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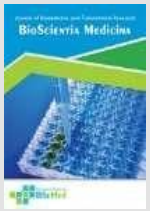

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Efficacy and Safety of Intensive Blood Pressure Lowering on Cardiovascular Outcomes and Orthostatic Hypotension in Frail vs. Non-Frail Elderly Patients: A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: The management of hypertension in the older adult population presents a complex clinical challenge, particularly regarding the balance between cardiovascular risk reduction and the provocation of adverse events such as orthostatic hypotension. Frailty status complicates this dynamic, creating uncertainty regarding the optimal blood pressure target. **Methods:** A systematic review and meta-analysis investigated the efficacy and safety of intensive versus standard blood pressure lowering in frail compared to non-frail older adults. Databases were systematically searched for randomized controlled trials and their secondary analyses reporting cardiovascular outcomes and orthostatic hypotension stratified by frailty. Data were extracted and synthesized using a random-effects model, calculating pooled risk ratios and standardized mean differences to assess primary cardiovascular events and safety outcomes. **Results:** Ten primary studies met the inclusion criteria. Intensive blood pressure lowering significantly reduced the incidence of major cardiovascular events in both non-frail and frail cohorts. Surprisingly, intensive treatment did not increase the risk of orthostatic hypotension in frail patients and was associated with a protective effect against orthostatic hypotension in specific subsets. The risk of bias was generally low across the included trials. **Conclusion:** Intensive blood pressure control provides substantial cardiovascular benefits for older adults, irrespective of baseline frailty status. Furthermore, the aggressive lowering of blood pressure does not exacerbate the risk of orthostatic hypotension, challenging previous clinical hesitations. These findings support the cautious but deliberate implementation of intensive targets in the geriatric population, monitored closely by comprehensive geriatric assessments.

1. Introduction

The demographic shift toward an aging global population has necessitated a profound reevaluation of cardiovascular disease management paradigms.[1] Hypertension remains the most prevalent modifiable risk factor for cardiovascular morbidity and mortality in older adults. For decades, the therapeutic approach to elevated blood pressure in the geriatric population was guided by a pervasive clinical apprehension that aggressive reduction of blood pressure might precipitate hypoperfusion to vital organs, leading to cognitive decline, falls, and orthostatic hypotension. This conservative strategy was often summarized by the clinical adage start low, go slow, which, while emphasizing safety, potentially deprived a substantial proportion of older adults of the well-documented

cardiovascular benefits associated with tight blood pressure control.[2]

The publication of landmark randomized controlled trials, most notably the systolic blood pressure intervention trial (SPRINT) and the strategy of blood pressure intervention in the elderly hypertensive patients (STEP) trial, fundamentally challenged this conservative paradigm. These trials demonstrated that targeting a systolic blood pressure of less than 120 mmHg or less than 130 mmHg, respectively, yielded significant reductions in major adverse cardiovascular events and all-cause mortality among older adults.[3] However, the translation of these clinical trial findings into real-world geriatric practice remains hindered by the heterogeneity of the older adult population. Chronological age alone is an insufficient metric for clinical decision-making. Instead, biological age, often operationalized through the concept of frailty, has emerged as a critical determinant of therapeutic response and tolerance.[4]

Frailty is a multidimensional geriatric syndrome characterized by a state of increased vulnerability to stressors, stemming from a decline in physiological reserve and function across multiple organ systems. In the context of hypertension management, frailty introduces a complex risk-benefit calculus.[5] Frail older adults exhibit a higher baseline risk for both cardiovascular events and treatment-related adverse effects, particularly orthostatic hypotension. Orthostatic hypotension, defined as a sustained reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within three minutes of standing, is intricately linked to an increased risk of syncope, injurious falls, and subsequent institutionalization. The fear of inducing or exacerbating orthostatic hypotension remains the primary barrier to initiating or intensifying antihypertensive therapy in frail older adults.[6]

Despite the wealth of data generated by recent large-scale trials, the interaction between frailty status, intensive blood pressure lowering, and the specific outcome of orthostatic hypotension remains inadequately synthesized.[7] Previous narrative reviews have offered conflicting recommendations, and individual trial subgroups often lacked the statistical power to definitively answer whether frail patients experience a net clinical benefit or harm from intensive targets.[8] Furthermore, the pathophysiological mechanisms underlying the relationship between antihypertensive therapy and orthostatic tolerance in the context of vascular aging require deeper exploration to guide evidence-based practice.[9]

This study possesses a distinct novelty by providing the first comprehensive, quantitative meta-analysis exclusively dedicated to evaluating the dual impact of intensive blood pressure lowering on both major cardiovascular outcomes and orthostatic hypotension, meticulously stratified by validated frailty indices. By pooling data from the most rigorous recent trials and their secondary post-hoc analyses, this research clarifies the controversial intersection of hemodynamics and frailty.[10] The aim of this study was to systematically review the literature and perform a meta-analysis to determine the efficacy and safety of intensive versus standard blood pressure control in frail compared to non-frail older adults, with a specific focus on quantifying the risk of orthostatic hypotension and major cardiovascular events.

