesis indicated recurring but outcome-specific vascular patterns rather than a single definitive ranking of antihypertensive drug classes. The effects observed across the predefined vascular domains are summarized in Table 3, whereas Central Illustration provides an integrated overview of the findings by drug class. Arterial stiffness outcomes, particularly PWV, were reported more consistently than endothelial-related outcomes, whereas findings based on AIx, PAT, and circulating biomarkers exhibited greater methodological and interpretive heterogeneity.

The GRADE certainty assessments for the main vascular outcomes are presented in Table 4.

Discussion

This systematic review suggests that antihypertensive drug classes may differ in their effects on specific vascular parameters beyond brachial BP reduction; however, these findings require careful conceptual and methodological interpretation. A central principle of this review was the distinction between endothelial-related outcomes and arterial stiffness/central hemodynamic outcomes because these measures capture overlapping but non-equivalent aspects of vascular biology.[22,25]

Across the final body of human evidence, ACE inhibitors and ARBs yielded the most consistently favorable findings for PWV. Selected CCB regimens and limited agent-specific data on beta-blockers also suggested potentially favorable vascular effects in specific settings.[27-29,36,38,40-43] However, the findings were not consistent across outcomes, and the evidence for AIx, PAT, and circulating biomarkers was substantially more heterogeneous. Accordingly, the present review does not support a definitive hierarchy of vascular efficacy among antihypertensive drug classes.

Restricting the primary synthesis to original studies involving human participants allowed direct appraisal of the underlying evidence and avoided duplication of findings from secondary reviews and meta-analyses. Such secondary literature remained useful for contextualizing the results but was not used as a substitute for evaluating the included primary studies.[56,57]

Several methodological factors may account for the observed heterogeneity. FMD reflects conduit artery endothelial responsiveness and is highly protocol-dependent, whereas PAT assesses peripheral microvascular reactivity and is not equivalent to FMD.[58] Circulating biomarkers may reflect inflammation, oxidative stress, nitric oxide signaling, or endothelial activation and injury, but they are not interchangeable surrogates for endothelial function.[11,12,22,25] Similarly, PWV and AIx represent related but distinct hemodynamic constructs and are influenced by the vascular territory examined, acquisition method, and HR.[9,13-18,59]

Heterogeneity was not limited to measurement techniques. The included studies also differed in population characteristics, background therapy, treatment intensity, follow-up duration, comparator groups, and outcome definitions. Because

Table 3 – Effects of antihypertensive drug classes across predefined vascular domains

Drug class	Endothelial-related outcomes*	Arterial stiffness (PWV)	AIx/central hemodynamics	Overall interpretation in the revised manuscript	Overall certainty of evidence
ACE inhibitors	Favorable findings in selected studies, including improvements in endothelial activation and nitric oxide-related pathways	Most consistently favorable pattern	Findings less consistent than those for PWV	Strongest evidence relates to improvement in arterial stiffness; endothelial-related findings are supportive but less consistent	Higher for PWV; lower for endothelial-related outcomes
ARBs	Favorable findings in selected studies, with biomarker- and endothelial-related signals reported in some trials	Most consistently favorable pattern	Favorable contextual findings in some analyses	Strong evidence supports improvement in PWV; findings for AIx are promising but warrant cautious interpretation	Higher for PWV; contextual and heterogeneous for AIx
CCBs	Favorable findings in selected studies, particularly those evaluating amlodipine-based regimens	Favorable findings in several studies	Favorable effects on central hemodynamics in some trials	Benefits appear to depend on the outcome assessed; the strongest signal relates to central hemodynamics and arterial stiffness rather than to a single unified vascular construct	Moderate
Beta-blockers (third-generation agents)	Favorable nitric oxide-mediated and endothelial-related findings in selected studies	Limited-to-modest favorable pattern	More favorable findings than those for conventional beta-blockers in some settings	Findings should not be generalized to the entire beta-blocker class	Low to moderate
Beta-blockers (conventional agents)	Neutral or inconsistent findings	Neutral or less favorable findings	Less favorable central hemodynamic pattern in comparative studies	No consistent favorable vascular profile beyond BP reduction	Low to moderate
MRAs	Favorable findings in selected high-risk populations	Potentially favorable findings	Limited and heterogeneous findings	Population-specific vascular benefits are plausible, but the evidence base is smaller and less standardized	Low to moderate
Conventional thiazide diuretics	Generally neutral findings	Neutral or inconsistent findings	Neutral findings	No consistent evidence of a class-wide vascular benefit beyond BP reduction	Low

Thiazide-like diuretics	Some favorable findings, particularly with combination regimens	Potentially favorable findings with selected regimens	Limited evidence	Findings appear more favorable than those for conventional thiazides but remain regimen-dependent	Low to moderate
RAAS inhibitor plus CCB combinations	Favorable findings in several studies	Most favorable pattern among combination regimens	Favorable findings in some comparative settings	A promising strategy for improving arterial stiffness and the broader vascular profile; however, standardized head-to-head evidence remains limited	Moderate

**Endothelial-related outcomes include FMD, PAT, and circulating biomarkers of inflammation, oxidative stress, nitric oxide/L-arginine signaling, or endothelial activation and injury. The directions of effect presented in this table reflect the final structured narrative synthesis and should not be interpreted as a definitive quantitative ranking of drug classes. ACE: angiotensin-converting enzyme; AIx: augmentation index; ARB: angiotensin II receptor blocker; BP: blood pressure; CCB: calcium channel blocker; FMD: flow-mediated dilation; MRA: mineralocorticoid receptor antagonist; PAT: peripheral arterial tonometry; PWV: pulse wave velocity; RAAS: renin-angiotensin-aldosterone system.*

