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Risk of New-Onset Diabetes with Thiazide Diuretics in Hypertensive patients: A Systematic Review and Meta-Analysis

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ABSTRACT: Background: thiazide diuretics are often recommended as the initial treatment of choice for hypertension. Due to their effectiveness and cardiovascular

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benefits. However, concerns regarding metabolic adverse effects, and particularly new-onset diabetes mellitus (NODM), remain and may deny any long-term advantage. This review and meta-analysis compared the risk of NODM and other classified outcomes using thiazide and thiazide-like diuretics versus not using thiazide diuretics.

Methods: Following the PRISMA 2020 guidelines, a systematic search of PubMed, Scopus, and EMBASE from January 2005 to 2025 was conducted for cohort and randomized controlled trials that reported outcomes of NODM. Extracted data included patient population, type of treatment, blood pressure, cardiovascular events, and adverse events. Combined odds ratios (ORs) were estimated using a random effects model.

Results: Five studies were included in this review (four randomized trials and one cohort; >22,000 patients). There was no significant association in NODM with thiazide treatment, compared with patients not treated with thiazide (OR 1.21, 95%CI 0.91-1.59, p=0.19; I^2=48%) A subgroup analysis showed mixed results, with one study demonstrating an increase in the incidence of diabetes while other studies showed no increase. Thiazide use did appear to confer an increase in risk of hypokalemia (OR 6.58, 95% CI 5.49-7.89, p<0.00001).

Conclusion: Thiazide diuretics remain safe and effective in the treatment of hypertension. Although we found risk of hypokalemia and a possible risk of NODM, these risks did not translate into increased cardiovascular morbidity or mortality. Glucose and potassium should be monitored in high-risk patients; however, thiazide will remain a foundation in hypertension therapy.

INTRODUCTION

Hypertension is a major global health problem that significantly increases the risk of cardiovascular diseases and mortality [1]. With a prevalence exceeding 24%, hypertension requires effective management strategies to reduce the risk of stroke, myocardial infarction, heart failure, and kidney disease [2]. Thiazide diuretics remain a cornerstone as first-line antihypertensive agents due to their proven efficacy in lowering blood pressure, combined with accessibility and affordability. Several key clinical trials have demonstrated that these medications effectively decrease cardiovascular events [3,4].

However, despite their benefits, thiazide diuretics are associated with certain metabolic side effects. Although generally well tolerated, they can adversely affect glucose metabolism, lipid profiles, and electrolyte balance [5,6]. Of particular concern is the development of new-onset diabetes mellitus in patients receiving thiazide diuretics. These metabolic disturbances may diminish the long-term cardiovascular benefits of blood pressure reduction since diabetes itself is a significant cardiovascular risk factor [5].

Research findings regarding the risk of new-onset diabetes vary, influenced by factors such as patient characteristics, duration and dosage of thiazide therapy, and concurrent medication use [7]. Therefore, a comprehensive evaluation of existing evidence is essential to clarify the risk of diabetes development in hypertensive patients treated with thiazide diuretics, supporting informed clinical decisions and guideline development.

This systematic review aims to critically appraise and synthesize the current evidence on the risk of new-onset diabetes mellitus among hypertensive patients treated with thiazide diuretics. By systematically identifying, evaluating, and summarizing relevant studies, this review seeks to quantify the risk and explore potential influencing factors, thereby contributing to a more nuanced understanding of the metabolic profile of

thiazide diuretics in routine clinical practice.

METHODOLOGY

Protocol Registration and Approval

The systematic review was conducted according to the Preferred Reporting guidelines for Systematic Reviews and Meta-Analyses (PRISMA) 2020 standards [8], to ensure ease of transparency and completeness of reporting. The protocol was

registered on International Prospective Register of Systematic Reviews (PROSPERO) with ID: CRD420251132113. Informed consent and ethical approval were not needed as the review was secondary analysis of data that had already been published.

Search Strategy

We systematically searched the PubMed database, In addition, we also searched Scopus, Embase, Medline, and the Cochrane Library, to identify studies published during the period from January 2005 to 2025. The search was carried out using Medical Subject Headings (MeSH) and free text keywords of thiazide or thiazide-like diuretic, hypertension, and type 2 diabetes mellitus. The following Boolean operators were used:

("(Hypertension"[Mesh] OR hypertension OR "high blood pressure") AND ((((“Thiazides"[Mesh] OR thiazide OR "thiazide diuretics" OR hydrochlorothiazide OR chlorthalidone OR indapamide OR Bendroflumethiazide) AND ("Diabetes Mellitus, Type 2"[Mesh] OR "diabetes mellitus" OR "type 2 diabetes" OR "new-onset diabetes" OR "incident diabetes" OR "diabetes risk").

Only full-text articles written in the English language were included. Hand searches of reference lists of included articles were performed to identify other relevant studies.

Study Selection Criteria

The trials were to be included as long as they involved adult patients of at least 18 years of age with a clear diagnosis of primary hypertension. The inclusion trials involved comparing the use of thiazide or thiazide-like diuretics such as hydrochlorothiazide, chlorthalidone, or indapamide alone or in combination with other agents for blood pressure reduction, with an expressed dose and for a specified duration of treatment. Trials had to be included if they contained a comparator group (placebo or non-diuretic antihypertensives) and new-onset diabetes mellitus (NOD) incidence as an outcome (incidence rate, relative risk, or hazard ratio). Trials also must have a follow-up of at least six months to be able to have enough outcome measurement. Included study designs were randomized controlled trials and prospective cohort studies. For the purpose of accessibility as well as consistency in reporting, only those English language studies between the years 2005 and 2025 with full-text availability were used.

They excluded studies with pediatric populations (subjects younger than 18 years) or pregnant women, or where subjects had pre-existing diabetes mellitus at baseline. They excluded studies where NOD was not defined and reported as an outcome, or which did not control for the effects of thiazide or thiazide-like diuretics from other therapy. Also excluded was evidence with a follow-up period of less than six months, or that utilized retrospective, case-control, or cross-sectional study designs. Meta-analyses, literature reviews, letters to the editor, case series, case reports, non-English language publications for which no translation was available, and studies published solely in abstract format (e.g., conference proceedings, dissertations, or unpublished data) were not included in the analysis., editorials, conference abstracts, or non-English articles without available translation.

Screening

A total of 1024 articles were initially retrieved and imported into PubMed. Duplicate records were removed. Two independent reviewers screened the titles and abstracts based on predefined inclusion and exclusion criteria, resulting in 29 articles selected for full-text review. These full-text articles were then independently assessed by the same reviewers, and 5 studies met the inclusion criteria to be included in the final analysis. Any disagreements regarding study eligibility were resolved through discussion or consultation with a third reviewer.

Data Extraction and Risk of Bias Assessment

Data from the included studies were independently extracted by two reviewers using a standardized data extraction form. Extracted data included study characteristics (such as study design, year of publication, and country), participant characteristics (age and sex), details of the interventions, comparator groups, and outcome measures related to the study objectives. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

The Cochrane Risk of Bias Tool was used to assess RCTs for sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting [9]. The Newcastle–Ottawa Scale will assess observational studies for selection,

comparability, and outcome domains [6,10]. Tow reviewers will perform the assessments independently, with disagreements resolved by discussion or third-party review.