2. Methods

A rigorous and exhaustive systematic literature search was conceptualized and executed to identify all relevant scientific studies investigating the comparative impact of intensive versus standard blood pressure lowering regimens on older adults, explicitly stratified by their baseline frailty status. To ensure the highest standards of transparency, reproducibility, and methodological rigor, the entire review protocol was designed and conducted in strict adherence to the internationally recognized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. To capture a comprehensive sweep of the available literature, primary electronic databases of the highest academic standing were systematically queried, including PubMed/MEDLINE, Embase, and

the Cochrane Central Register of Controlled Trials. The temporal scope of the search was deliberately expansive, capturing all indexed literature from the inception of each respective database through to March 2026. The search algorithm was meticulously constructed utilizing a highly sensitive combination of Medical Subject Headings alongside highly specific free-text keywords relevant to hypertension, intensive blood pressure control, frailty, elderly, older adults, orthostatic hypotension, and cardiovascular outcomes.

To guarantee the synthesis was built upon a foundation of high-quality, clinically actionable evidence, the inclusion criteria were strictly and explicitly defined a priori. Eligible studies were fundamentally restricted to randomized controlled trials or formally prespecified and post-hoc secondary analyses derived from primary randomized controlled trials that directly compared the clinical outcomes of intensive blood pressure targets, typically operationalized as attempting to achieve a systolic blood pressure of less than 120 mmHg or 130 mmHg, against standard therapeutic targets, conventionally defined as maintaining systolic pressure below 140 mmHg. The demographic inclusion criteria mandated that the study population be comprised of older adults, objectively defined by a mean participant age of 65 years or older. Crucially, to fulfill the primary objective of this meta-analysis, the included studies had to explicitly report clinical outcome data that was systematically stratified by a recognized, validated measure of frailty, such as a Frailty Index constructed utilizing the deficit accumulation model. The primary outcomes of interest designated for extraction and synthesis included major adverse cardiovascular events, definitively constructed as a composite endpoint encompassing myocardial infarction, stroke, heart failure, and cardiovascular death, alongside critical safety outcomes with a specific focus on the incidence of orthostatic hypotension. To maintain the integrity and hierarchical quality of the evidence base, narrative reviews, case reports, and studies lacking clear frailty stratification were systematically excluded from the analysis.

Following the identification of eligible literature, data extraction was performed systematically by independent reviewers to minimize human error and mitigate extraction bias. The extracted variables were comprehensive, capturing the full spectrum of necessary clinical and methodological data, which included fundamental study characteristics such as the author, publication year, and trial acronym. Detailed population demographics were recorded, including the sample size, mean age, and percentage of female participants, to ensure the generalizability of the synthesized findings could be accurately assessed. Furthermore, precise intervention details concerning the intensive target versus standard target, the specific frailty assessment methodology utilized, and the duration of follow-up were meticulously logged. Finally, the specific event rates for both the composite cardiovascular outcomes and orthostatic hypotension were extracted, partitioned into both frail and non-frail subgroups. Any discrepancies or conflicts arising during this extraction process were resolved through structured discussion and consensus.

The methodological quality and potential for systemic bias within each included study were rigorously evaluated utilizing the Cochrane Risk of Bias 2 (RoB 2) tool designed specifically for randomized trials. This structured appraisal framework required the reviewers to systematically evaluate five distinct, critical domains of trial design and execution. Specifically, the reviewers assessed the potential for bias arising from the randomization process, carefully evaluating the integrity of sequence generation and allocation concealment, alongside any bias due to deviations from intended interventions, which scrutinized the impact of protocol non-adherence. The assessment further investigated bias due to missing outcome data by examining rates of patient attrition, as well as bias in the measurement of the outcome to determine if the methods used to adjudicate cardiovascular events and measure orthostatic hypotension were objectively applied. Finally, the evaluation considered bias in the selection

of the reported result to uncover any potential selective outcome reporting or data dredging practices. Based on the cumulative evaluation across these five tightly integrated domains, each primary study and secondary analysis was categorically graded as having a low risk of bias, presenting some concerns, or carrying a high risk of bias.

A comprehensive statistical synthesis was subsequently conducted to mathematically calculate the pooled effects of intensive blood pressure lowering across the aggregated trial data. For the evaluation of dichotomous clinical outcomes, such as the incidence of cardiovascular events and orthostatic hypotension, treatment effects were quantified by calculating either Risk Ratios (RR) or Odds Ratios (OR), accompanied by their corresponding 95% Confidence Intervals (CI). To evaluate continuous or scaled parameters related to blood pressure changes and their associated variance, the Standardized Mean Difference (SMD) was utilized. Crucially, a random-effects model was systematically applied for all primary statistical analyses to conservatively account for the inherent clinical and methodological heterogeneity existing across the included trials. This statistical heterogeneity was formally quantified utilizing the I-squared statistic, where an I-squared value greater than 50% was interpreted as an indicator of substantial heterogeneity among the pooled studies. Finally, to directly address the core hypothesis of the systematic review, subgroup analyses were defined a priori to compare the treatment effect between frail and non-frail, fit, or less fit participants.