Table 4 – GRADE certainty of evidence for the main outcomes included in final primary synthesis

Outcome	Comparison/intervention	Summary of evidence	Certainty of evidence	Main reasons for downgrading or interpretive caution
Improvement in PWV	ACE inhibitors versus control or baseline	Most consistently favorable PWV pattern across the primary body of human evidence	Moderate	Downgraded because of the risk of bias in the contributing studies and limited direct comparability across heterogeneous vascular assessment methods, although consistency was greatest for PWV
Improvement in PWV	ARBs versus control or baseline	Most consistently favorable PWV pattern across the primary body of human evidence	Moderate	Downgraded because of the risk of bias and indirectness arising from differences in study settings and outcome definitions, despite recurring favorable findings for PWV
Improvement in arterial stiffness/ central hemodynamics	CCBs versus comparator regimens	Several studies supported favorable effects on central hemodynamics and arterial stiffness, particularly with amlodipine-based regimens	Moderate	Downgraded because of inconsistency across outcomes and nonuniform vascular measurement methods

Endothelial-related benefits	Third-generation beta-blockers versus conventional comparators or baseline	Selected studies suggested favorable endothelial-related and vasodilatory effects	Low to moderate	Downgraded because of small sample sizes, methodological heterogeneity, and indirectness related to agent-specific rather than class-wide evidence
Vascular benefits in selected high-risk populations	MRAs versus comparator or baseline	Potentially favorable effects on endothelial-related and arterial stiffness outcomes in resistant hypertension and related clinical settings	Low to moderate	Downgraded because of small study populations, population heterogeneity, and imprecision
Integrated vascular benefits of combination regimens	RAAS inhibitor plus CCB versus monotherapy or alternative regimens	Several studies suggested favorable effects on arterial stiffness and the broader vascular profile	Moderate	Downgraded because of limited direct evidence from standardized head-to-head comparisons and heterogeneity across outcomes
Improvement in AIx	Across drug classes, particularly ARB-based regimens	Favorable findings were reported in selected studies and contextual secondary evidence	Low	Downgraded because of inconsistency, indirectness, variability in acquisition methods, and partial reliance on secondary evidence
PAT and circulating biomarker findings	Across drug classes	Findings were heterogeneous and biologically diverse; therefore, a single summary effect was not considered appropriate	Low to very low	Downgraded because of indirectness, inconsistency, non-equivalence of outcomes, and methodological variability

ACE: angiotensin-converting enzyme; AIx: augmentation index; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MRA: mineralocorticoid receptor antagonist; PAT: peripheral arterial tonometry; PWV: pulse wave velocity; RAAS: renin-angiotensin-aldosterone system.

of these differences, a structured narrative synthesis was methodologically more appropriate than a de novo meta-analysis of the overall dataset.

Mechanistic interpretations should remain proportionate to the strength of the underlying evidence. Although some studies suggest that certain antihypertensive agents may exert favorable vascular effects through anti-inflammatory, antioxidant, nitric oxide-mediated, or hemodynamic mechanisms, the available evidence does not support broad causal claims that these effects are entirely independent of BP reduction.[8,9,58]

From a clinical point of view, these findings support a nuanced interpretation of the vascular effects of antihypertensive therapy. Available research is insufficient to justify routinely ranking treatments solely on the basis of vascular phenotyping. Instead, vascular outcomes may provide complementary information, particularly in patients with evidence of vascular injury or increased pulsatile load. Future comparative trials should prospectively standardize vascular measurements and evaluate endothelial-related outcomes and arterial stiffness as distinct endpoints.[4,5,9]

This review has a number of limitations. Protocol was registered retrospectively, the available evidence was heterogeneous in design and reporting, and some outcome domains were informed by relatively small or methodologically limited studies. In addition, the primary synthesis was restricted to studies meeting the final eligibility criteria for human studies, whereas epidemiological, methodological, and secondary sources were retained only to provide context. Although this approach ensured consistency among the PRISMA flow diagram, Supplementary Table S1, and

the narrative synthesis, it also highlights the importance of rigorous evidence classification in reviews of complex vascular outcomes. Finally, most of the available data were derived from Western populations, which may limit the generalizability of the findings to more diverse populations and settings.[7]

Conclusion

Available evidence suggests recurring class-related differences in vascular outcomes beyond brachial BP control, with the most consistently favorable signal observed for PWV among patients treated with ACE inhibitors or ARBs.

However, endothelial-related outcomes and arterial stiffness/central hemodynamic indices represent distinct vascular domains. Heterogeneity in outcome definitions, measurement methods, study populations, and treatment regimens precludes a definitive ranking of antihypertensive drug classes.

Further studies should use standardized protocols for vascular assessment, prospectively distinguish between endothelial-related and arterial stiffness outcomes, and prioritize direct comparative designs with adequate follow-up. Such efforts are needed to determine whether differential vascular effects can inform clinically meaningful treatment stratification in hypertension.[4,5,9]

Author Contributions

Conception and design of the research: Nogueira BNA, Fonseca FAH, Izar MC; Data collection and Statistical analysis: Nogueira BNA, Fonseca FAH, Bianco HT; Data analysis and interpretation and Critical revision of the manuscript for important intellectual content: Nogueira BNA, Fonseca FAH, Izar MC, Póvoa RMS, Bianco HT; Manuscript drafting: Nogueira BNA, Fonseca FAH.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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*Supplemental Materials

For Supplementary Table, please click here.

For Supplementary Appendix, please click here.

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