Outcome Measures

The primary outcome assessed was the incidence of new-onset diabetes mellitus (NOD) in patients using thiazide or thiazide-like diuretics. Effect measures included relative risk (RR), hazard ratio (HR), or odds ratio (OR) when reported.

Data Synthesis

A qualitative synthesis will summarize study characteristics, population details, types/doses of thiazide diuretics, and reported diabetes incidence. Where data are sufficiently homogeneous, a meta-analysis will be conducted to estimate pooled risk ratios (RRs), odds ratios (ORs), or hazard ratios (HRs) using a random-effects model. Heterogeneity will be assessed using χ^2 and I^2 statistics, with I^2 >50% indicating substantial heterogeneity [11]. Publication bias will be evaluated using funnel plots

Statistical Analysis

Statistical analyses were conducted using Review Manager (RevMan, version 5.4, Cochrane Collaboration). Pooled prevalence estimates were calculated with a random-effects model and expressed with 95% confidence intervals (CIs). For each study, proportions and standard errors were derived from the reported number of cases and total sample size. Heterogeneity was quantified using the I^2 statistic. To account for heterogeneity, subgroup analyses were performed by age group (pediatric vs adult). Publication bias was assessed visually using funnel plots, and small-study effects were considered when asymmetry was observed. All p-values < 0.05 were regarded as statistically significant.

Reporting

All findings from the systematic review will be reported following the PRISMA 2020 guidelines to ensure clarity, transparency, and reproducibility.

RESULTS

A total of 1024 records were identified through database searches including PubMed, Scopus and EMBASE. Following the removal of 40 duplicate records, 984 titles and abstracts were screened, of which 888 full-text articles were sought for retrieval. 29 reports were retrieved and assessed for eligibility. Of these, 24 reports were excluded for the following reasons: wrong study design (n = 11), irrelevant intervention or exposure (n = 4), and irrelevant outcomes (n = 9). Ultimately, five studies met the eligibility criteria and were included in the systematic review (**Figure1**).

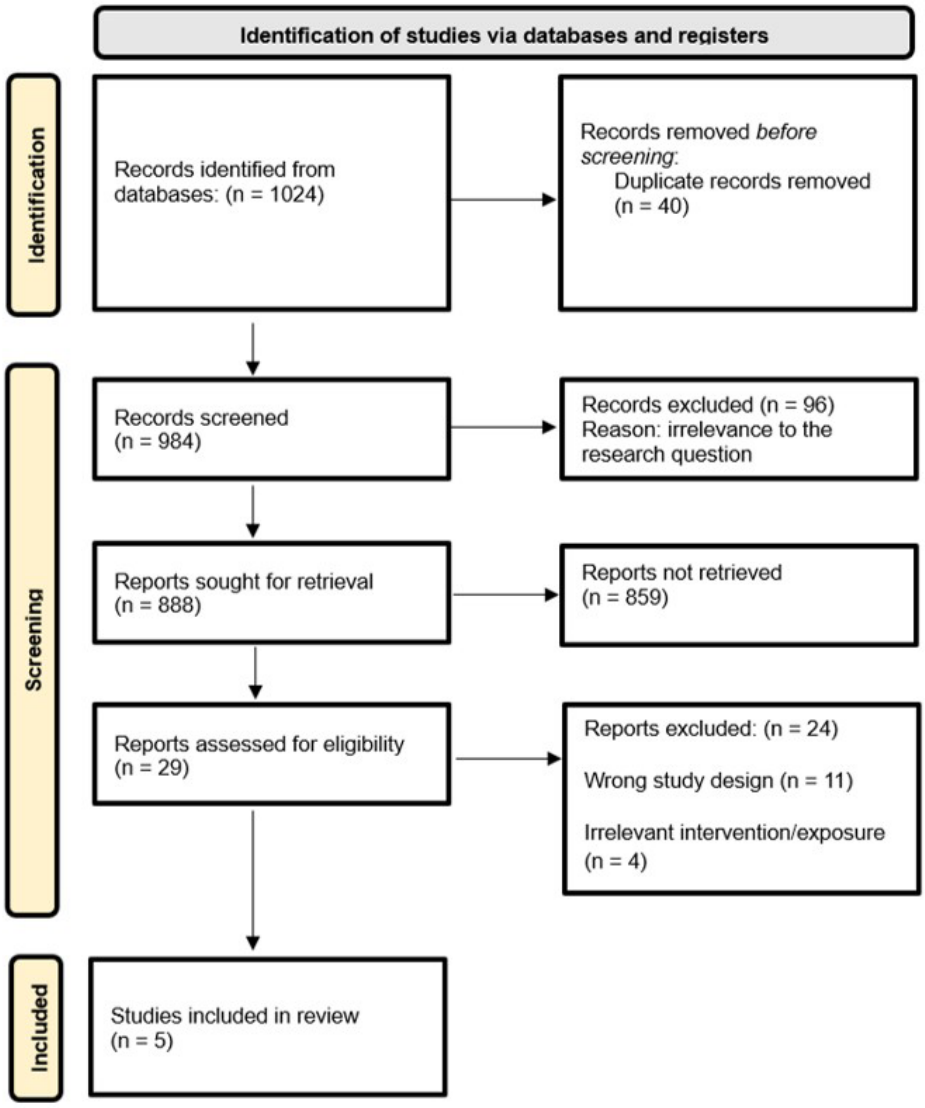

Figure 1: PRISMA Flow Diagram of Study Identification and Screening

BASELINE DEMOGRAPHICAL CHARACTERISTICS OF INCLUDED STUDIES

The baseline characteristics highlight the diversity of the included studies in terms of geography, sample size, and study design (**Table 1**) [12-16]. Wright et al. in 2002, reporting on the ALLHAT trial, was the largest randomized controlled trial (RCT) with more than 33,000 participants split across the chlorthalidone reference arm and three comparator arms (amlodipine, lisinopril, doxazosin). The study population was older, with a mean age of 67 years and over one-third aged 70 years or above. Both sexes were represented almost equally, reflecting the pragmatic nature of the trial across the United States, Canada, Puerto Rico, and the U.S. Virgin Islands [12]. Bakris et al. in 2006 conducted a smaller PROBE-design RCT in the United States, enrolling 240 patients randomized equally to fixed-dose losartan/hydrochlorothiazide or trandolapril/verapamil. The mean age was mid-50s, with a balanced sex distribution. Follow-up extended for approximately one year [13].

Taylor et al. in 2006 contributed evidence from a large prospective cohort analysis pooling data from the Nurses' Health Study I and II and the Health Professionals Follow-up Study. Over 44,000 individuals were included, with mean ages in the early to mid-50s. The cohort reflected the gender composition of the parent studies, with women predominating in NHS and men in HPFS. This long-term observational analysis provided detailed definitions of new-onset diabetes (NODM) across several decades of follow-up. Two Japanese RCTs added Asian population data [14]. Ogihara et al. in 2012 analyzed a subset of the

COPE trial, including 1,094 patients in the thiazide arm and 2,199 in comparator groups. Participants were elderly, with mean age just over 63 years, and the trial carefully captured cardiovascular endpoints such as myocardial infarction, stroke, peripheral arterial disease, and heart failure [15]. Ueda et al. in 2014 presented results from the DIME trial, which randomized 544 patients to thiazide diuretics and 586 to non-thiazide agents. Participants were again elderly, with mean age in the mid-60s, and follow-up extended for over four years with high retention (>95%) [16].