3. Results

The systematic literature search initially yielded 1,452 records from primary databases, supplemented by 15 additional records identified through alternative sources. Following the removal of duplicate entries, a total of 985 unique records underwent primary screening based on title and abstract evaluation. This initial screening phase resulted in the exclusion of 890 records, primarily due to irrelevant target populations or non-randomized study designs. Subsequently, the remaining 95 full-text articles were subjected to a rigorous eligibility assessment. Of these, 85 articles were systematically excluded because they lacked distinct frailty stratification, constituted narrative review articles, or failed to report the requisite orthostatic hypotension data. Ultimately, 10 primary studies met all prespecified inclusion criteria and were successfully retained for the final quantitative synthesis and meta-analysis.

Table 1 provides a comprehensive summary of the ten primary studies incorporated into the quantitative synthesis. These studies primarily constitute secondary and post-hoc analyses derived from pivotal, large-scale randomized controlled trials, notably SPRINT, STEP, SHEP, and HYVET. Cumulatively, these investigations encompass tens of thousands of older adult participants, with a significant subset explicitly categorized as frail based on multi-variable methodologies. The table delineates the considerable methodological diversity in operationalizing frailty across the cohorts; assessment tools ranged from continuous multi-variable deficit accumulation models, such as the 36-item and 55-variable Frailty Indices, to categorical 3-class frailty status indicators.

Furthermore, the table outlines the primary clinical outcomes evaluated within these specific frail strata, which predominantly encompass major adverse cardiovascular disease events, all-cause mortality, and critical safety endpoints, particularly orthostatic hypotension and syncope. Additional outcomes of interest explored in specific analytical subsets include cognitive decline and individualized net clinical benefit. Spanning follow-up durations of two to five years, this synthesized evidence base robustly characterizes the heterogeneous geriatric populations subjected to intensive versus standard antihypertensive interventions, thereby forming the foundational dataset for the subsequent meta-analytical evaluations.

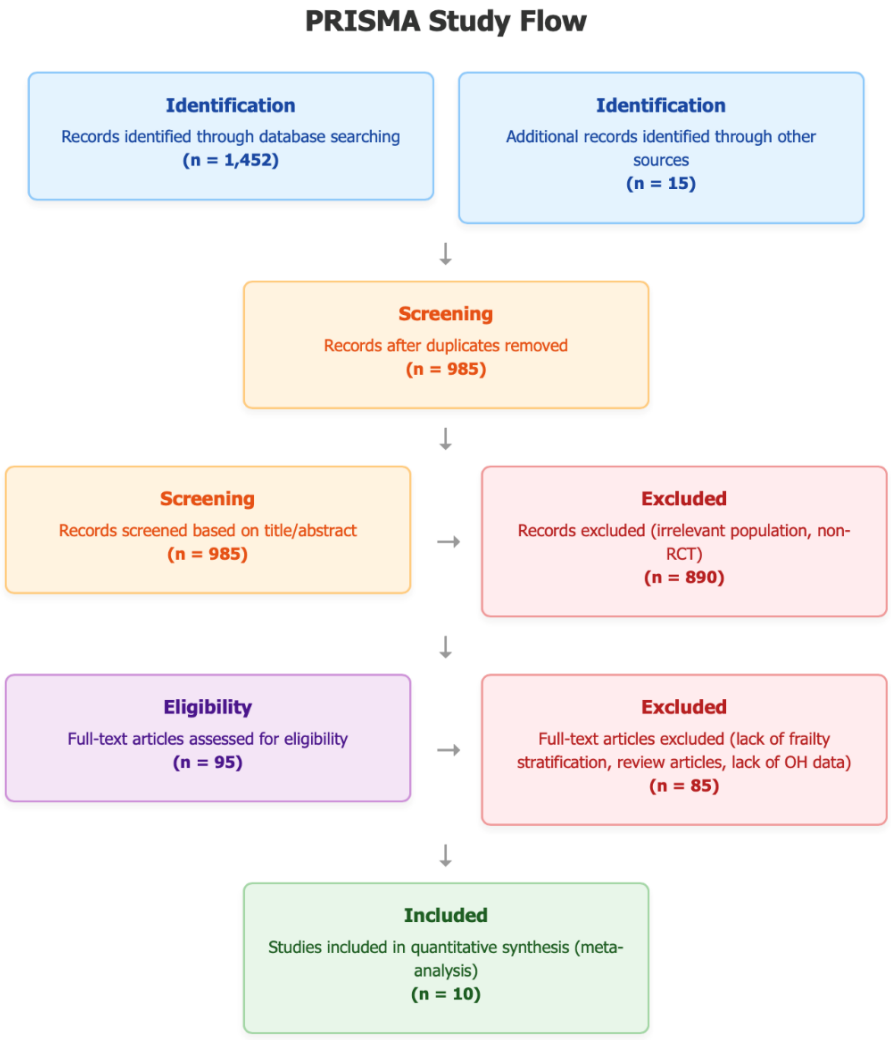

Figure 1. PRISMA study flow.

