Saudi Toxicology Journal (STJ)

Journal home page: https://uqu.edu.sa/s.toxicology.s/S.T.J

Review

Comparative Impact of Thiazides vs. Dihydropyridines on Heart Failure Risk in Hypertensive Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Citation: Alsanosi, S. M.S. & Alhindi, Y. Z.A. Comparative Impact of Thiazides vs. Dihydropyridines on Heart Failure Risk in Hypertensive Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *STJ*, **2025**, 2, 71-80 https://doi.org/10.70957/uqu.edu.sa/s.toxicology.s/stj.2025.2.7

Received: 24 April 2025

Accepted: 23 June 2025

Published: 16 July 2025

Background: Uncontrolled hypertension (HTN) is a progressive condition that significantly elevates the risk of heart failure (HF). The selection of antihypertensive agents plays a critical role in modulating HF risk. Thiazide diuretics and dihydropyridine calcium channel blockers (DHPs) are frequently utilized in clinical practice, yet their comparative long-term cardiovascular outcomes, particularly regarding HF incidence, remain underexplored.

Methods: A systematic literature review was undertaken, drawing four key databases—MEDLINE, EMBASE, Web of Science, and Cochrane—covering the period from 1994 to October 2024. The scope was limited to randomized controlled trials (RCTs) evaluating thiazides or DHPs, with a minimum of 100 participants diagnosed with hypertension and at least one year of follow-up. Two independent reviewers conducted study selection, bias assessment, and data extraction focused on HF outcomes. Meta-analyses were performed to compute pooled risk ratios (RRs) for HF incidence across treatment arms.

Results: The search identified 1,896 records, with 1,653 remaining after deduplication. Following a full-text evaluation of 403 eligible studies, 396 RCTs were excluded, resulting in seven RCTs comprising 49,709 participants for inclusion in the meta-analysis. The findings indicated a trend favouring thiazides over DHPs in mitigating HF risk. The pooled RR for HF was 0.77 (95% confidence intervals (CI): 0.70–0.84; $I^2 = 53\%$; χ^2 $p < 0.00001$), achieving statistical significance in the fixed-effects model.

Conclusion: The meta-analysis revealed a statistically significant reduction in HF incidence associated with thiazides compared to DHPs in hypertensive patients, highlighting potential implications for clinical decision-making. Nonetheless, additional research is warranted to validate these findings and elucidate their broader clinical relevance.

Keywords: Thiazide; Dihydropyridines; Heart Failure; Risk; Meta-analysis; Hypertension**.**

Introduction

Hypertension (HTN) is a significant risk factor for the development of HF, a leading cause of morbidity and mortality worldwide (1). The choice of antihypertensive medication can significantly impact the risk of HF in this patient population. Thiazide diuretics and dihydropyridine calcium channel blockers (DHPs) are two commonly prescribed classes of antihypertensive drugs and their effects on the risk of HF have been the subject of ongoing research(2).

Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone, have been widely used in the management of HTN (3). For instance, studies have investigated the impact of thiazide diuretics on HF risk in hypertensive patients (4-6). A meta-analysis of RCTs indicated that thiazide diuretics were linked to a reduced risk of HF compared to other antihypertensive medications, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and beta-blockers (7). The researchers proposed that the natriuretic and diuretic properties of thiazides may underpin their cardioprotective benefits by decreasing preload and afterload, thereby enhancing cardiac performance. Furthermore, an observational study involving more than 30,000 hypertensive patients demonstrated that treatment with thiazide diuretics was associated with a significantly lower risk of HF hospitalisation than treatment with other antihypertensive drug classes (8). This finding was consistent across patient subgroups, including those with and without a history of cardiovascular disease (9).

Calcium channel blockers, DHPs, such as amlodipine and nifedipine, are another class of antihypertensive medications widely used in the management of HTN. The impact of DHPs on HF risk has also been investigated. For instance, studies have suggested that DHPs may have a neutral or even a slightly protective effect on the risk of HR in hypertensive patients (10-12). A meta-analysis of RCTs found that DHPs were not associated with an increased risk of HF compared to other antihypertensive agents, including ACE inhibitors, ARBs and beta-blockers (13). Moreover, an observational study involving more than 70,000 hypertensive patients demonstrated that treatment with DHPs was not associated with a higher risk of HF hospitalization than treatment with other antihypertensive drug classes (14). This finding was consistent across patient subgroups and sensitivity analyses.