Table 1. Baseline Characteristics of Included Studies: Study Design, Demographics, Age, and Gender Distribution

First Author (Year)	Journal	Country	Study Design	Total Participants (Thiazide / Non-thiazide)	Mean Age (Range) — Thiazide / Non-thiazide	Gender — Thiazide / Non-thiazide	Follow-up / Notes
Wright (2002) [12]	*JAMA* (ALLHAT)	USA, Canada, Puerto Rico, USVI	RCT	15,255 / 18,102	67 y (≥55; ~36% ≥70)	~47% M / 53% F (overall trial)	Long-term; MACE defined as CHD events; landmark ALLHAT
Bakris (2006) [13]	*Diabetes Care*	USA	PROBE RCT	121 / 119 (total 240)	55.4 ± 9.7 y / 57.7 ± 10.3 y (eligibility ≥21 y)	51.2% M, 48.8% F / 46.2% M, 53.8% F	Follow-up ≈ 1 year (46.9 ± 13.5 weeks)
Taylor (2006) [14]	*Diabetes Care*	USA	Prospective cohort (NHS I/II, HPFS)	10,049 / 34,142	54.2 y / 52.3 y	40.4% M, 59.6% F / 18.3% M, 81.7% F	NHS I 1994–2002 (8 y); NHS II 1991–2001 (10 y); HPFS 1986–2002 (16 y); detailed NODM definitions
Ogihara (2012) [15]	*Hypertension Research* (COPE sub-analysis)	Japan	RCT	1,094 / 2,199	63.10 y (40–85) / 63.06 y (40–85)	50.5% M / 49.5% F (overall arm)	Cardiovascular endpoints captured (stroke, MI, PAD, HF)
Ueda (2014) [16]	*BMJ Open* (DIME)	Japan	RCT	544 / 586	66.4 y (≥55–~80s) / 66.5 y (≥55–~80s)	NR	4.4 y follow-up; >95% retained; allowed ACEi/ARB/CCB/β-blocker/statin use

Abbreviations: RCT: randomized controlled trial, PROBE: prospective randomized open, blinded endpoint, NHS: Nurses' Health Study, HPFS: Health Professionals Follow-up Study, USA: United States of America, USVI: United States Virgin Islands, MACE: major adverse cardiac events, CHD: coronary heart disease, MI: myocardial infarction, PAD: peripheral arterial disease, HF: heart failure, ARB: angiotensin receptor blocker, ACEi: angiotensin-converting enzyme inhibitor, CCB: calcium channel blocker.

Antihypertensive Interventions: Thiazide-Based Regimens Compared With Non-Thiazide Therapies

In ALLHAT by Wright in 2002, chlorthalidone served as the reference therapy against amlodipine, lisinopril, and doxazosin, under a standardized protocol with cardiovascular outcomes tracked as major adverse cardiac events (MACE) [12]. Bakris et al. in 2006 compared a fixed-dose combination of losartan/hydrochlorothiazide against trandolapril/verapamil, with blinded endpoint assessment over roughly one year [13] (**Table 2**).

In the large cohort analysis by Taylor et al. in 2006, patients were exposed to a range of thiazides (chlorthalidone, hydrochlorothiazide, bendroflumethiazide), with comparator groups using β-blockers, ACE inhibitors, calcium channel blockers, or other agents. The models also accounted for concomitant therapies such as furosemide, digoxin, and lipid-lowering agents, ensuring adjustment for confounding in long-term observational follow-up [14].

Ogihara et al. in 2012 compared benidipine with adjunctive thiazides against benidipine with either an ARB or β-blocker. This design reflected common Japanese practice for elderly hypertensives, and cardiovascular outcomes were formally assessed [15]. Ueda et al. in 2014 evaluated three thiazide diuretics at low doses (hydrochlorothiazide 12.5 mg, indapamide 1 mg, or trichlormethiazide 1 mg daily). These were compared with a range of non-thiazide regimens, including ACE inhibitors, ARBs, calcium channel blockers, β-blockers, and statins, which were permitted concomitantly. The pragmatic design allowed real-world polypharmacy, with follow-up lasting 4.4 years [16].

Table 2. Antihypertensive Interventions: Thiazide-Based Regimens Compared With Non-Thiazide Therapies

First Author (Year)	Thiazide Intervention & Dose	Comparator / Non-thiazide Intervention	Concomitant / Background Therapy	Follow-up / Trial Notes
Wright (2002) **[12]**	Chlorthalidone (reference arm in ALLHAT)	Amlodipine, Lisinopril, Doxazosin	Standard of care per protocol	Long-term; MACE = CHD events; combined CVD also tracked
Bakris (2006) **[13]**	Losartan/Hydrochlorothiazide (fixed-dose)	Trandolapril/Verapamil (fixed-dose)	—	~1 year; blinded endpoint assessment
Taylor (2006) **[14]**	Chlorthalidone, Hydrochlorothiazide, Bendroflumethiazide	β-blockers, ACE inhibitors, CCBs, other antihypertensives	Models adjusted for furosemide, digoxin, lipid-lowering drugs	NHS I/II/HPFS long-term medication exposure
Ogihara (2012) **[15]**	Benidipine 4 mg/day + Thiazide diuretic	Benidipine 4 mg/day + ARB or + β-blocker	As per COPE protocol	Elderly hypertensives; CV endpoints recorded
Ueda (2014) **[16]**	HCTZ 12.5 mg/day, Indapamide 1 mg/day, Trichlormethiazide 1 mg/day	ACE inhibitors, ARBs, CCBs, β-blockers, statins	Concomitant ACEi/ARB/CCB/β-blocker/statin permitted	4.4 years; >95% follow-up

Abbreviations: HCTZ: hydrochlorothiazide, ARB: angiotensin receptor blocker, ACEi: angiotensin-converting enzyme inhibitor, CCB: calcium channel blocker, MACE: major adverse cardiac events, CV: cardiovascular, NHS: Nurses' Health Study, HPFS: Health Professionals Follow-up Study.

Clinical Outcomes: New-Onset Diabetes, Blood Pressure Control, and Cardiovascular Events Across Studies

Clinical outcomes varied substantially across trials (Table 3). In ALLHAT, Wright et al. in 2002 did not provide explicit new-onset diabetes incidence within this summary, but glycemic indices showed modest elevations in fasting glucose for chlorthalidone compared with other arms. Blood pressure was well controlled in both groups, with final mean systolic and diastolic pressures in the mid-130s and mid-70s, respectively. Cardiovascular outcomes demonstrated fewer coronary heart disease events and heart failure cases in the thiazide arm compared with comparators, reinforcing chlorthalidone's efficacy despite metabolic concerns [12].

Bakris et al. in 2006 reported significantly higher rates of new-onset diabetes in patients treated with losartan/hydrochlorothiazide (26.6%) compared with trandolapril/verapamil (11.0%). Glycemic deterioration was evident, with greater rises in fasting glucose and HbA1c in the thiazide-containing arm. Nevertheless, blood pressure reductions were comparable, with systolic and diastolic values reaching approximately 129/79 mmHg in both groups by trial end [13]. Taylor et al. in 2006 observed modestly higher incidence of new-onset diabetes in thiazide users (4.6%) compared with non-thiazide users (4.0%) across decades of follow-up. This large cohort analysis added weight to concerns regarding diabetes risk, although absolute differences were small [14].

