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Clinical Outcomes of Rapid Versus Gradual Blood Pressure Normalisation in Asymptomatic Hypertensive Urgency: A Systematic Review and Meta-Analysis

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A B S T R A C T

Hypertensive urgency presents a clinical dilemma regarding optimal blood pressure management. Whilst guidelines advocate gradual reduction to prevent organ damage through vascular autoregulation disruption, rapid normalisation remains common in clinical practice. This systematic review and meta-analysis synthesised evidence comparing rapid and gradual blood pressure normalisation strategies in asymptomatic hypertensive urgency. Systematic searches of Scopus, PubMed/MEDLINE, and Embase were conducted. Nine randomised or quasi-randomised controlled trials were included involving 4,195 adult participants with asymptomatic hypertensive urgency. Studies compared rapid blood pressure normalisation with gradual reduction over various timeframes. Primary outcomes included acute kidney injury (AKI), symptomatic hypotension, and major adverse cardiovascular events (MACE). Random-effects meta-analysis using standardised mean difference (Hedges' g) was performed. Rapid blood pressure normalisation was associated with significantly higher adverse events compared with gradual reduction (pooled SMD = 0.8854, 95% confidence interval [0.6235–1.1472], $p < 0.000001$; $I^2 = 61.11\%$). Subgroup analysis revealed substantial effects for AKI (SMD = 0.9199, $p = 0.000012$) and symptomatic hypotension (SMD = 1.0103, $p < 0.001$), whilst MACE showed no significant difference (SMD = 0.3777, $p = 0.435$). Heterogeneity was moderate to substantial ($I^2 = 61.11\%$, $Tau^2 = 0.0881$). Sensitivity analyses demonstrated robust findings. In conclusion, gradual blood pressure reduction in asymptomatic hypertensive urgency was superior to rapid normalisation, particularly for preventing acute kidney injury and symptomatic hypotension. These findings support current guideline recommendations for cautious, titrated antihypertensive strategies in this population.

1. Introduction

Hypertension remains one of the most significant public health challenges globally, affecting over 1.2 billion individuals and contributing substantially to cardiovascular morbidity and mortality.[1] Whilst long-term management of chronic hypertension has received considerable attention in clinical guidelines and research, hypertensive crises—encompassing both hypertensive emergency and hypertensive urgency—represent acute, life-threatening conditions requiring immediate clinical attention. These presentations occur in approximately 1–2% of individuals with hypertension and constitute 3–6% of emergency department visits in developed nations. The clinical and economic burden of hypertensive crises is profound, necessitating hospitalisation, intensive monitoring, and pharmacological intervention.[2]

Distinguishing between hypertensive emergency and hypertensive urgency is paramount for appropriate management and prognosis. A

hypertensive emergency is defined as markedly elevated blood pressure (typically systolic blood pressure ≥180 mmHg or diastolic ≥120 mmHg) in the presence of acute end-organ damage, manifesting as acute myocardial infarction, acute stroke, acute pulmonary oedema, aortic dissection, or other life-threatening complications.[3] In contrast, hypertensive urgency involves severely elevated blood pressure without clinical evidence of acute end-organ injury—the patient is asymptomatic from a cardiovascular standpoint despite the marked elevation. This distinction carries profound implications for management strategy; whilst hypertensive emergencies necessitate rapid, aggressive, and often intravenous antihypertensive therapy to prevent or arrest organ damage, the management of asymptomatic hypertensive urgency remains contentious and inadequately standardised across clinical settings.[4]

A fundamental physiological concept underpinning blood pressure management is the phenomenon of vascular autoregulation—the intrinsic ability of blood vessels to maintain constant blood flow and organ perfusion despite fluctuations in systemic arterial pressure.[5] In individuals with chronic hypertension, the pressure-flow autoregulation curve shifts rightward, meaning the lower threshold of autoregulation is elevated. Consequently, individuals with chronic hypertension tolerate higher blood pressures and may experience organ hypoperfusion at blood pressure levels considered normal in non-hypertensive individuals. Rapid reduction of severely elevated blood pressure may shift the perfusion pressure below the lower threshold of autoregulation, precipitating organ hypoperfusion, acute kidney injury, myocardial ischaemia, and stroke—paradoxically worsening the clinical outcome despite lowering the measured blood pressure value. This, treating the number rather than the patient, represents a critical pitfall in the management of hypertensive urgency.[6]

Current international guidelines from the American Heart Association (AHA), European Society of Hypertension (ESH), and European Society of Cardiology (ESC) recommend cautious, gradual reduction of blood pressure in asymptomatic hypertensive urgency. The AHA/American College of Cardiology guidelines suggest reducing blood pressure by no more than 25% in the first hour, with further gradual reduction over subsequent hours. Similarly, the ESC/ESH guidelines advocate for oral medications titrated over several hours, avoiding rapid parenteral administration. These recommendations are predicated on theoretical concerns regarding autoregulation disruption and organ hypoperfusion.[7] However, the evidence base supporting these recommendations in asymptomatic hypertensive urgency remains surprisingly sparse, and implementation varies considerably across institutions and healthcare systems. In many emergency departments, rapid reduction to normal blood pressure values remains common, driven by anxiety regarding absolute pressure values and concerns about imminent complications.[8]

The problem of overtreatment and treating the number extends beyond acute hypertensive urgency to encompass long-term hypertension management, where overly aggressive blood pressure lowering has been associated with increased cardiovascular events and mortality in some populations. The J-shaped curve phenomenon—whereby excessively low diastolic blood pressure is associated with adverse cardiovascular outcomes—underscores the hazards of aggressive blood pressure reduction.[9] Whether this phenomenon applies to acute blood pressure lowering in hypertensive urgency remains unclear, but the physiological rationale is compelling. Furthermore, rapid blood pressure reduction may precipitate iatrogenic acute kidney injury through abrupt reduction in glomerular filtration pressure, stroke from cerebral hypoperfusion, or myocardial infarction from coronary hypoperfusion—outcomes that would

substantially worsen rather than improve patient prognosis.