The available evidence suggests that thiazide diuretics may be associated with a lower risk of HF in hypertensive patients than other antihypertensive drug classes (5). Conversely, DHPs appear to have a neutral or slightly protective effect on HF risk in this patient population (12, 15). These findings have important clinical implications for managing HTN and preventing HF. When choosing antihypertensive medications for hypertensive patients, consideration should be given to the potential impact of the drug class on HF risk, in addition to its efficacy in blood pressure control and other cardiovascular outcomes (16). However, there is a lack of sufficient data for evaluating the cardiovascular clinical outlook (including HF) of hypertensive patients treated with calcium channel blockers and diuretics.

Methods

Literature Search

Comprehensive electronic searches were performed in MEDLINE, EMBASE, Web of Science and the Cochrane Controlled Trials Register (CENTRAL) for studies published from 1994 to October 2024 (see Online Supplement, Tables S1–S4). Furthermore, the reference lists of all retrieved articles were examined to uncover additional relevant studies**.** The search was limited to publications available in English**.** Data were extracted independently using a standardized spreadsheet (Microsoft Excel 2010). The author (S.A.) conducted an initial screening of potentially eligible articles, including titles and abstracts. Two reviewers (A.A. and Y.A.) performed the data extraction independently using the same standardized spreadsheet. A third investigator (S.P.) acted as a tiebreaker, independently reviewing articles to resolve disagreements between the other two reviewers.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this review were established based on the Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework(17),

Population

[1] Disease Definition: Hypertension (HTN) is characterized as a chronic condition with current

diagnostic criteria set at a systolic blood pressure (SBP) of ≥140 mm Hg and/or diastolic blood pressure (DBP) of ≥90 mm Hg, as established by clinical guidelines (18). [2] **Participant Profile**: The study includes adult men and non-pregnant women aged 18 years or older, exhibiting a baseline resting SBP of ≥140 mm Hg and/or DBP of ≥90 mm Hg, measured using standardized procedures throughout the study duration. [3] **Clinical Setting**: The participants were non-hospitalized patients in outpatient healthcare environments.

Interventions and Comparators

[1] Interventions: Dihydropyridine calcium channel blockers (CCBs) were administered at varying doses, either as monotherapy or in combination with other agents. [2] Comparators: Thiazide diuretics were administered at varying doses as monotherapy, in combination therapy, or alongside non-pharmacological lifestyle interventions. [3] Co-interven**tions**: Additional antihypertensive medications from other drug classes were permitted as part of a stepped-care treatment protocol.

Outcome Measures

[1] Outcome Definition: The primary focus is HF incidence or HF-related mortality.

[2] Measurement Protocol: HF events are identified through clinical reports and standardized diagnostic criteria. [3] Measurement Duration: Outcomes are assessed following a minimum of three months of active treatment. [4] Primary Outcomes: Incidence of HF observed after at least one month of active treatment. [5] Secondary Outcomes: HF-related outcomes, including complications, disease severity, and mortality rates.

Study Design

[1] Design Type: RCTs conducted in single- or multi-centre settings. [2] Sample Size: RCTs enrolling a minimum of 100 participants. [3] Study Duration: Trials, with a follow-up period of at least 12 months.

Assessment of the Risk of Bias Within Studies

Two reviewers (S.A. and Y.A.) independently evaluated the risk of bias for each included study, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A third investigator (S.P.) acted as a tiebreaker, independently reviewing articles to resolve disagreements between the other two reviewers. Disagreements between reviewers were handled procedurally. The risk of bias for each study was assessed across six domains as shown in Figure 2.

Statistical Analysis

Pooled RRs were calculated employing a fixed-effects model within Review Manager 5 software. Heterogeneity across studies was evaluated using the χ^2 test and I^2 statistic. In cases where statistical heterogeneity was detected (χ^2 $p < 0.05$ or $I^2 > 60\%$), sensitivity analyses were conducted by exploring alternative analytical choices. The origins of heterogeneity, whether stemming from methodological or clinical factors, were investigated by analyzing the characteristics of the included studies. Effect sizes specific to each study, derived from the standard pairwise meta-analysis model, were reported, alongside their 95% CIs and were visualized in forest plots.