In the COPE sub-analysis, Ogihara et al. in 2012 reported similar new-onset diabetes rates between thiazide (3.4%) and non-thiazide (3.1%) arms. Blood pressure was tightly controlled, with systolic averages near 134 mmHg and diastolic averages near 77 mmHg. Notably, major cardiovascular outcomes were lower in the thiazide group, including heart failure rates (1.3% vs. 2.5%) [15]. Ueda et al. in 2014 demonstrated balanced diabetes risk across groups, with 4.6% in the thiazide arm and 4.9% in the non-thiazide arm. Final fasting glucose and HbA1c were nearly identical between arms, indicating no clinically significant glycemic disadvantage. Blood pressure control was excellent, with mean systolic and diastolic values at 135/78 mmHg in both groups. Cardiovascular outcomes were mixed: stroke occurred slightly more frequently in the thiazide group, while myocardial infarction and peripheral arterial disease were marginally higher in the comparator group. Heart failure events were less frequent among thiazide users (0.4% vs. 1.1%) [16].

Table 3. Clinical Outcomes: New-Onset Diabetes, Blood Pressure Control, and Cardiovascular Events Across Studies

First Author (Year)	NODM events / At-risk — Thiazide	NODM events / At-risk — Non-thiazide	Fasting Glucose (end) — Thiazide / Non-thiazide	HbA1c Δ — Thiazide / Non-thiazide	Hypokalemia — Thiazide / Non-thiazide	SBP end — Thiazide / Non-thiazide	DBP end — Thiazide / Non-thiazide	MACE (N, %) — Thiazide / Non-thiazide	At-risk for MACE — Thiazide / Non-thiazide	Heart failure (N, %) — Thiazide / Non-thiazide	Notes
Wright (2002)			126.3 ± 55.6 / 122.5 ± 51–52			133.9 ± 15.7 / 135.1 ± 16.1	74.9 ± 10.3 / 75.6 ± 10.2	1,418/15,255 (9.3%) / 2,046/18,102 (11.3%)	15,255 / 18,102 (both 100%)	1,158/15,255 (7.7%) / 1,710/18,102 (9.4%)	MACE per sheet = CHD events
Bakris	25/94 (26.6%)	10/91 (11.0%)	6.57 ± 2.95 /	+0.4 ± 0.1%		128.8 ± 14.0 /	78.8 ± 8.8 /				Fixed-dose ARB/H

(2006)			6.11 ± 1.12	/ +0.1 ± 0.1%		130.6 ± 15.7	78.7 ± 10.0				CTZ vs ACEi/CCB
Taylor (2006)	461/10,049 (4.6%)	1,368/34,142 (4.0%)									NODM definitions before/after 1996 explicitly specified
Ogihara (2012)	32/1,094 (3.4%)	58/2,199 (3.1%)				134.00 ± 14.46 / 133.97 ± 15.24	76.79 ± 10.59 / 77.18 ± 10.43	14/1,094 (1.28%) / 54/2,199 (2.46%)	1,094 / 2,199 (both 100%)		"At risk of diabetes" shown: 936/1,094 (85.5%) vs 1,890/2,199 (86%)
Ueda (2014)	25/544 (4.6%)	29/586 (4.9%)	102 ± 14 / 103 ± 16	5.4 ± 0.4 / 5.4 ± 0.4	2/544 (0.4%) / 1/586 (0.2%)	135 ± 16 / 135 ± 15	78 ± 11 / 77 ± 11	Stroke 11/544 (2.2%), MI 2/544 (0.4%), PAD 2/544 (0.4%) / Stroke 5/586 (1.1%), MI 5/586 (1.0%), PAD 3/586 (0.5%)	544 / 586 (both 100%)	2/544 (0.4%) / 6/586 (1.1%)	Pragmatic, multi-drug background allowed

Abbreviations: NODM: new-onset diabetes mellitus, HbA1c: glycated hemoglobin, SBP: systolic blood pressure, DBP: diastolic blood pressure, MACE: major adverse cardiac events, CHD: coronary heart disease, MI: myocardial infarction, PAD: peripheral arterial disease, HF: heart failure, ARB: angiotensin receptor blocker, ACEi: angiotensin-converting enzyme inhibitor, CCB: calcium channel blocker.

Meta-analysis of Clinical Outcomes: New-Onset Diabetes, Blood Pressure, and Cardiovascular Events

The pooled analysis of four studies evaluating the risk of new-onset diabetes mellitus (NODM) among thiazide users compared with non-thiazide users demonstrated no statistically significant difference between groups (OR 1.21, 95% CI 0.91–1.59, p = 0.19) (**Figure 2**). While the largest trial by Taylor et al. contributed nearly half of the overall weight and showed a modest but significant association (OR 1.15, 95% CI 1.03–1.28), the remaining studies yielded heterogeneous results, with Bakris et al. reporting an elevated risk and Ueda et al. suggesting no increased risk. Between-study heterogeneity was moderate (I^2 = 48%, p = 0.13). The funnel plot revealed a relatively symmetrical distribution of studies around the central effect estimate, though the small number of included trials limits the ability to reliably assess publication bias (**Figure 3**).

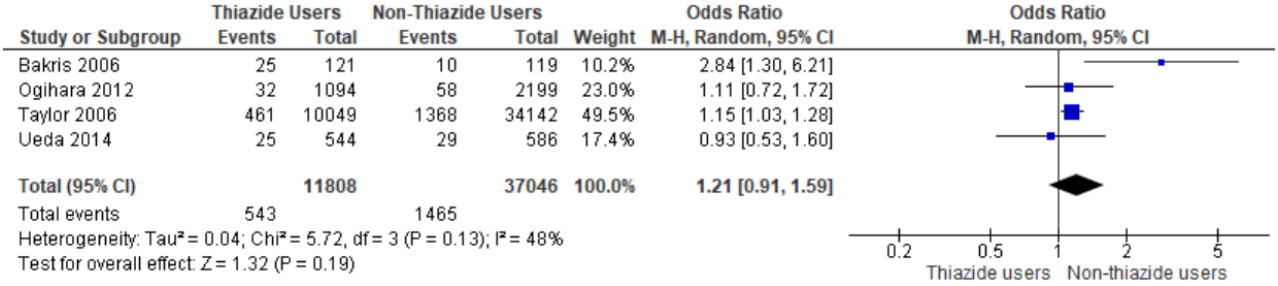

Figure 2: Forest plot 1: Thiazide vs Non Thiazide users, Outcome: New Onset Diabetes Mellitus (NODM)

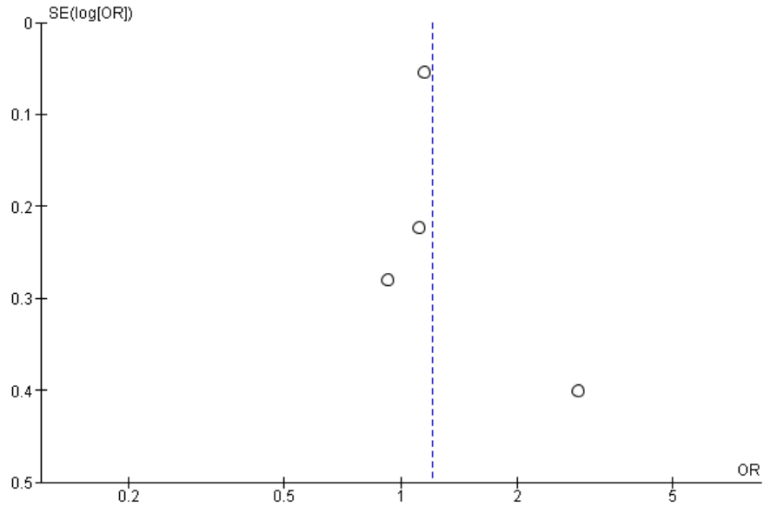

Figure 3: Funnel plot 1: Thiazide vs Non Thiazide users, Outcome: New Onset Diabetes Mellitus