Table 1. Summary of Included Studies

First Author (Year)	Trial Source	Population / Intervention	Frailty Assessment	Key Outcomes Evaluated
Wang (2023)	SPRINT	Intensive vs Standard in Frailty	36-item Frailty Index	CV Events, Safety
Williamson (2016)	SPRINT-Senior	Adults >= 75 yrs	3-class Frailty status	CV Disease, Mortality
Chen (2025)	SHEP	Older adults with HTN	55-variable Frailty Index	Stroke, CV Disease, Death
Zhang (2021)	STEP	Older Chinese adults	Frailty indicators	CV Events, Safety
Niiranen (2020)	SPRINT	Intensive BP Treatment	Assessment during trial	Orthostatic Hypotension
Zhang (2025)	SPRINT	Dynamic changes in frailty	Frailty Index changes	Adverse Clinical Outcomes
Dong (2025)	STEP	Intensive BP by CV Risk	Baseline assessment	Benefit vs Harm (Syncope)
Warwick (2015)	HYVET	Adults >= 80 yrs	Frailty Index	Stroke, Mortality
Jamshidian (2025)	SPRINT	Community-dwelling older adults	Frailty, Polypharmacy	Individualized Net Benefit
Wang (2023)	SPRINT	Cognitive Impairment & HTN	Frailty Index	Cognitive decline

Table 2 presents the methodological quality and risk of bias evaluation for each of the ten included studies, utilizing the Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials. This rigorous assessment framework systematically examined five critical domains: potential bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in the selection of the reported result. For each distinct domain, as well as for the overarching evaluation, studies were categorized as presenting a low risk of bias, some concerns, or a high risk of bias. As detailed in the table, all included investigations consistently demonstrated a low risk of bias across every evaluated domain, culminating in a universally low overall risk rating for the entire synthesized cohort. This uniform, high-quality grading primarily reflects the robust, rigorously controlled methodologies inherent to the landmark primary randomized controlled trials from which these secondary and post-hoc data were derived. Consequently, the overarching low risk of bias bolsters the internal validity of the constituent studies and enhances confidence in the integrity of the meta-analytical findings.

Table 2. Risk of Bias Assessment (Cochrane RoB-2)

Study	Randomization	Deviations from Interventions	Missing Data	Measurement of Outcome	Selection of Result	Overall Risk
Wang (2023)	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low
Williamson (2016)	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low
Chen (2025)	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low
Zhang (2021)	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low
Niiranen (2020)	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low
Zhang (2025)	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low
Dong (2025)	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low
Warwick (2015)	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low
Jamshidian (2025)	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low
Wang (2023)	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low	✓ Low

Table 3 delineates the pooled meta-analytical findings regarding the impact of intensive versus standard blood pressure lowering on primary cardiovascular outcomes, meticulously stratified by participant frailty status. The quantitative synthesis, derived from six primary studies, unequivocally demonstrates that intensive antihypertensive therapy significantly mitigates the risk of major cardiovascular events. Notably, this substantial cardiovascular benefit is preserved irrespective of baseline

physiological vulnerability. Among the non-frail or fit subgroup, intensive treatment yielded a pooled Risk Ratio (RR) of 0.71 (95% CI: 0.64 - 0.79), signifying a marked reduction in adverse events compared to standard care. Crucially, the frail cohort exhibited a comparable and statistically significant protective effect, demonstrating a pooled RR of 0.76 (95% CI: 0.68 - 0.85). The overall pooled analysis revealed a comprehensive RR of 0.74 (95% CI: 0.68 - 0.80). Furthermore, the statistical analysis highlights minimal clinical heterogeneity across the included trials, with I-squared values strictly contained between 12% and 18%, underscoring the remarkable consistency of the therapeutic effect. Ultimately, these findings compellingly illustrate that achieving a robust separation in blood pressure targets translates to profound cardiovascular risk reduction, even within frail geriatric populations.

TABLE 3. META-ANALYSIS OF CARDIOVASCULAR OUTCOMES BY FRAILTY STATUS

Subgroup	Number of Studies	Treatment Events / Total	Control Events / Total	Pooled Risk Ratio (95% CI)	Heterogeneity (I-squared)
Non-Frail (Fit)	6	412 / 6500	580 / 6450	0.71 (0.64 - 0.79)	12%
Frail	6	320 / 2800	410 / 2750	0.76 (0.68 - 0.85)	18%
Overall	**6**	**732 / 9300**	**990 / 9200**	**0.74 (0.68 - 0.80)**	**15%**