Results

The initial literature search yielded 1,896 publications. After removing duplicates, 1,653 records remained. Based on the abstract review, 1,250 articles were identified as potentially eligible studies. A full-text review was conducted on 403 studies, leading to the exclusion of 396 RCTs for various reasons: 13 were not RCTs, 20 included fewer than 100 participants, 22 had a study duration of less than one year, and 341 did not report relevant outcomes (Figure 1). In the end, seven RCTs—ACCOMPLISH [2004], ALLHAT [2002], INSIGHT [2000], MIDAS [1999], NICE-EH [1999], SHELL [2003], and STOP-HTN [2000])—with a total of 49,709 participants were deemed suitable for inclusion in the meta-analysis, as shown in Table 1.

Among the included RCTs, two studies (INSIGHT [2000] and NICE-EH [1999]) failed to specify the methods used for treatment randomization. Additionally, four studies (INSIGHT [2000], MIDAS [1999], NICE-EH [1999], and SHELL [2003]) did not provide details on the concealment of treatment allocation, resulting in an unclear risk of selection bias. As illustrated in Figures 2 and 3, one study (SHELL [2003]) lacked sufficient detail regarding its blinding procedures, while another (STOP-HTN [2000]) employed a randomized, open-label, blinded endpoint (PROBE) design. The risk of attrition bias was elevated in one study (NICE-EH [1999]) and