The analysis comparing thiazide users with non-thiazide users for risk of developing new-onset diabetes mellitus (NODM) demonstrated no significant difference between groups (OR 0.98, 95% CI 0.80–1.19, p = 0.83) (**Figure 4**). Only two studies contributed estimable data, with Ogihara et al. carrying the majority of the weight, and both showed effect estimates crossing unity. Heterogeneity was negligible (I^2 = 0%, p = 0.76), suggesting consistency in findings across studies. The funnel plot displayed a symmetrical pattern, although the limited number of included studies constrains reliable assessment of publication bias (**Figure 5**). Overall, these results indicate that thiazide therapy does not appear to increase the risk of being at risk for NODM.

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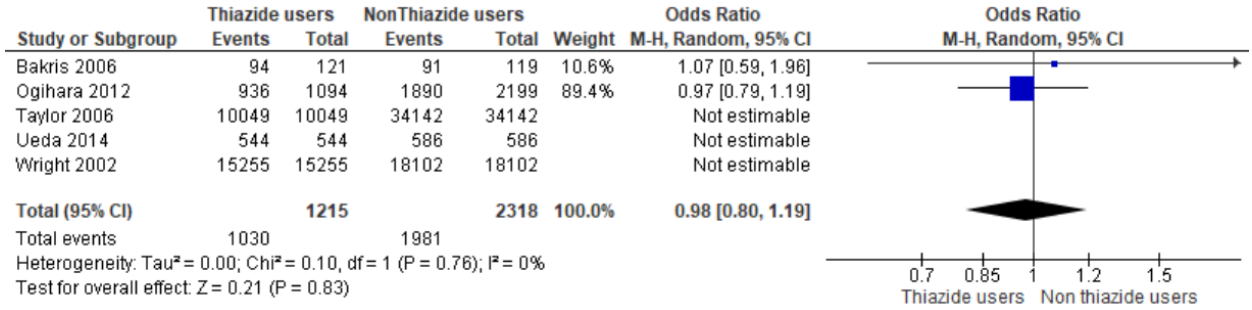

Figure 4: Forest plot 2: Thiazide vs Non Thiazide users, Outcome: At risk for New Onset Diabetes Mellitus (NODM)

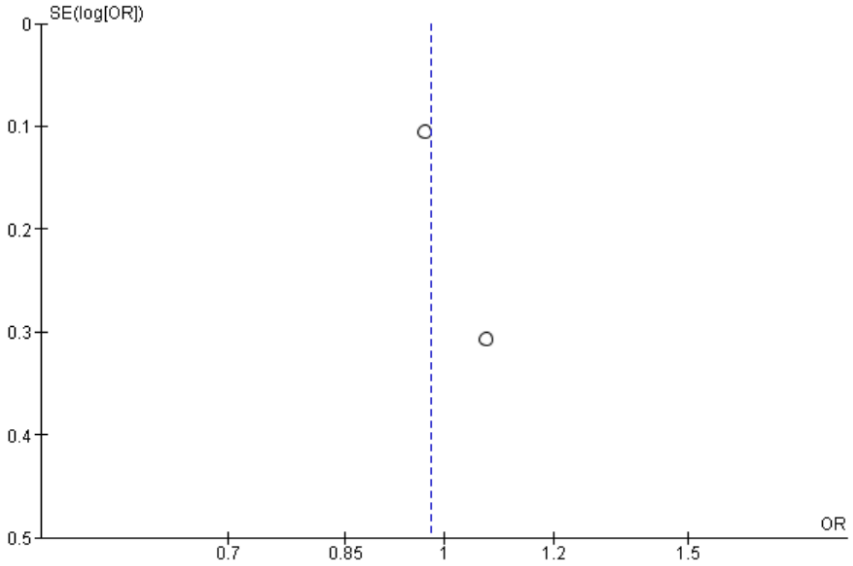

Figure 5: Funnel plot 2: Thiazide vs Non Thiazide users, Outcome: At risk for New Onset Diabetes Mellitus (NODM)

The pooled analysis of two trials assessing fasting glucose at study end between thiazide and non-thiazide users found no significant overall difference (mean difference 1.45 mg/dL, 95% CI –3.26 to 6.15, p = 0.55) (**Figure 6**). Wright et al. reported a modest elevation in fasting glucose among thiazide users, whereas Ueda et al. observed a slight reduction, resulting in substantial heterogeneity (I^2 = 95%, p < 0.00001). This marked inconsistency suggests variability in study populations or interventions may have influenced outcomes. The funnel plot indicated an imbalanced distribution, though the small number of studies precludes firm conclusions regarding publication bias (**Figure 7**). Overall, the findings do not support a consistent effect of thiazides on fasting glucose levels.

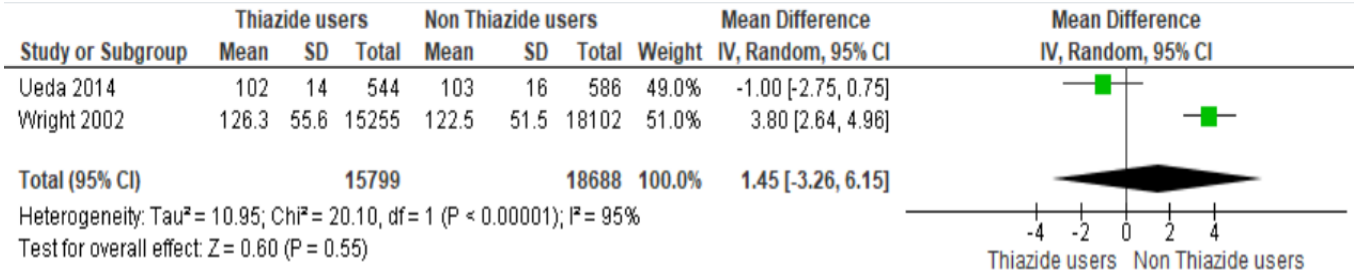

Figure 6: Forest plot 3: Thiazide vs Non Thiazide users, Outcome: Fasting glucose at study end