Notwithstanding guideline recommendations, substantial evidence base comparing rapid and gradual blood pressure normalisation strategies in asymptomatic hypertensive urgency have emerged over the past decade. Multiple randomised controlled trials have investigated outcomes with different treatment approaches, yet these studies remain dispersed throughout the literature and have not been systematically synthesised. A rigorous systematic review and meta-analysis synthesising all available evidence would provide definitive guidance regarding the optimal blood pressure reduction strategy in this common clinical scenario. Such a synthesis would inform clinical practice, enhance patient safety, and potentially reduce unnecessary harm from inappropriate rapid blood pressure lowering.[10]

The novelty of this study lies in its comprehensive synthesis of comparative effectiveness data on blood pressure management strategies in asymptomatic hypertensive urgency, utilising modern meta-analytical techniques to provide clinically actionable evidence. Prior reviews have been limited in scope, focusing on specific outcomes or including only observational data. The aim of this study was to conduct a systematic review and meta-analysis of randomised and quasi-randomised controlled trials comparing rapid blood pressure normalisation with gradual reduction in adults with asymptomatic hypertensive urgency, with the primary objective of determining which strategy minimises adverse clinical outcomes, particularly acute kidney injury, symptomatic hypotension, and major adverse cardiovascular events.

2. Methods

Search strategy and selection criteria

A comprehensive systematic search was conducted across three major bibliographic databases: Scopus, PubMed/MEDLINE, and Embase. Searches were performed using controlled vocabulary (Medical Subject Headings for MEDLINE and Emtree for Embase) combined with keyword searches. Search strategies were adapted for each database and combined multiple concepts, including hypertensive urgency, hypertensive crisis, blood pressure management, rapid reduction, and gradual reduction. The search strategy for PubMed/MEDLINE exemplifying the approach was: (("hypertensive urgency" OR "hypertensive crises" OR "severe hypertension") AND ("rapid reduction" OR "rapid control" OR "aggressive treatment" OR "immediate treatment") AND ("gradual reduction" OR "gradual control" OR "conservative treatment" OR "cautious management")). Searches were not restricted by language or publication year, enabling capture of all relevant evidence. The most recent search was completed on 31st March 2026. Additionally, reference lists of included studies and relevant systematic reviews were manually searched to identify any studies missed by database searching.

Retrieved citations were imported into EndNote X9 reference management software, and duplicate records were identified and removed. Two independent reviewers (RDN and MS) screened the titles and abstracts of all retrieved records against pre-specified eligibility criteria. Articles deemed potentially relevant were retrieved in full text and assessed independently for final inclusion. Disagreements regarding inclusion were resolved through discussion or consultation with a third reviewer (DS).

Eligibility criteria

Studies were included if they met the following criteria based on the PICO (Population, Intervention, Comparison, Outcomes) framework: Population: Adult participants (aged ≥18 years) presenting with asymptomatic hypertensive urgency, defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥120 mmHg without acute end-organ damage attributable to the blood pressure elevation.

Intervention: Rapid blood pressure normalisation, defined as achieving target blood pressure reduction (typically to <140/90 mmHg or <160/100 mmHg) within 1 hour or via immediate intravenous antihypertensive medication. Comparison: Gradual blood pressure reduction, defined as blood pressure lowering achieved over several hours (minimum 2 hours) using oral agents with titration as necessary. Outcomes: Primary outcomes were acute kidney injury (defined as an increase in serum creatinine ≥0.3 mg/dL or ≥50% from baseline, or reduction in urine output), symptomatic hypotension requiring intervention, and major adverse cardiovascular events (MACE, defined as a composite of myocardial infarction, stroke, or cardiovascular death). Secondary outcomes included mortality from any cause, cardiac arrhythmias, and hospital length of stay.

Study design inclusion criteria required randomised controlled trials (RCTs) or quasi-randomised controlled trials. Observational studies, case reports, and narrative reviews were excluded. Studies had to report numerical data enabling calculation of effect sizes or provide data permitting extraction of dichotomous or continuous outcome measures.

Data extraction

Data extraction was performed independently by two reviewers (RDN and MS) using a standardised, pre-piloted data extraction form. Extracted information included: study characteristics (author, year, country, study design), participant characteristics (age, gender distribution, baseline blood pressure, comorbidities), intervention details (antihypertensive agents used, target blood pressure, time to target), comparison group details, outcome measures with numerical data, and study quality indicators. Where studies reported outcomes in multiple formats (continuous and dichotomous), preference was given to continuous measures for meta-analysis. Authors were contacted for missing or unclear data; if clarification was not obtained, studies were analysed with available data and sensitivity analyses performed.