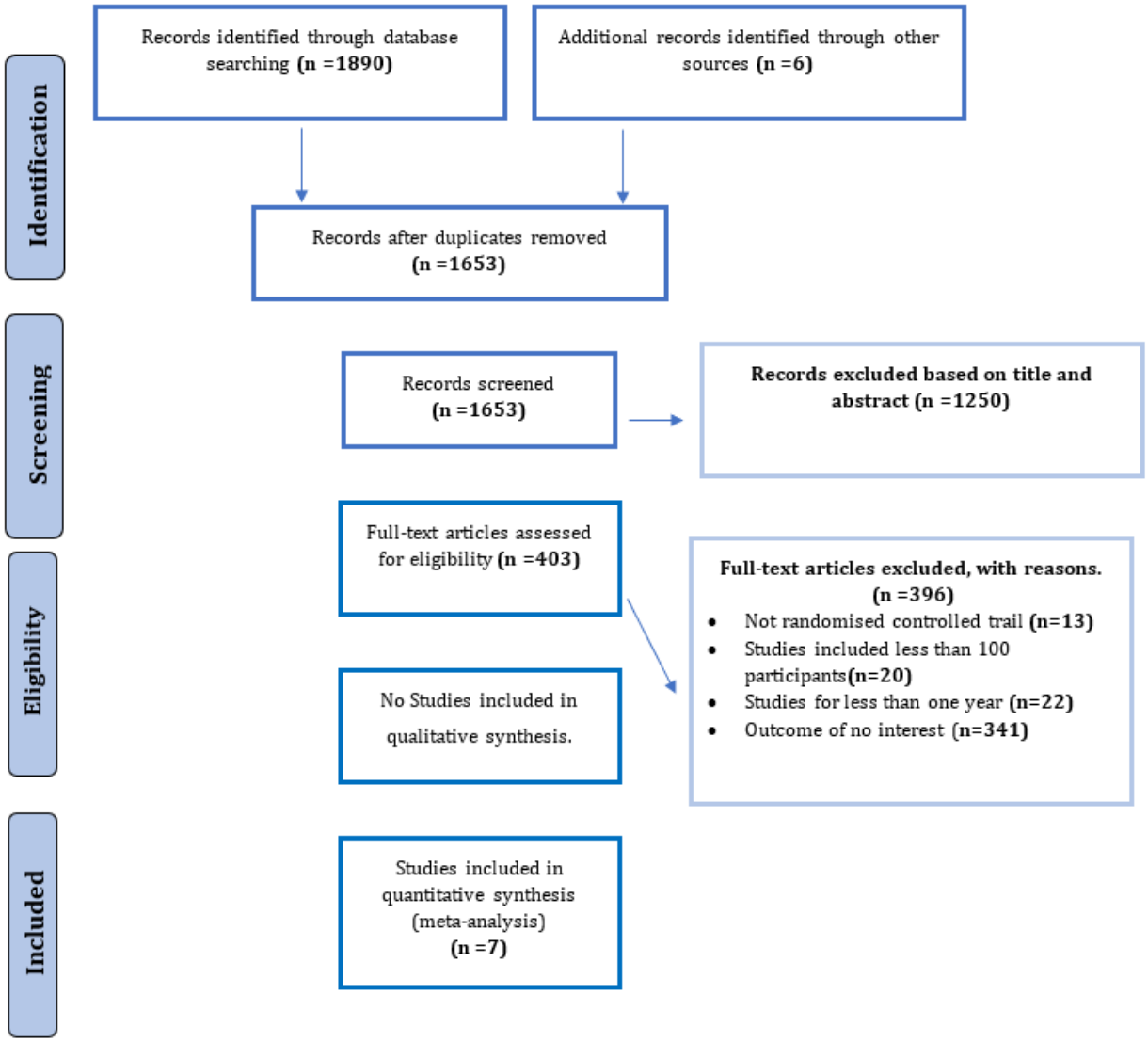

Figure 1: Diagram illustrating the process of trial selection for inclusion in the meta-analysis.

uncertain in another (ACCOMPLISH [2004]). In contrast, the risk of reporting bias was consistently low across all included studies.

As shown in Figure 3, the analysis indicated a tendency for thiazides to be more effective than DHPs in lowering the risk of Hf. The pooled relative risk (RR) for HF was 0.77 (95% CI: 0.70–0.84; $I^2 = 53\%$; χ^2 $p < 0.00001$), demonstrating statistical significance in the fixed-effects model.

Discussion

This systematic review and meta-analysis examined the impact of thiazide diuretics and DHPs on the risk of HF in hypertensive patients. The meta-analysis included seven RCTs with 49,409 participants, focusing on the HF outcomes of the two drug classes. The pooled RR for HF was 0.77 (95% CI: 0.70–0.84; $I^2 = 53\%$; χ^2 $p < 0.00001$), suggesting a tendency for thiazides to outperform DHPs in reducing the risk of HF.

Previous research supports these findings by attributing thiazides' cardioprotective effects to their ability to reduce preload and afterload through natriuretic and diuretic mechanisms (18). These findings underscore the synergistic potential of thiazide diuretics and DHPs within the evolving paradigm of antihypertensive therapy (19). In the context of precision medicine, thiazides may offer distinct advantages for patients predisposed to HF, owing to their cardioprotective

Table 1: Description of included studies.

Study	Duration	Design	Participants	Intervention	Primary Outcomes
ACCOMPLISH [2004] (20)	42 months	RCT	11,506	Amlodipine 5 mg + Benazepril 20 mg once daily vs. Hydrochlorothiazide 12.5 mg + Benazepril 20 mg once daily	Composite of CV death, non-fatal MI, non-fatal stroke, angina hospitalization, resuscitated cardiac arrest, and coronary revascularization
ALLHAT [2002] (21)	57 months	RCT	33,357	Amlodipine 2.5–10 mg daily vs. Chlorthalidone 12.5–25 mg daily	Primary: Combined fatal CHD and non-fatal MI Secondary: All-cause mortality, stroke, total CHD, and overall CVD events
INSIGHT [2000] (22)	48 months	RCT	6,575	Nifedipine 30 mg daily vs. Amiloride 2.5 mg + Hydrochlorothiazide 25 mg daily	CV death, MI, HF, or stroke
MIDAS [1996] (23)	36 months	RCT	883	Isradipine 2.5–5 mg twice daily vs. Hydrochlorothiazide 12.5–25 mg twice daily	Maximum carotid artery IMT, vascular measurements, and incidence of vascular events or procedures
NICE-EH [1999] (24)	60 months	RCT	429	Nicardipine 20 mg SR daily vs. Trichlormethiazide 2 mg daily	Cardiovascular complications
SHELL [2003] (25)	60 months	RCT	1,882	Lacidipine 4 mg daily vs. Chlorthalidone 12.5 mg daily	Combined CV and CVE outcomes including stroke, sudden death, MI, and HF
STOP-HTN [2000] (26)	54 months	RCT	6,614	Felodipine or Isradipine (2.5–5 mg daily) vs. Hydrochlorothiazide 25 mg + Amiloride 2.5 mg	Combined fatal outcomes: stroke, MI, and other fatal cardiovascular conditions