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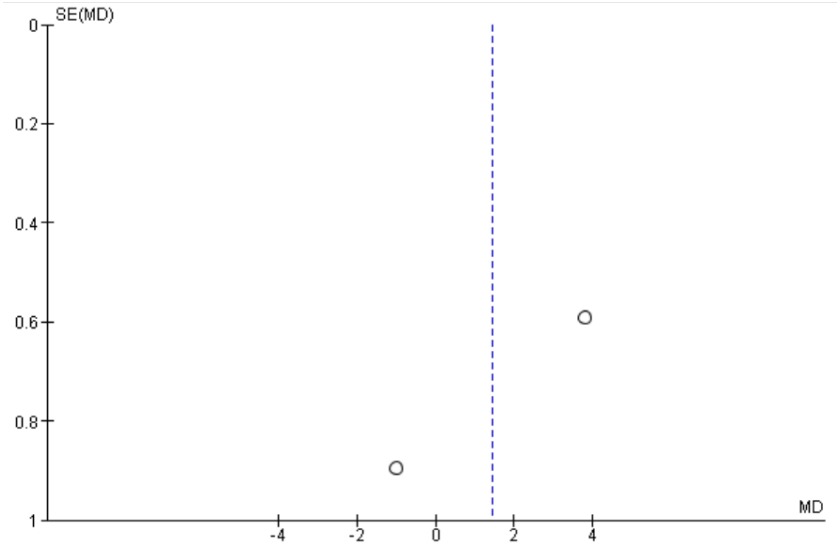

Figure 7: Funnel plot 3: Thiazide vs Non Thiazide users, Outcome: Fasting glucose at study end

The pooled analysis of three studies demonstrated a markedly higher risk of hypokalemia among thiazide users compared with non-thiazide users (OR 6.58, 95% CI 5.49–7.89, p < 0.00001) (**Figure 8**). Wright et al. contributed the majority of the weight and showed a strong association, consistent with the findings of Ogihara et al., while Ueda et al. reported a nonsignificant effect due to the small number of events. Heterogeneity was negligible (I^2 = 0%, p = 0.56), indicating a stable and consistent direction of effect across studies. The funnel plot showed a symmetrical distribution, supporting the robustness of the findings (**Figure 9**). Overall, these results strongly confirm that thiazide therapy is significantly associated with an increased risk of hypokalemia.

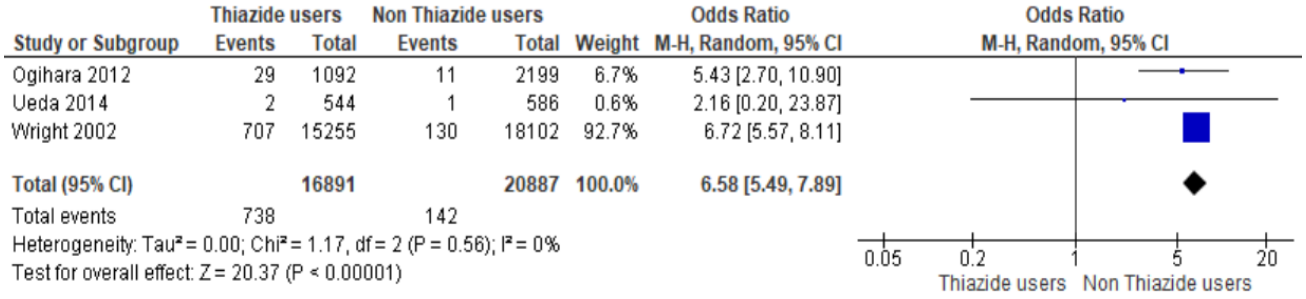

Figure 8: Forest plot 4: Thiazide vs Non Thiazide users, Outcome: Hypokalemia

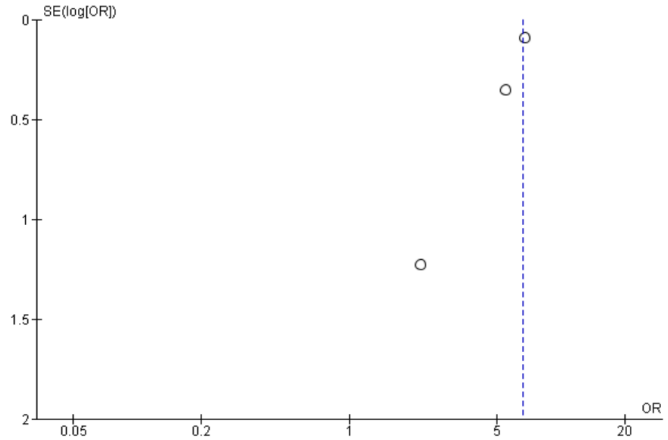

Figure 9: Funnel plot 4: Thiazide vs Non Thiazide users, Outcome: Hypokalemia

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The pooled analysis of four studies comparing systolic blood pressure (SBP) at study end between thiazide and non-thiazide users showed no statistically significant difference (mean difference –0.67 mmHg, 95% CI –1.54 to 0.19, p = 0.13) (**Figure 10**). Individual study estimates were variable: Wright et al. suggested a modest SBP reduction with thiazides, while Ogihara and Ueda reported negligible differences. Heterogeneity was moderate (I^2 = 51%, p = 0.11), indicating some inconsistency in treatment effects across studies. The funnel plot showed a relatively balanced distribution of studies around the central line, with no clear evidence of publication bias (**Figure 11**). Collectively, the findings indicate that thiazides do not significantly lower SBP compared with non-thiazide therapies at study completion.

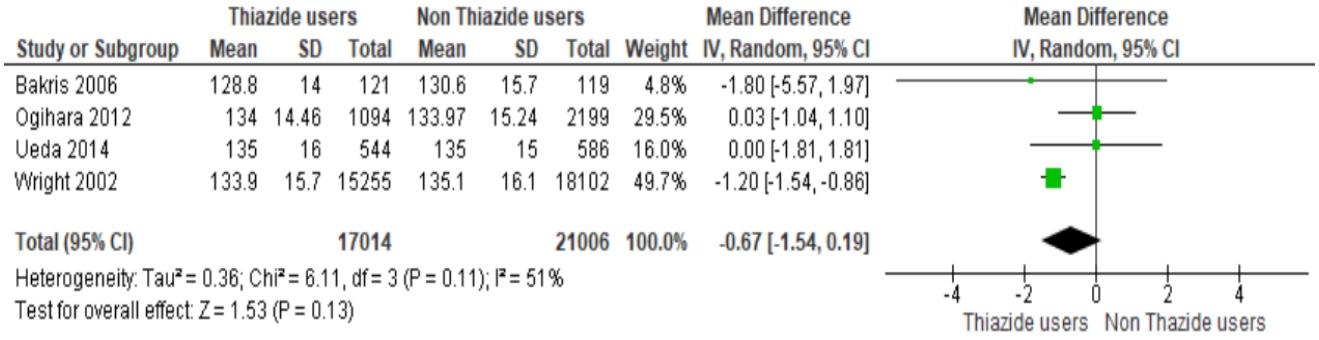

Figure 10: Forest plot 5: Thiazide vs Non Thiazide users, Outcome: Systolic Blood Pressure (SBP) at study end

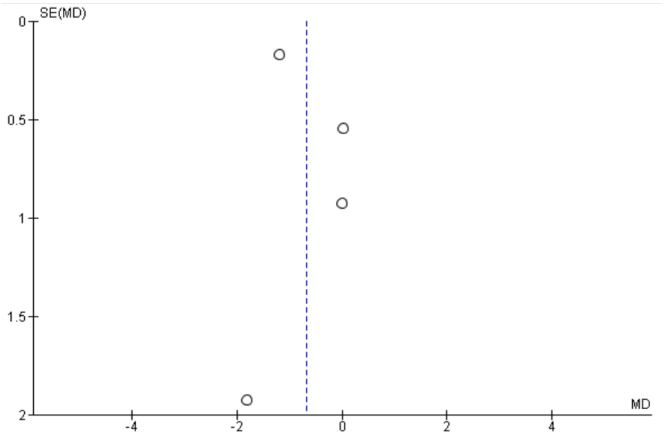

Figure 11: Funnel plot 5: Thiazide vs Non Thiazide users, Outcome: Systolic Blood Pressure (SBP) at study end

The pooled analysis of four studies evaluating diastolic blood pressure (DBP) at study end between thiazide and non-thiazide users revealed no statistically significant difference (mean difference –0.25 mmHg, 95% CI –0.93 to 0.42, p = 0.46) (**Figure 12**). Individual trials reported small, directionally inconsistent effects, with Wright et al. showing a modest reduction in DBP among thiazide users, while Ueda et al. observed a slight increase. Moderate heterogeneity was present (I^2 = 59%, p = 0.06), suggesting variability in study outcomes. The funnel plot showed a balanced spread of studies, with no apparent indication of publication bias (**Figure 13**). Overall, thiazide therapy does not appear to significantly alter DBP compared with non-thiazide regimens.