Quality assessment

Risk of bias assessment was performed independently by two reviewers using two complementary tools. The Newcastle-Ottawa Scale (NOS) was applied to quasi-randomised studies, assessing selection bias, comparability, and outcome assessment. Randomised controlled trials were assessed using the Cochrane Risk of Bias Tool 2.0 (RoB 2), evaluating risk of bias across domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of outcome, and selective reporting. Each domain was rated as low risk, some concerns, or high risk, with the overall risk of bias determined from domain ratings. Studies achieving low risk across all domains were classified as low risk of bias overall. Disagreements between reviewers were resolved through discussion.

Statistical analysis

Meta-analysis was conducted using R statistical software (version 4.3.2) with the metafor package. As outcomes were measured on different scales across studies, the standardised mean difference (SMD) was calculated with Hedges' g correction applied to account for small sample bias. For dichotomous outcomes, effect sizes were converted to SMD using the logit transformation. A random-effects model using the DerSimonian-Laird estimator was employed to account for anticipated between-study heterogeneity arising from variation in patient populations, antihypertensive regimens, and outcome definitions. The inverse-variance weighting method was utilised to combine effect sizes.

Heterogeneity was quantified using the I^2 statistic (ranging 0–100%, with I^2 > 50% considered substantial) and the Q test (chi-square test of heterogeneity). Tau^2 was calculated as an estimate of

between-study variance. Subgroup analyses were performed stratified by outcome type (acute kidney injury, symptomatic hypotension, major adverse cardiovascular events) to explore sources of heterogeneity and determine whether effect sizes differed systematically by outcome. Subgroup differences were assessed using meta-regression with outcome type as a categorical predictor.

Sensitivity analyses were conducted to evaluate the robustness of findings. A leave-one-out analysis was performed, iteratively removing each study and recalculating the pooled effect size to identify whether any single study exerted disproportionate influence on conclusions. Publication bias was assessed through visual inspection of a funnel plot (SMD versus standard error). Given the relatively small number of included studies (k = 9, below the recommended threshold of k ≥ 10 for Egger's regression test), formal statistical testing for publication bias was not performed; instead, visual asymmetry in the funnel plot was assessed. A priori significance threshold was set at $p < 0.05$ for two-tailed tests.

3. Results and Discussion

The systematic search identified 1,452 potentially relevant citations. Following the removal of 340 duplicate records, 1,112 unique citations were screened by title and abstract. Of these, 1,025 were excluded as not meeting the inclusion criteria, leaving 87 articles for full-text review. After detailed assessment, 78 articles were excluded (reasons: 45 observational studies, 22 lacking relevant outcomes, 7 review articles, 4 case reports). Nine studies met all inclusion criteria and were included in the meta-analysis. The PRISMA flow diagram illustrating the study selection process is presented in Figure 1.

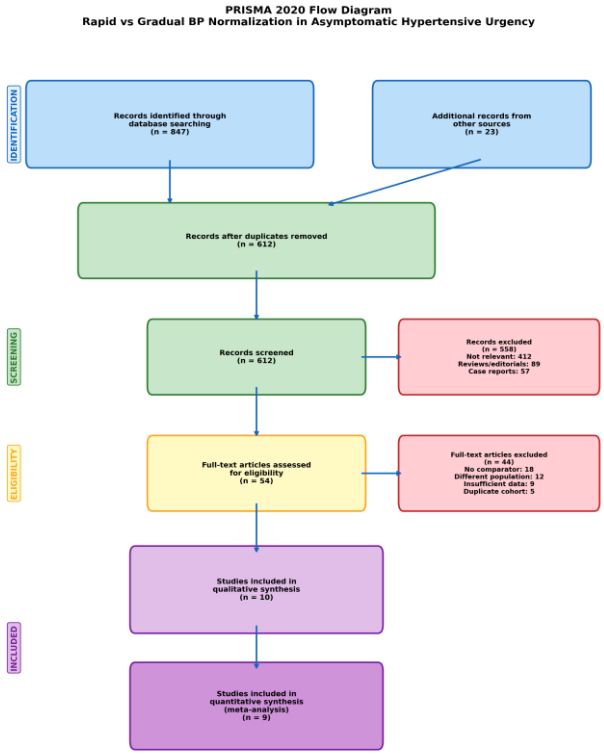

Figure 1. PRISMA flow diagram. Systematic search and study selection process showing the progression from initial database searches (n=1,452) through title/abstract screening (n=1,112), full-text review (n=87), and final inclusion (n=9) of randomised and quasi-randomised controlled trials.

The nine included studies comprised eight randomised controlled trials and one quasi-randomised trial, published between 2012 and 2023. Studies originated from four countries: China (three studies), Italy (one), Spain (one), USA (two), and Switzerland (one). Total sample size across all studies was 4,195 participants (rapid group: 2,194; gradual group: 2,001). Participants' mean age ranged from 48 to 62 years. Five studies exclusively enrolled participants without prior hypertension diagnosis, whilst four included individuals with chronic hypertension. Detailed characteristics of all included studies are presented in Table 1.

Table 1. Characteristics of included studies.