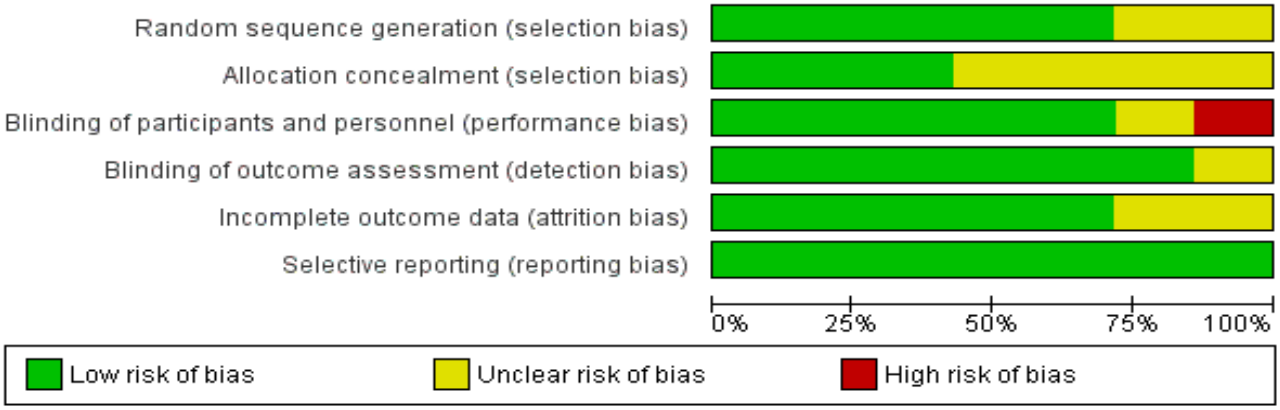

Figure 2: Risk of bias chart: Summary of the review authors' assessments for each bias domain, shown as percentages across all included studies.

modulation of ventricular dynamics (27). Nevertheless, DHPs continue to serve as a pharmacologically sound alternative, particularly for individuals exhibiting diuretic intolerance or contraindications to volume modulation therapies (27, 28).

As cardiovascular medicine advances toward algorithm-driven personalization, effective hypertension management demands a multidimensional strategy—one that transcends simple blood pressure reduction to integrate projections of long-term cardiovascular trajectories. Clinical decision-making must, therefore, be calibrated to the patient's composite risk profile, accounting for comorbid conditions, pharmacogenomic data, and susceptibility to adverse events. Such a tailored approach enhances therapeutic efficacy while reducing the probability of future cardiovascular incidents (28).