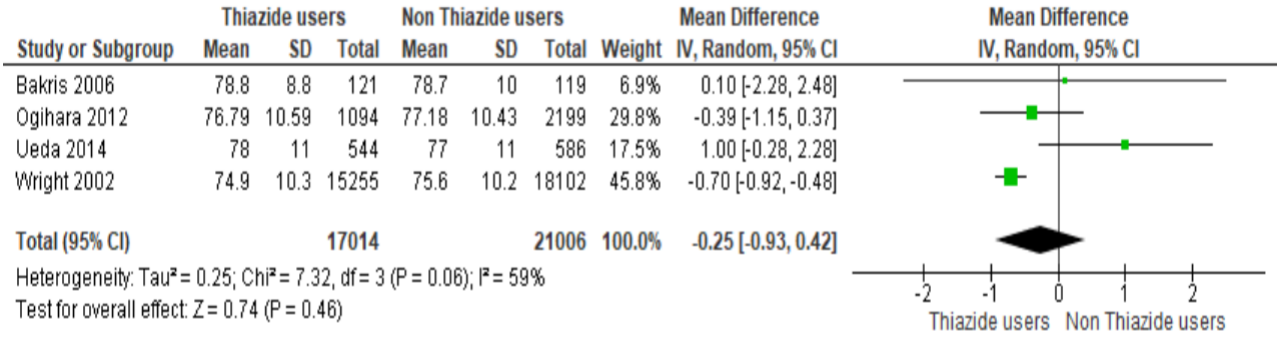

Figure 12: Forest plot 6: Thiazide vs Non Thiazide users, Outcome: Diastolic Blood Pressure (DBP) at study end

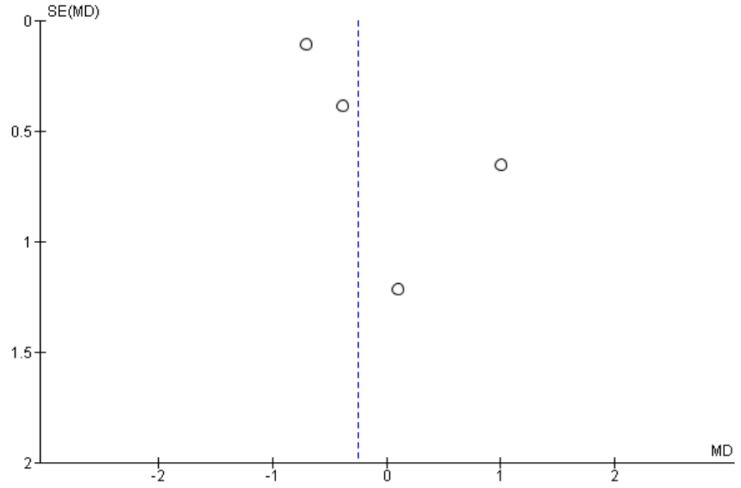

Figure 13: Funnel plot 6: Thiazide vs Non Thiazide users, Outcome: Diastolic Blood Pressure (SBP) at study end

The pooled analysis of three studies comparing thiazide versus non-thiazide users for the risk of major adverse cardiac events (MACE) showed no statistically significant difference between groups (OR 0.78, 95% CI 0.56–1.09, p = 0.14) (**Figure 14**). Ogihara et al. reported a protective effect of thiazides, whereas Ueda et al. observed a nonsignificant increased risk, and Wright et al. demonstrated a modest reduction, with all confidence intervals crossing or approaching unity. Moderate heterogeneity was present (I^2 = 43%, p = 0.17), reflecting some variability among studies. The funnel plot appeared generally symmetrical, suggesting no major evidence of publication bias, though interpretation remains limited by the small number of studies (**Figure 15**). Collectively, these findings indicate that thiazide therapy does not significantly alter the risk of MACE compared with non-thiazide regimens.

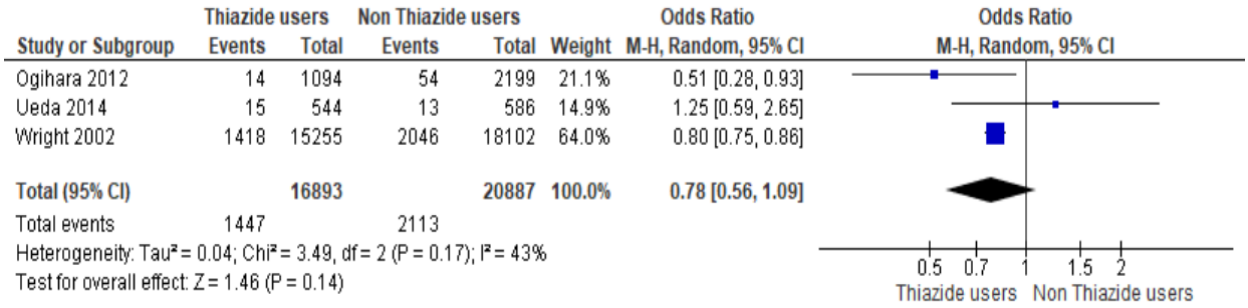

Figure 14: Forest plot 7: Thiazide vs Non Thiazide users, Outcome: Major Adverse Cardiac Events (MACE)

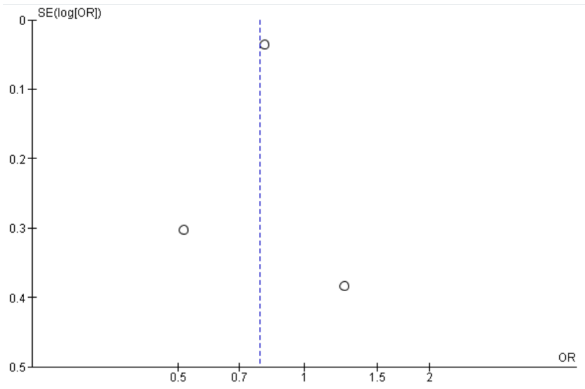

Figure 15: Funnel plot 7: Thiazide vs Non Thiazide users, Outcome: Major Adverse Cardiac Events (MACE)

The pooled analysis of two studies evaluating the incidence of heart failure among thiazide versus non-thiazide users showed no significant difference between groups (OR 0.84, 95% CI 0.35–2.02, p = 0.69) (**Figure 16**). Wright et al. contributed most of the weight and reported a neutral effect, while Ueda et al. suggested a nonsignificant protective association, though with wide confidence intervals due to the small number of events. Moderate heterogeneity was observed (I^2 = 43%, p = 0.18), reflecting variability between study results. The funnel plot revealed a scattered but balanced pattern, with no strong indication of publication bias, though conclusions remain limited by the small sample of studies (**Figure 17**). Collectively, these findings suggest that thiazide therapy does not significantly influence the risk of developing heart failure compared with non-thiazide regimens.