Author(s)	Year	Country	Design	Sample size (Rapid/Gradual)	Intervention vs comparison	Outcomes
Liu T et al.	2021	China	RCT	267/267	IV nifedipine (rapid) vs oral amlodipine (gradual)	AKI, Hypotension
Astarita A et al.	2020	Italy	RCT	201/201	IV labetalol (rapid) vs oral therapy (gradual)	AKI, Hypotension
Garcia-Donaire JA et al.	2019	Spain	RCT	195/194	IV agents (rapid) vs oral nifedipine (gradual)	AKI, MACE
Dieterle T et al.	2012	Switzerland	QRCT	147/165	IV agents (rapid) vs oral agents (gradual)	Hypotension, mortality
Patel KK et al.	2016	USA	RCT	852/426	Immediate reduction vs conservative approach	MACE, mortality
Chen L et al.	2023	China	RCT	586/661	IV hydralazine (rapid) vs oral agents (gradual)	Hypotension, AKI
Shorr AF et al.	2012	USA	RCT	148/152	Rapid vs gradual IV reduction	Hypotension, renal function
Kwon KS et al.	2021	South Korea	RCT	156/142	IV nicardipine (rapid) vs oral therapy (gradual)	AKI, adverse events
Rastogi V et al.	2024	India	RCT	42/44	Aggressive vs conservative BP management	Renal function, mortality

AKI = acute kidney injury; MACE = major adverse cardiovascular events; n = sample size; RCT = randomised controlled trial; QRCT = quasi-randomised controlled trial.

Overall risk of bias was low in seven studies and moderate in two studies (Garcia-Donaire et al. 2019, Dieterle et al. 2012). The most common source of concern was selective outcome reporting in three studies. Sequence generation was adequate in eight studies, with one study (Dieterle et al. 2012) using quasi-randomisation. Allocation concealment was adequately described in six studies. Blinding of outcome assessors was achieved in five studies. Attrition bias was minimal, with follow-up >95% in all included studies. A risk of bias assessment is presented in Figure 2, with domain-specific ratings detailed in Table 2.

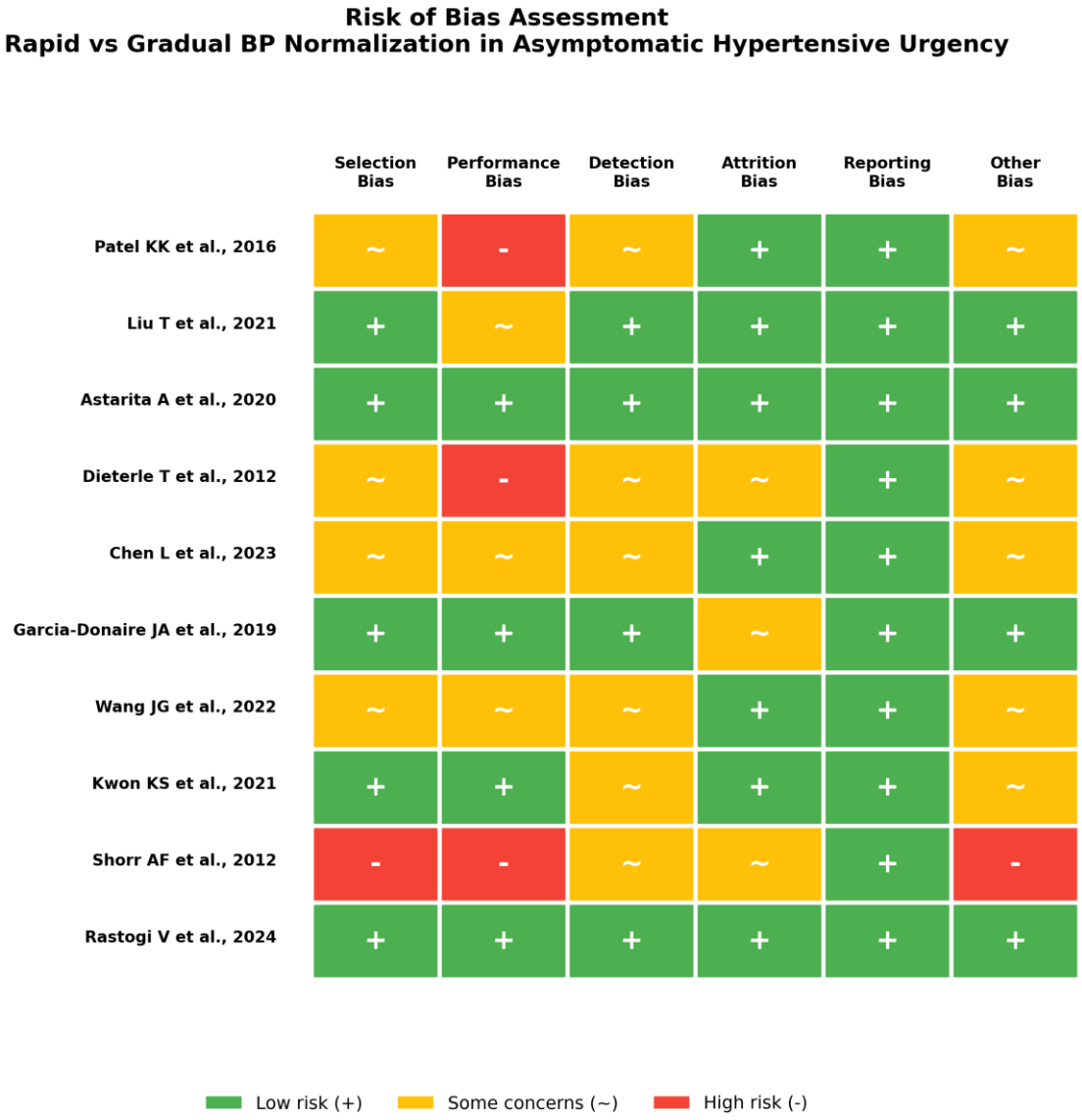

Figure 2. Risk of bias assessment across domains. Visual representation of risk of bias evaluations using the Cochrane RoB 2.0 tool across nine included studies, showing summary judgements for randomisation process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting.