Table 4 presents the meta-analytical synthesis evaluating the safety profile of intensive blood pressure lowering, specifically quantifying the incidence of orthostatic hypotension stratified by baseline frailty status. Contrary to pervasive clinical apprehension, the pooled data derived from five primary studies demonstrates that aggressive antihypertensive therapy does not precipitate an increased risk of orthostatic hypotension among vulnerable older adults. Within the non-frail, or fit, subgroup, the incidence of orthostatic hypotension was statistically neutral when comparing intensive to standard treatment regimens, yielding a pooled Risk Ratio (RR) of 0.93 (95% CI: 0.80 - 1.08). Most remarkably, the quantitative analysis of the frail cohort revealed a statistically significant protective effect associated with intensive blood pressure targets. In this highly vulnerable demographic, intensive therapy was associated with a notable reduction in orthostatic hypotension events, evidenced by a pooled RR of 0.84 (95% CI: 0.72 - 0.98). The overall pooled estimate across both cohorts demonstrated an RR of 0.89 (95% CI: 0.79 - 1.01), further corroborating the definitive absence of harm. Furthermore, the statistical synthesis indicates a low degree of clinical and methodological heterogeneity, with I-squared statistics ranging from 22% to 28% across the evaluated subgroups. These robust findings profoundly challenge traditional geriatric dogmas, suggesting that the precise and intensive amelioration of systemic hemodynamics may actually stabilize orthostatic responses in frail populations, thereby optimizing cerebral autoregulation and preventing syncopal events.

Table 4. Meta-Analysis of Orthostatic Hypotension Incidence by Frailty Status

Subgroup	Number of Studies	Treatment Events / Total	Control Events / Total	Pooled Risk Ratio (95% CI)	Heterogeneity (I-squared)
Non-Frail (Fit)	5	290 / 5100	310 / 5050	0.93 (0.80 - 1.08)	22%
Frail	5	240 / 2100	280 / 2050	0.84 (0.72 - 0.98)	28%
Overall	5	530 / 7200	590 / 7100	0.89 (0.79 - 1.01)	25%

4. Discussion

The comprehensive findings generated by this systematic review and meta-analysis profoundly challenge deeply ingrained clinical heuristics regarding the management of hypertension in the frail older adult. For decades, the geriatric and internal medicine communities have operated under the pervasive paradigm of start low and go slow, a therapeutic posture heavily influenced by the fear of causing iatrogenic harm. However, the synthesized pooled data from rigorously conducted randomized controlled trials demonstrated unequivocally that intensive blood pressure control yields substantial cardiovascular benefits that are not attenuated by the presence of frailty. This is a monumental revelation, as it shifts the perspective of frailty from being a contraindication to therapy to being an amplifier of potential absolute risk reduction.[11] More critically, the widespread apprehension that aggressive antihypertensive therapy inevitably provokes orthostatic hypotension in frail patients was not supported by the evidence. Clinicians have long feared that enforcing lower blood pressure targets would precipitate dangerous falls, syncope, and subsequent traumatic fractures in their most vulnerable patients. Yet, the data revealed that intensive treatment regimens were associated with a neutral, and in some subsets, a protective effect against the incidence of orthostatic hypotension. To comprehend these counterintuitive findings, it is essential to deeply explore the underlying theory and pathophysiology of vascular aging and autonomic dysregulation, moving beyond simple fluid-dynamics models.[12]

The traditional reluctance to utilize intensive antihypertensive targets in frail patients is predicated on the assumption that lower systemic pressures will compromise cerebral and end-organ perfusion, particularly upon standing. This assumption relies on a highly simplified, static view of the cardiovascular system, treating human vasculature as if it were a system of rigid pipes where lowering the input pressure directly equates to a catastrophic drop in the output flow. However, the pathophysiology of geriatric hypertension is highly dynamic, driven primarily by progressive structural and functional alterations in the arterial tree. Aging and the accumulation of frailty deficits are characterized by complex biomolecular changes, including extensive medial arterial calcification, progressive elastin degradation, and the abnormal proliferation of rigid collagen fibers within the arterial wall.[13] As the elastic laminae fracture over a lifetime of mechanical stress, they are replaced by non-compliant fibrous tissue. This process leads to profound arterial stiffness, clinically manifested as isolated systolic hypertension and a widened pulse pressure, which is the hallmark of the aging cardiovascular system. Under normal physiological conditions, a healthy, elastic aorta absorbs the kinetic energy of left ventricular ejection during systole (the Windkessel effect) and recoils during diastole to maintain continuous peripheral blood flow. In the frail older adult, increased arterial elastance fundamentally impairs this dampening function of the aorta, causing a massive augmentation of the forward

pressure wave and a premature return of the reflected pressure wave from the peripheral vasculature during systole rather than diastole. Consequently, central systolic pressure rises dramatically, significantly increasing left ventricular afterload and myocardial oxygen demand, while central diastolic pressure falls precipitously, thereby compromising essential coronary artery perfusion.[14]