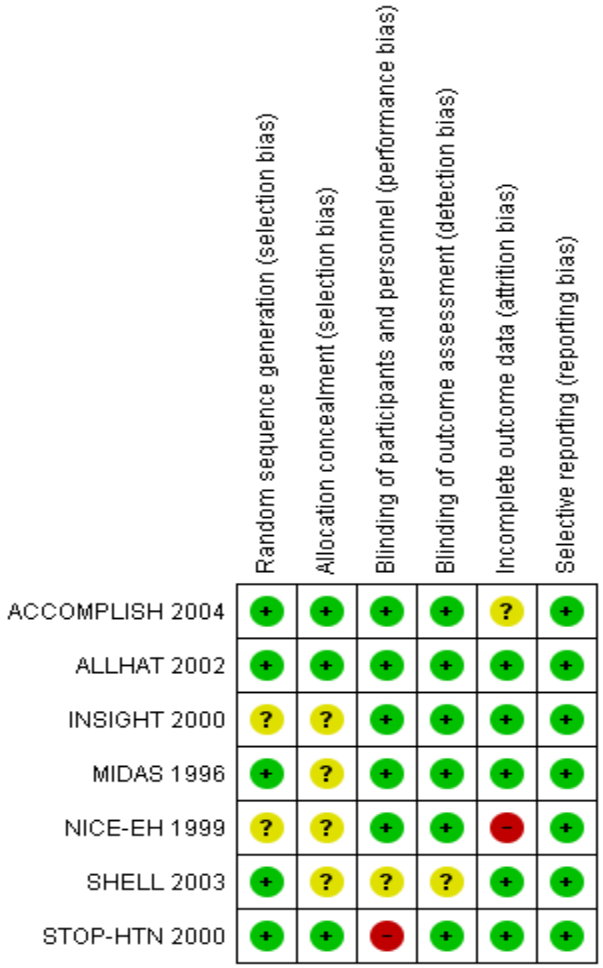

Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

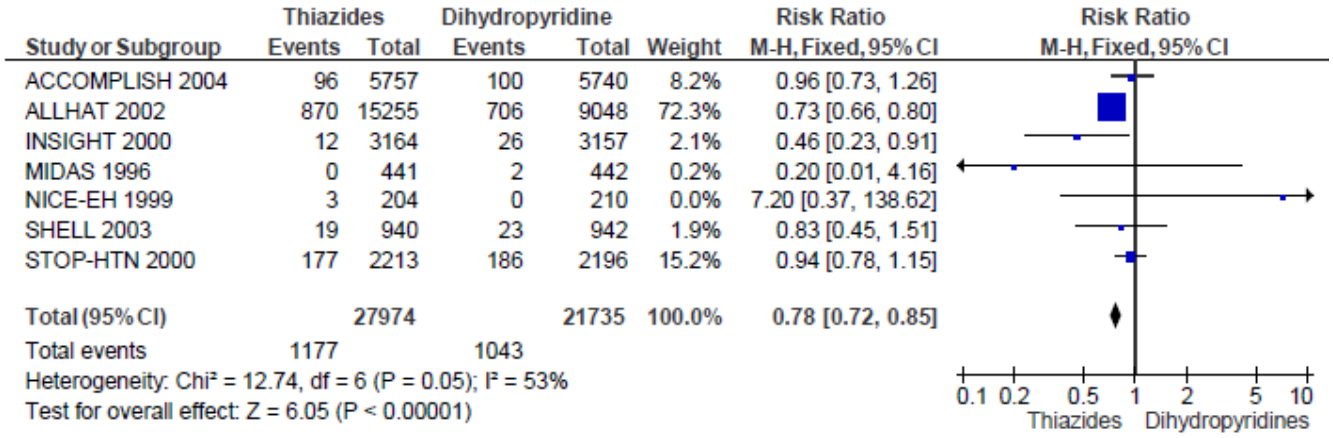

Figure 4: Forest plot comparing Thiazides and Dihydropyridines for heart failure outcomes (Fixed-Effects model): Presented in both graphical and numerical formats (mmHg, 95% CI), with the overall effect indicating the combined relative risk estimate.

This study's strengths lie in its systematic approach and large sample size, drawing data from seven RCTs with 49,709 participants. This robust dataset enhances the reliability and statistical power of the findings, enabling meaningful comparisons between thiazides and DHPs. Additionally, the study's focus on HF risk as the primary outcome addresses a critical gap in understanding the cardiovascular effects of these drug classes, providing valuable insights for clinical decision-making in hypertensive patients. However, this study has limitations. The exclusion of non-English studies and the reliance on published RCTs may introduce publication bias, potentially skewing the results.

In addition, the findings of this study have significant implications for hypertension management. Thiazides may be prioritized for patients at high risk of HF due to their ability to reduce preload and afterload, thereby enhancing cardiac functioning. Meanwhile, the neutral effects of DHPs on the risk of HF make them a viable alternative, particularly for patients who cannot tolerate diuretics (29). Clinicians should carefully consider both the efficacy of antihypertensive drugs in controlling blood pressure and their long-term impact on cardiovascular outcomes. Personalized treatment plans tailored to patient-specific factors, such as comorbidities and risk profiles, are essential to optimize therapeutic outcomes (2, 30).