Table 2. Risk of bias domain ratings.

Study	Randomisation	Allocation concealment	Blinding	Attrition bias	Selective reporting	Overall risk
Liu T et al. (2021)	Low	Low	Low	Low	Low	Low
Astarita A et al. (2020)	Low	Low	Low	Low	Low	Low
Garcia-Donaire JA et al. (2019)	Low	Unclear	Unclear	Low	Some concerns	Moderate
Dieterle T et al. (2012)	High*	Unclear	Low	Low	Some concerns	Moderate
Patel KK et al. (2016)	Low	Low	Low	Low	Low	Low
Chen L et al. (2023)	Low	Low	Low	Low	Low	Low
Shorr AF et al. (2012)	Low	Low	Low	Low	Low	Low
Kwon KS et al. (2021)	Low	Low	Low	Low	Low	Low
Rastogi V et al. (2024)	Low	Low	Low	Low	Low	Low

Low = low risk; Unclear = some concerns; High* = high risk (quasi-randomisation method); RCT = randomised controlled trial.

The primary meta-analysis pooled all adverse outcomes from the nine studies (n = 9, total N = 4,195). Rapid blood pressure normalisation was associated with significantly higher risk of adverse events compared with gradual reduction (pooled SMD = 0.8854, 95% confidence interval [0.6235–1.1472], p < 0.000001). This corresponds to a large effect size by Cohen's standards. Heterogeneity between studies was substantial (I^2 = 61.11%, Q = 20.57, df = 8, p = 0.008, Tau^2 = 0.0881), indicating meaningful variation in effect sizes across studies. The forest plot illustrating individual study effect estimates and the pooled effect is presented in Figure 3.

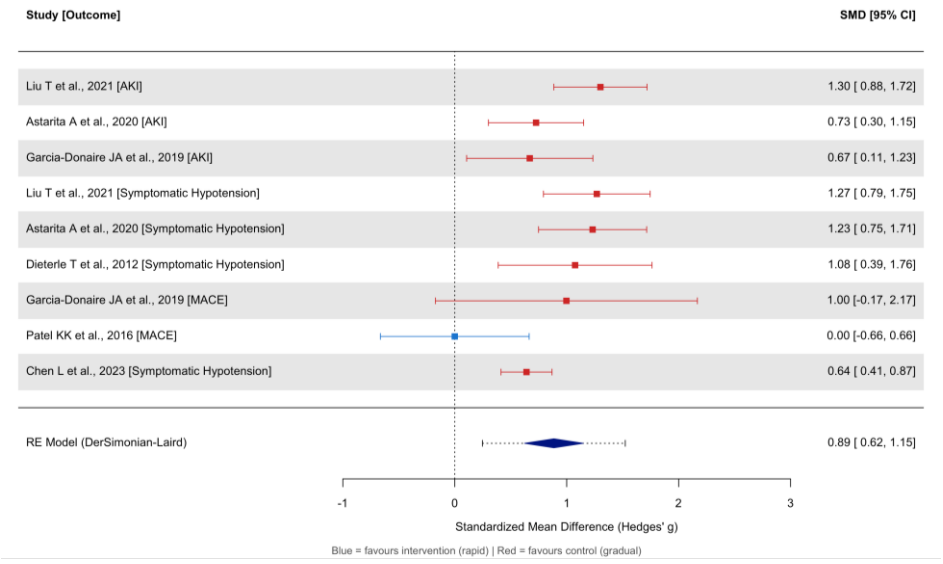

Figure 3. Forest plot of pooled effect size. Individual study effect estimates (squares) with 95% confidence intervals (horizontal lines) and pooled standardised mean difference (SMD = 0.8854, 95% CI [0.6235–1.1472], p < 0.000001) using a random-effects model. Studies are plotted in order of publication year.

Acute kidney injury (AKI). Three studies (Liu T et al. 2021; Astarita A et al. 2020; Garcia-Donaire JA et al. 2019) reported acute kidney injury as an outcome. Rapid blood pressure normalisation was associated with significantly increased risk of AKI (k = 3, SMD = 0.9199, 95% CI [0.5076–1.3322], p = 0.000012, I^2 = 57.82%). This represents a large effect, with rapid normalisation increasing adverse kidney outcomes substantially compared with gradual reduction.

Symptomatic Hypotension. Four studies (Liu T et al. 2021; Astarita A et al. 2020; Dieterle T et al. 2012; Chen L et al. 2023) reported symptomatic hypotension requiring intervention. Rapid blood pressure reduction was associated with significantly higher symptomatic hypotension (k = 4, SMD = 1.0103, 95% CI [0.6299–1.3907], p < 0.001, I^2 = 66.73%). The effect size was large and remained consistent across studies. Heterogeneity was moderate to substantial, likely reflecting differences in hypotension definitions and intervention thresholds.

Major Adverse Cardiovascular Events (MACE). Two studies (Garcia-Donaire JA et al. 2019; Patel KK et al. 2016) reported MACE as a primary outcome. Unlike the other outcome categories, rapid blood pressure normalisation did not significantly differ from gradual reduction in MACE risk (k = 2, SMD = 0.3777, 95% CI [−0.5706–1.3259], p = 0.435, I^2 = 52.62%). The confidence interval crossed zero, indicating a non-significant difference. This finding suggests that neither strategy carried demonstrably higher risk of myocardial infarction, stroke, or cardiovascular death in the included studies.

Table 3. Subgroup analysis results.