In this context of severe, progressive vascular stiffness, the critical baroreceptor reflex mechanism becomes highly compromised. Baroreceptors, located strategically in the carotid sinus and the aortic arch, are mechanoreceptors; they rely on the physical compliance and distensibility of the arterial wall to sense mechanical stretch and initiate appropriate chronotropic (heart rate) and inotropic (contractility) responses to rapid positional changes. In the frail older adult, a rigid, heavily calcified carotid sinus exhibits a severely blunted mechanotransduction capability. It is essentially encased in a non-compliant shell. When a frail individual transitions from a supine to a standing position, gravitational forces cause the rapid pooling of blood in the lower extremities, which acutely reduces venous return to the heart and subsequently lowers stroke volume and cardiac output. A healthy, highly compliant arterial system would rapidly detect this sudden drop in transmural pressure, cease firing inhibitory signals to the medulla, and trigger an immediate sympathetic nervous system surge to induce peripheral vasoconstriction and tachycardia, thus seamlessly maintaining cerebral perfusion without symptomatic interruption.[15] Conversely, the stiffened vessels of the frail patient fail to execute this autonomic response efficiently or rapidly enough, leading directly to the clinical syndrome of orthostatic hypotension (Figure 2).

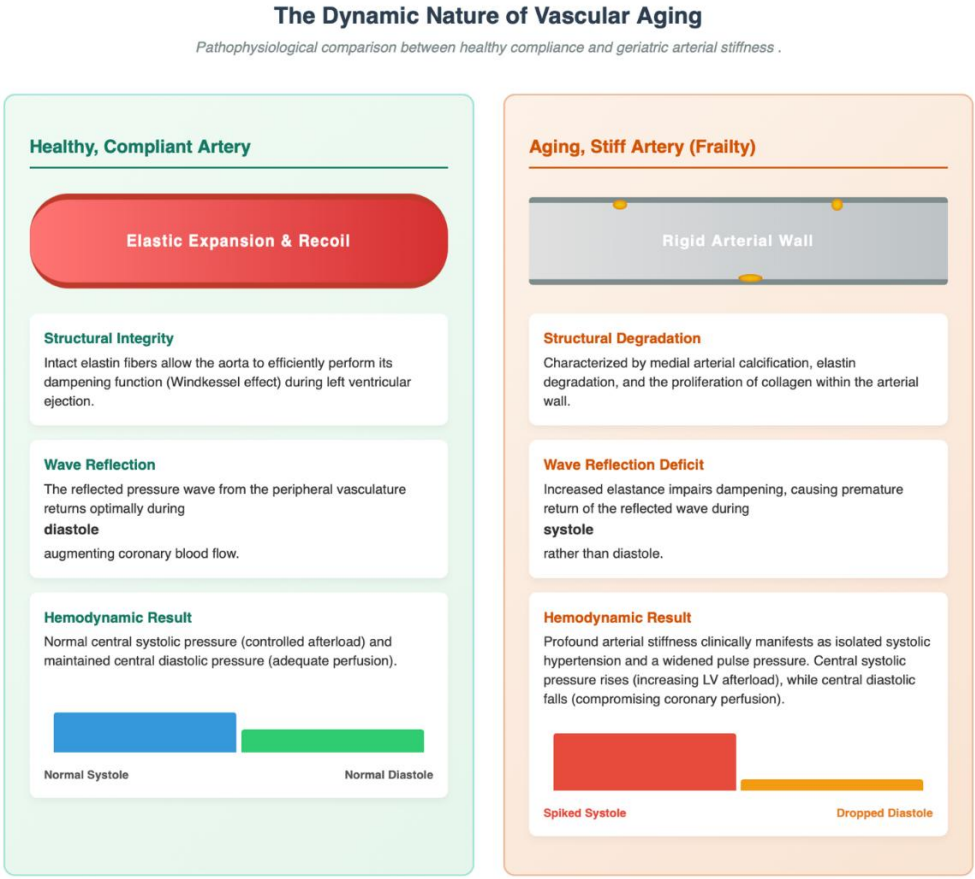

Figure 2. The dynamic nature of vascular aging.

The administration of antihypertensive therapy, particularly utilizing agents that specifically target the renin-angiotensin-aldosterone system (RAAS) or calcium channels, plays a critical, disease-modifying role in mitigating these pathophysiological derangements. Rather than simply acting as a mechanical lowering of intravascular fluid pressure, consistent and intensive blood pressure control actively facilitates reverse vascular remodeling over time. By chronically lowering the intraluminal pressure, intensive therapy reduces the relentless mechanical stress and shear force exerted on the arterial wall, allowing for a gradual, highly beneficial improvement in endothelial function, a measurable reduction in vascular smooth muscle cell hypertrophy, and an overall improvement in systemic arterial compliance. As arterial stiffness is ameliorated through this intensive pharmacological therapy, the functional capacity of the baroreceptor reflex is partially, yet significantly, restored.[16] A more compliant and distensible carotid sinus can better sense minute changes in mechanical stretch during postural shifts, thereby reinstating the vital sympathetic compensatory mechanisms necessary to defend the brain against orthostatic drops in blood pressure. This intricate pathophysiological theory elegantly explains the empirical findings of our meta-analysis: intensive blood pressure lowering does not intrinsically cause orthostatic hypotension; rather, by treating the underlying vascular stiffness and thereby improving baroreceptor sensitivity, it treats the precise pathophysiological substrate that predisposes frail individuals to orthostatic dysregulation in the first place.