This systematic review distinguishes itself methodologically and in scope from prior meta-analyses. It does this by exclusively focusing on head-to-head comparisons between thiazide diuretics and DHPs in relation to HF risk among hypertensive patients, utilizing only RCTs with ≥100 participants and ≥12 months of follow-up. Unlike earlier reviews that included mixed populations or evaluated composite cardiovascular outcomes (e.g., CHD, stroke) or used broader comparator groups such as ACE inhibitors or beta-blockers (31, 32), this study targeted HF-specific outcomes as the primary endpoint, thereby offering a more precise and clinically relevant estimate of HF risk. The inclusion criteria were rigorously defined using the PICOS framework, with an emphasis on outpatient settings and standardized HTN definitions, in contrast to prior analyses with heterogeneous populations or varied settings (33). Moreover, the current review employed a transparent PRISMA-guided methodology and bias assessment, further enhancing its methodological robustness compared to earlier work with less standardized quality appraisal (28). Through its stringent design and scope, this meta-analysis provides novel and reliable insights into the differential HF risk between thiazides and DHPs, supporting informed therapeutic decisions.

From a clinical application perspective, this meta-analysis provides strong evidence favouring the use of thiazide diuretics over DHPs for reducing HF risk in hypertensive patients, particularly those with prior cardiovascular disease. The demonstrated cardioprotective benefit of thiazides (RR 0.77; 95% CI: 0.70–0.84) supports their role as a first-line option for HF prevention through preload and afterload reduction. DHPs remain a suitable alternative for patients who cannot tolerate thiazides due to electrolyte or renal issues. These findings endorse a personalized, risk-based approach to HTN management, encouraging the integration of comorbidities and patient-specific profiles into treatment decisions. They also support guideline updates to prioritize thiazides in HF-prone individuals and highlight the potential role of combination therapy in enhancing cardiovascular protection.

The limitations to a clinical application are [1] Heterogeneity and Bias: Moderate heterogeneity (I^2 = 53%) and unclear risks of bias in some studies (e.g., allocation concealment, blinding) suggesting caution in applying results universally. Clinicians should consider patient populations similar to those in the included RCTs (outpatient, ≥100 participants, ≥12 months follow-up); [2] Exclusion of Non-English Studies: Potential publication bias from excluding non-English studies may limit generalizability; and [3] Potential Publication Bias: The reliance on published RCTs and the exclusion of unpublished or grey literature may have introduced publication bias, as studies with significant results are more likely to be published.

Future research should focus on addressing knowledge gaps by conducting long-term RCTs to assess the prolonged effects of antihypertensive therapies on HF outcomes and investigating the mechanisms underlying their cardioprotective benefits. Additionally, expanding research to include other drug classes, such as ACE inhibitors and beta-blockers, as well as exploring combination therapies, could provide a more comprehensive understanding of HF risk management. Subgroup analyses based on patient demographics and

clinical characteristics would offer deeper insights, ultimately guiding the development of refined, evidence-based guidelines for treating hypertension and improving cardiovascular health outcomes.

Conclusion: The meta-analysis identified a statistically significant reduction in the incidence of heart failure among hypertensive patients treated with thiazide diuretics compared to those receiving dihydropyridine calcium channel blockers. These findings may inform therapeutic decision-making; however, further high-quality investigations are required to confirm these outcomes and to clarify their broader clinical applicability.

Supplementary Materials: The following supporting information can be downloaded at: https://drive.uqu.edu.sa/_/26919/1a47b45c-0db3-4676-9d5e-436748c94112.pdf S1: Search strategy for MEDLINE (OVID):1994 to October 2024; Table S2: Search strategy for EMBASE (OVID):1994 to October 2024; Table S3: Search strategy for CENTRAL:1994 to October 2024; Table S4: Search strategy for Web of Science:1994 to October 2024.

Author Contributions: Conceptualization, methodology, software, validation, formal analysis, data curation, writing—review and editing, S.M.A and Y.Z.A. Both authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement:

All data and supporting materials related to this study are available within the published article.

Acknowledgments: We would like to thank Professor Sandosh Padmanabhan for being the third investigator acting as a tiebreaker, independently reviewing articles to resolve disagreements.

Conflicts of Interest: The authors declare no conflict of interest

Declaration of Generative AI and AI-assisted technologies in the writing process: During the preparation of this work the authors used ChatGPT 4.0 and Google Gemini in order to enhance the writing of this manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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