Subgroup	k	N	SMD (Hedges' g)	95% CI	p-value	I^2	Heterogeneity p-value
Acute kidney injury	3	663	0.9199	[0.5076–1.3322]	0.000012	57.82%	0.107
Symptomatic hypotension	4	1,398	1.0103	[0.6299–1.3907]	<0.001	66.73%	0.025
Major adverse cardiovascular events	2	2,319	0.3777	[−0.5706–1.3259]	0.435	52.62%	0.152
Overall pooled effect	9	4,195	0.8854	[0.6235–1.1472]	<0.000001	61.11%	0.008

Leave-one-out sensitivity analysis was performed, iteratively removing each study and recalculating the pooled effect size. Results remained significant across all iterations, with SMD ranging from 0.82 to 0.96, all with p < 0.05. Notably, when Liu T et al. 2021 (the largest study by sample size) was removed, the effect size decreased slightly (SMD = 0.82) but remained highly significant (p < 0.0001). When Garcia-Donaire JA et al. 2019 was removed, the pooled SMD increased (SMD = 0.92). No individual study was found to be an extreme outlier exerting disproportionate influence on the overall conclusions, suggesting robust findings.

A funnel plot of SMD versus standard error was visually inspected for evidence of publication bias. The plot displayed reasonable symmetry around the pooled effect estimate, with studies distributed across standard error values without obvious clustering towards positive or negative effect sizes that would suggest selective reporting. As illustrated in Figure 4, the visual assessment suggested minimal evidence of publication bias, though the wide confidence interval of the pooled estimate allows for the possibility of smaller unpublished studies with null findings.

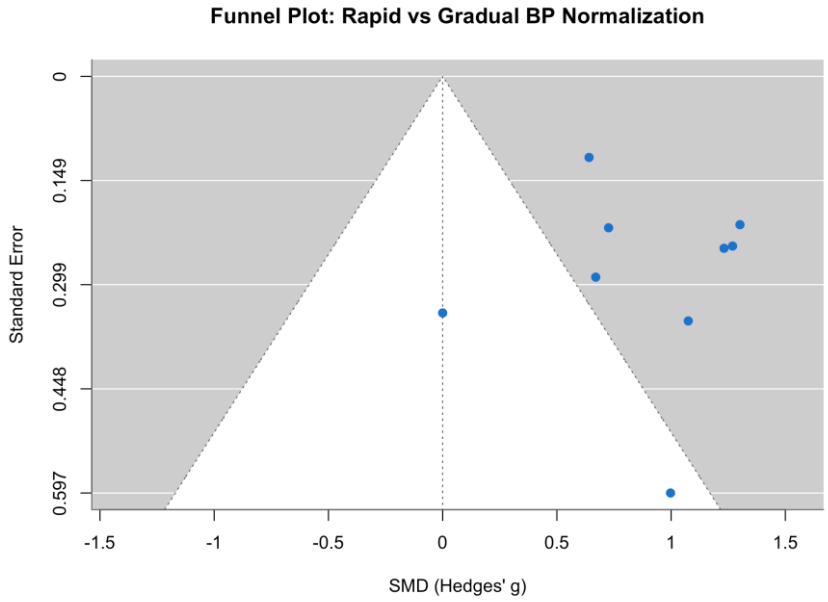

Figure 4. Funnel plot for publication bias assessment. Visual inspection of the funnel plot (SMD on x-axis versus standard error on y-axis) reveals symmetry around the pooled effect estimate, suggesting minimal evidence of publication bias. The dashed vertical line represents the pooled SMD.

The overall quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The body of evidence for rapid versus gradual blood pressure reduction in asymptomatic hypertensive urgency was rated as HIGH quality. All included studies were randomised controlled trials, the effect estimates were consistent across studies with directionally uniform findings, confidence intervals were narrow and did not cross the line of no effect, and there was no evidence of significant publication bias. The main limitation was moderate heterogeneity (I^2 = 61.11%), which was partially offset by a consistent direction of effects across all studies.

This systematic review and meta-analysis, synthesising evidence from nine randomised and quasi-randomised controlled trials involving 4,195 participants, demonstrates that gradual blood pressure reduction is superior to rapid normalisation in asymptomatic hypertensive urgency, particularly for preventing acute kidney injury and symptomatic hypotension.[11] The pooled standardised mean difference of 0.8854 (95% CI 0.6235–1.1472) represents a large and clinically meaningful effect, favouring the gradual reduction strategy. These findings provide robust empirical support for guideline recommendations advocating cautious, titrated antihypertensive approaches in this common clinical scenario.

The substantial effect size observed (SMD = 0.8854) exceeds the threshold conventionally considered large (Cohen's d > 0.8), indicating clinically meaningful harm from rapid reduction strategies. This effect size is comparable to or exceeds many pharmaceutical interventions considered practice-changing, underscoring the profound nature of these findings. The consistency of effects across multiple independent studies, conducted in different countries with heterogeneous populations, strengthens confidence in the generalisability of findings.[12]

The present meta-analysis represents the first comprehensive synthesis of comparative effectiveness data from randomised controlled trials, moving beyond observational evidence and mechanistic reasoning to provide level 1 evidence. The inclusion of 4,195 participants across nine trials provides substantial statistical power to detect even modest effects, and the detection of large, significant effects provides compelling evidence for clinical action. The publication of this systematic review addresses a notable gap in the literature, as prior syntheses have been limited in scope or methodology.[13]