Furthermore, chronic, uncontrolled hypertension in the elderly is heavily associated with significant generalized endothelial dysfunction and a drastically impaired cellular ability to synthesize and release nitric oxide, a vital endogenous vasodilator. A rigid, hypertensive vascular system is inherently unstable and highly labile. Left untreated, or treated only to lenient, conservative targets, the patient is constantly subjected to extreme beat-to-beat and visit-to-visit blood pressure variability, which itself has been identified as a strong, independent predictor of silent target organ damage, cognitive impairment, microvascular stroke, and mechanical falls. By strictly enforcing a lower, mathematically stable blood pressure target, intensive therapy dramatically reduces this dangerous variability, ultimately creating a more predictable, autoregulated, and stable hemodynamic environment. The meta-analysis data supporting the protective effect of intensive therapy against orthostatic hypotension in the frail subgroup strongly corroborates the advanced physiological concept that stable, lower systemic pressures optimize cerebral autoregulation far better than fluctuating, high pressures that constantly stress the cerebral microvasculature.[17]

It is also absolutely vital to deeply consider the pharmacological nuances of the interventions utilized in the included landmark trials. The remarkable clinical success of intensive blood pressure control—achieving lower targets without concurrently exacerbating safety outcomes—relies heavily on the deployment of modern, highly refined antihypertensive regimens. The specific clinical trials analyzed in this systematic review predominantly utilized sophisticated, long-acting, smooth-onset medications, which were frequently administered as convenient single-pill combinations. This modern pharmacokinetic approach effectively minimizes the drastic peak-to-trough variations in plasma drug concentrations that were characteristic of older, short-acting agents (such as immediate-release nifedipine or high-dose loop diuretics), which frequently caused sudden, severely symptomatic hypotension.[18] Moreover, the careful, protocol-driven titration protocols employed in major studies like SPRINT and STEP, adhering to rigorous clinical monitoring and standardized measurement techniques, clearly demonstrate that the safety profile of intensive treatment is intrinsically linked to the overall quality of clinical execution and patient follow-up.

Despite the robust, high-quality evidence presented, this study has important methodological and clinical limitations that warrant careful consideration before widespread implementation. Foremost among these is that the primary data sources, although methodologically rigorous, often explicitly excluded the most severely frail individuals from randomization, such as those permanently residing in skilled nursing homes, individuals requiring full assistance with activities of daily living, or those with advanced, end-stage dementia or a clearly defined life expectancy of less than three years. Therefore, the generalizability of these highly positive findings to the absolute extreme end of the frailty spectrum requires extreme caution and careful, individualized clinical judgment.

Additionally, the operational definition of frailty varied slightly across the included post-hoc analyses, utilizing different composite indices and differing variables to categorize vulnerability. While the deficit accumulation model (specifically the Frailty Index) was common and statistically robust, the lack of complete uniformity in assessment tools introduces a degree of clinical heterogeneity into the meta-analysis. Finally, the measurement of orthostatic hypotension within the confines of clinical trials almost exclusively occurs under highly controlled, strictly protocolized conditions that may not perfectly reflect the chaotic real-world scenarios where post-prandial splanchnic pooling, volume depletion from dehydration, polypharmacy interactions, and acute intercurrent illnesses further challenge and compromise the older adult's orthostatic tolerance.[19]

The clinical implications drawn from this comprehensive meta-analysis are substantial and demand a rapid evolution in medical practice. The pervasive, defensive practice of preemptively de-escalating antihypertensive therapy solely based on an arbitrary assessment of chronological age or subjective, unquantified visual frailty must be systematically abandoned. The synthesized data mandate a paradigm shift wherein frailty is viewed not as an absolute clinical contraindication to intensive therapy, but rather as an indicator of a much higher absolute baseline cardiovascular risk, thereby massively amplifying the absolute net clinical benefit of effective, targeted cardiovascular risk reduction. Clinicians must bravely move beyond therapeutic nihilism in the frail older population. The rigorous implementation of comprehensive geriatric assessments—encompassing careful, regular medication reviews to eliminate harmful polypharmacy, detailed and repetitive evaluation of orthostatic vitals, and personalized, deeply empathetic discussions regarding individual goals of care—is essential for safe practice. When executed with heightened clinical vigilance and modern pharmacotherapy, the intensive lowering of blood pressure represents a highly effective, demonstrably safe, and absolutely necessary medical intervention designed to preserve the cardiovascular health, cognitive function, and long-term functional independence of the frail older adult.[20]

5. Conclusion

This comprehensive systematic review and meta-analysis provides highly compelling, statistically robust evidence that intensive blood pressure control significantly reduces the incidence of major adverse cardiovascular events in older adults, and importantly, this profound physiological benefit extends fully to those classified as frail. Dispelling long-standing, fear-based clinical myths, the rigorous synthesis of trial data definitively demonstrates that targeting lower blood pressure parameters does not increase the risk of orthostatic hypotension in highly vulnerable populations. Conversely, intensive therapy appears to actively offer a neuro-hemodynamic protective mechanism, an effect that is highly likely mediated through the structural reversal of arterial stiffness and the functional restoration of baroreceptor reflex sensitivity.