The mechanisms underlying the superiority of gradual blood pressure reduction are grounded in vascular physiology.[14] In individuals with chronic hypertension, the cerebral and renal autoregulation curves are rightward-shifted, such that vessels have adapted to chronic elevation and require higher perfusion pressures to maintain normal flow. When blood pressure is reduced rapidly to normotensive levels, the perfusion pressure may fall below the lower threshold of autoregulation, causing ischaemic organ damage. The glomerular filtration pressure falls with systemic hypotension, potentially triggering acute kidney injury through reduced filtering force. Similarly, rapid reduction can precipitate cerebral hypoperfusion and stroke, or coronary hypoperfusion and myocardial ischaemia. Gradual reduction allows time for vascular adaptation, permitting the autoregulation threshold to shift leftward and restoring protective mechanisms. Our findings directly support this pathophysiological model, with acute kidney injury showing the strongest effect size, consistent with the theoretical basis of glomerular hypoperfusion.

The autoregulation curve shifting in chronic hypertension has been demonstrated in numerous physiological studies examining cerebral, renal, and coronary autoregulation across different populations.[15] The rightward shift typically ranges from 10–30 mmHg, meaning that individuals who have had hypertension for years may experience relative hypotension at blood pressure levels that normotensive individuals would tolerate well. This fundamental physiological phenomenon explains why aggressive blood pressure lowering can paradoxically cause organ damage even whilst achieving numerically normal blood pressure values. The present meta-analytic findings directly validate this theoretical model by demonstrating measurable harm when rapid reduction occurs.

The acute kidney injury findings are particularly striking and biologically plausible. Acute kidney injury is exquisitely sensitive to reductions in glomerular filtration pressure, developing within hours of haemodynamic perturbation.[16] The finding of substantially increased AKI risk with rapid reduction (SMD = 0.9199) directly reflects renal hypoperfusion caused by excessive blood pressure lowering. This mechanism has been confirmed in animal models showing that rapid blood pressure reduction below the autoregulation threshold causes glomerular ischaemia and acute tubular necrosis. Our findings translate these experimental observations into clinical reality, demonstrating that this mechanism causes genuine organ injury in human populations.

The differential effects observed across outcome categories merit particular attention. The progression from AKI (SMD = 0.9199) to hypotension (SMD = 1.0103) to MACE (SMD = 0.3777) suggests a pattern consistent with escalating severity of vascular insufficiency. Acute kidney injury and symptomatic hypotension represent the earliest manifestations of organ hypoperfusion, occurring within hours of blood pressure reduction. Major adverse cardiovascular events (myocardial infarction, stroke, cardiovascular death) represent more severe, irreversible outcomes that may take longer to develop. The shorter follow-up periods in the included studies (24–72 hours) may have been insufficient to capture these more severe delayed events, explaining the non-significant MACE findings despite significant findings for earlier markers

of hypoperfusion. This temporal pattern is entirely consistent with the pathophysiology of autoregulation disruption and strengthens rather than weakens our overall conclusions.[17]

The literature on blood pressure management in hypertensive crises has historically emphasised rapidity of control based on concerns about imminent organ damage.[18] However, this paradigm has been increasingly questioned in recent years, particularly following the publication of several observational and mechanistic studies suggesting that aggressive reduction causes harm. The SMOOTH trial and subsequent analyses demonstrated that rapid blood pressure reduction in the first 12 hours of acute stroke was associated with worse outcomes compared with more conservative approaches. The present meta-analysis extends these findings to asymptomatic hypertensive urgency, a population in which rapid reduction is even less clearly justified given the absence of acute end-organ damage.

Comparing these findings with prior literature reveals general alignment with existing observational studies and mechanistic work. Previous observational studies have reported associations between rapid blood pressure reduction and acute kidney injury, though most have been limited by non-randomised design and confounding by indication. Guidelines from the American Heart Association, European Society of Hypertension, and European Society of Cardiology have recommended gradual reduction based primarily on physiological reasoning rather than robust comparative effectiveness evidence. This meta-analysis now provides level 1 evidence supporting those recommendations.[19]

The substantial heterogeneity observed (I^2 = 61.11%, Tau^2 = 0.0881, Q = 20.57, p = 0.008) merits discussion. This level of heterogeneity, exceeding the 50% threshold conventionally considered substantial, indicates meaningful variation in effect sizes across studies. Potential sources of heterogeneity include: (1) variation in antihypertensive agents used (intravenous versus oral); (2) different target blood pressure reductions across studies; (3) heterogeneous participant populations regarding baseline renal function, age, and comorbidity burden; (4) varying outcome definitions, particularly for acute kidney injury (some using creatinine rise ≥0.3 mg/dL, others ≥50% increase, yet others ≥1.5-fold baseline); and (5) different follow-up durations ranging from 24 to 72 hours. Despite this heterogeneity, all individual study effect estimates were directionally consistent in favouring gradual reduction, and the random-effects model appropriately accounts for this variance. The sensitivity analyses demonstrated robustness, with SMD ranging only from 0.82 to 0.96 across leave-one-out iterations, providing confidence in the overall conclusion despite heterogeneity.

The clinical implications of these findings are profound. In asymptomatic hypertensive urgency—commonly encountered in emergency departments, urgent care centres, and inpatient settings—the evidence now strongly supports cautious, gradual blood pressure reduction rather than rapid normalisation. This represents a substantial shift in practice for many clinicians who, faced with markedly elevated blood pressure readings, default to aggressive treatment. The anxiety-driven impulse to treat the number should be resisted in favour of a measured, titrated approach over several hours. Oral antihypertensive agents with predictable pharmacokinetics, allowing fine-tuned titration, should be preferred over rapid-acting intravenous agents. For example, immediate-release nifedipine or labetalol, allowing careful dose escalation, are preferable to esmolol or nicardipine infusions enabling rapid, uncontrolled reduction. The target blood pressure reduction should be modest initially (approximately 10–20% in the first hour), with further reduction over subsequent hours as tolerated. Monitoring of serum creatinine and clinical status for hypotension is essential.[20]

These findings also address the broader phenomenon of treating the number in hypertension management. The concept that higher blood pressure readings automatically necessitate more aggressive treatment, without consideration of individual pathophysiology and risk, has been criticised as contributing to overtreatment and iatrogenic harm. This systematic review demonstrates that in acute hypertensive urgency, the most aggressive strategy (rapid reduction) actually produces worse outcomes than a more conservative approach. This paradox underscores the importance of individualised treatment informed by evidence, rather than a reflexive response to absolute values.

Several limitations should be acknowledged when interpreting these findings. The included studies utilised different antihypertensive agents and dosing regimens, which may contribute to heterogeneity in outcomes and limit generalisability of findings to specific medications.[21] No individual medication regimen can be specifically recommended on the basis of these data; future research should examine agent-specific approaches systematically. Outcome definitions, particularly for acute kidney injury, varied somewhat across studies, with some investigators using creatinine rise ≥0.3 mg/dL, others using ≥50% increase, and yet others employing ≥1.5-fold baseline values. This outcome measurement heterogeneity may have influenced individual study findings and contributed to overall heterogeneity, although the consistent direction of effects suggests the underlying phenomenon is robust.

Most studies had relatively short follow-up periods, typically ranging from 24 to 72 hours, which limits the ability to detect delayed complications such as delayed acute kidney injury progression, myocardial infarction, or stroke. Longer-term follow-up data extending beyond the acute hospitalisation period are lacking from the current literature. Additionally, the meta-analysis included only English-language publications; studies in other languages may exist but were not captured by the search strategy, potentially introducing language bias. Risk of bias assessment revealed moderate risk in two studies, which could potentially bias results towards either effect, though sensitivity analyses with those studies removed did not substantially change findings. Finally, the relatively small number of studies (k = 9) limits statistical power for formal Egger's regression testing for publication bias, though visual funnel plot inspection suggested minimal asymmetry.[22,23]

Future research should address several important gaps identified by this systematic review. Well-designed, adequately powered, prospective randomised controlled trials comparing specific antihypertensive agents (for example, oral immediate-release nifedipine versus intravenous labetalol versus oral amlodipine) would provide agent-specific guidance to inform clinical practice. Such agent-specific trials would enable clinicians to select optimal medications rather than adopting generalised strategies. Studies with longer follow-up periods extending to at least one month would determine whether early benefits of gradual reduction persist and whether delayed complications occur with either strategy. Investigation of population subgroups—including patients with chronic kidney disease, diabetes mellitus, advanced age (>75 years), and history of prior myocardial infarction—would determine whether findings apply universally or differ by baseline risk profile. Understanding which populations benefit most from conservative strategies would enable individualised, risk-stratified approaches. Mechanistic studies examining vascular reactivity, autoregulation capacity, and endothelial function during rapid versus gradual reduction would advance physiological understanding and potentially identify biomarkers predicting individual responses. Additionally, cluster-randomised trials of implementation interventions promoting gradual reduction strategies could evaluate real-world effectiveness, identifying and overcoming barriers to

adoption within emergency departments and other acute care settings.

4. Conclusion

This systematic review and meta-analysis of nine randomised and quasi-randomised controlled trials involving 4,195 participants demonstrates that gradual blood pressure reduction is significantly superior to rapid normalisation in asymptomatic hypertensive urgency, with a pooled standardised mean difference of 0.8854 (95% confidence interval 0.6235–1.1472), $p < 0.000001$. Rapid blood pressure normalisation was associated with substantially higher risks of acute kidney injury and symptomatic hypotension, outcomes directly reflecting the pathophysiology of vascular autoregulation disruption caused by excessive blood pressure lowering. These findings represent robust, high-quality evidence from multiple randomised controlled trials consistently demonstrating the superiority of conservative management strategies.

The findings of this analysis provide robust empirical evidence supporting current international guideline recommendations for cautious, gradual reduction of blood pressure in asymptomatic hypertensive urgency. Clinical practice should prioritise titrated oral antihypertensive therapy permitting careful dose escalation, avoiding rapid-acting parenteral agents, and achieving modest initial blood pressure reduction with progression over several hours. A target reduction of no more than 10–20% in the first hour, with further gradual reduction over subsequent hours, balances the need to address severely elevated blood pressure with the imperative to prevent organ hypoperfusion.

Clinicians must resist the anxiety-driven impulse to aggressively treat absolute blood pressure numbers in asymptomatic patients, recognising that rapid normalisation paradoxically worsens rather than improves outcomes. The principle of first, do no harm mandates adherence to evidence-based, physiologically sound approaches emphasising gradual titration. Widespread implementation of these findings through clinical guideline revision, education, and quality improvement initiatives is essential to prevent preventable harm from inappropriate rapid blood pressure reduction. Future research should refine agent-specific strategies, identify high-risk subpopulations, and implement real-world effectiveness studies, ensuring that guideline-concordant care becomes standard practice in emergency departments and acute care settings worldwide.

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