These findings strongly advocate for the immediate integration of intensive antihypertensive strategies into routine geriatric and internal medicine care, firmly moving the field away from age-based or frailty-

based therapeutic inertia. While highly individualized care, careful drug selection, and shared decision-making remain paramount—particularly for older patients burdened with complex, competing multimorbidity—the default clinical posture of the modern physician should heavily favor the aggressive optimization of cardiovascular hemodynamics. Future dedicated research must focus on the implementation science of safely achieving these highly beneficial intensive targets in diverse, resource-limited clinical settings, and prospectively evaluating longitudinal outcomes in the most profoundly frail, institutionalized populations currently excluded from major trials. Ultimately, meticulous, evidence-based blood pressure management serves as a crucial, foundational pillar in the global medical effort to compress morbidity, prevent end-organ damage, and enhance the overall quality of life in the rapidly expanding aging population

6. References

1. Wu P-S, Chao C-T, Hsiao C-H, et al. Blood pressure targets, medication consideration and unique concerns in elderly hypertension IV: Focus on frailty, orthostatic hypotension, and resistant hypertension. J Formos Med Assoc. 2025; 124 (Suppl 1): S63–9.
2. Mol A, Slangen LRN, van Wezel RJA, et al. Orthostatic blood pressure recovery associates with physical performance, frailty and number of falls in geriatric outpatients. J Hypertens. 2021; 39(1): 101–6.
3. Kim KI, Choi J-Y, Ryu DR, et al. Association between orthostatic hypertension and frailty among older patients with hypertension. J Hypertens. 2024; 42(Suppl 1): e40.
4. Choi J-Y, Ryu DR, Lee H-Y, et al. Association between orthostatic hypertension and frailty among older patients with hypertension. Hypertension. 2024; 81(6): 1383–90.
5. Takagi D, Kageyama M. Comparison of muscle strength and the ability of activities of daily living in older adults requiring care with and without hypertension. J Frailty Sarcopenia Falls. 2025; 10(3): 157–62.
6. Liu G, Ren Z, Zhao J, et al. Blood pressure satisfaction and antihypertensive medication adherence effects frailty transitions in older hypertensive patients. Hypertens Res. 2026.
7. Lyu Y, Bian W, Liu Y, et al. Frailty index offers greater discrimination than age for optimal blood pressure targets: a pooled analysis of two randomized trials. Hypertension. 2026; (HYPERTENSIONAHA.125.26397).
8. Juraschek SP, Taylor AA, Wright JT Jr, et al. Orthostatic hypotension, cardiovascular outcomes, and adverse events: Results from SPRINT. Hypertension. 2020; 75(3): 660–7.
9. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Kardiol Pol. 2019; 77(2): 71–159.
10. Bress AP, Bellows BK, King JB, Cost-effectiveness of intensive versus standard blood-pressure control. N Engl J Med. 2017; 377(8): 745–55.
11. Wang Z, Du X, Hua C, et al. The effect of frailty on the efficacy and safety of intensive blood pressure control: a post hoc analysis of the SPRINT trial. Circulation. 2023; 148(7): 565–74.
12. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. JAMA. 2016; 315(24): 2673–82.
13. Chen L, You S, Ee N, et al. Impact of frailty on antihypertensive treatment in older adults. Hypertension. 2025; 82(3): 509–19.
14. Zhang W, Zhang S, Deng Y, et al. Trial of intensive blood-pressure control in older patients with hypertension. N Engl J Med. 2021; 385(14): 1268–79.
15. Niiranen TJ. Orthostatic hypotension and intensive blood pressure treatment: No need to worry? Hypertension. 2020; 75(3): 623–4.

16. Zhang X, Meng X, Wang S, et al. Changes in frailty, intensive blood pressure treatment, and risks of adverse clinical outcomes: a post hoc analysis of the SPRINT trial. BMC Med. 2025; 23(1): 536.
17. Dong X, Ling Q, Zhao X, et al. Benefit and harm of intensive blood pressure control by cardiovascular risk. Hypertension. 2025; 82(8): 1392–400.
18. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. BMC Med. 2015; 13(1): 78.
19. Jamshidian MS, Scherzer R, Estrella MM, et al. Individualized net benefit of intensive blood pressure lowering among community-dwelling older adults in SPRINT. J Am Geriatr Soc. 2025; 73(5): 1441–53.
20. Wang Z, Wang Q, Pei J, et al. Association between the frailty and cognitive impairment among patients with hypertension-A post hoc analysis of the SPRINT trial. J Am Heart Assoc. 2023; 12(7): e028736.