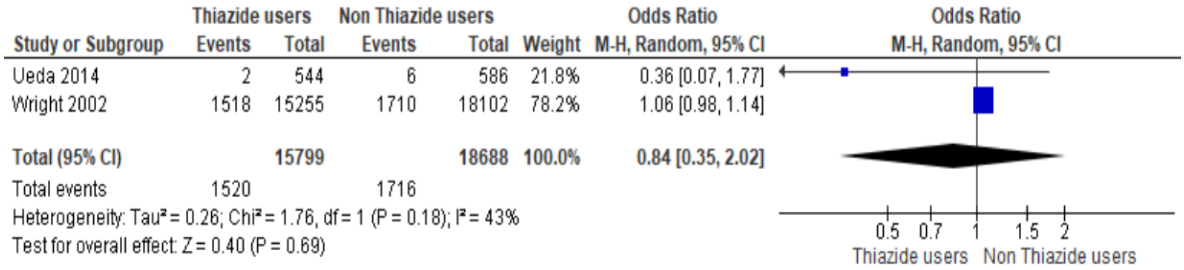

Figure 16: Forest plot 8: Thiazide vs Non Thiazide users, Outcome: Heart Failure

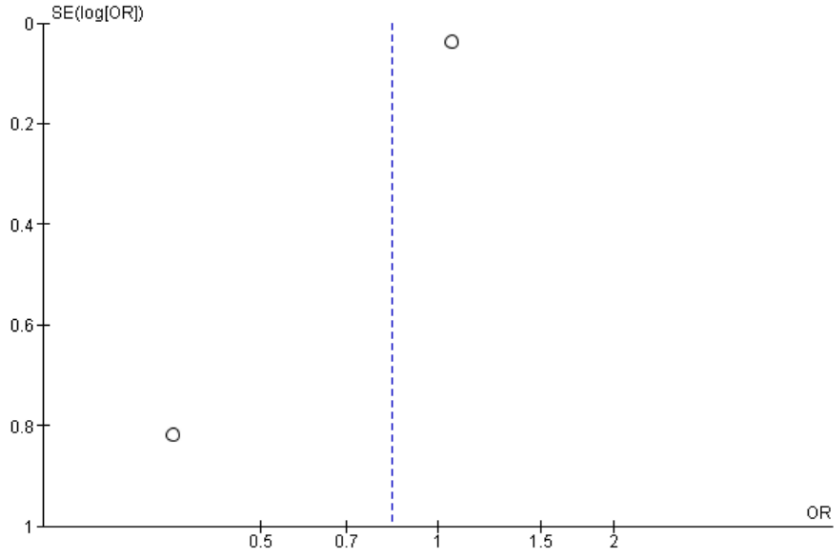

Figure 17: Funnel plot 8: Thiazide vs Non Thiazide users, Outcome: Heart Failure

Risk of Bias assessment

The Cochrane RoB 2.0 tool was used to assess the included randomized controlled trials (**Figure 18**). Most randomized trials demonstrated low risk across the majority of domains, particularly in randomization processes and outcome measurement. Some concerns arose in selective reporting and deviations from intended interventions, reflecting the challenges of long-term antihypertensive trials. Overall, the evidence base from RCTs was judged to be of good methodological quality, supporting the reliability of findings regarding thiazide use and outcomes.

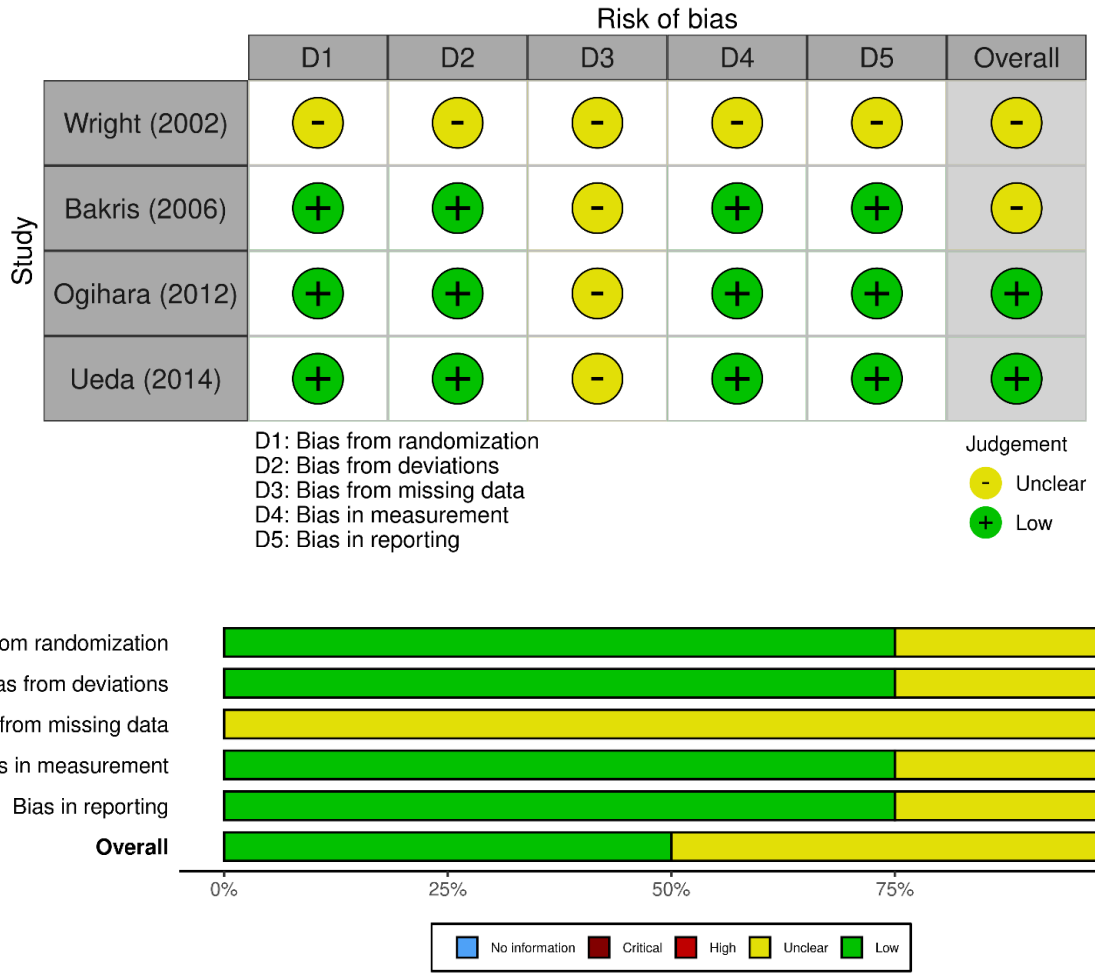

Figure 18: a. Risk of bias traffic plot for randomized clinical trials assessed using the Cochrane RoB 2.0 tool across five domains. b. Summary plot showing the distribution of judgments (high, low, or some concerns) across all included randomized clinical trials

The single included cohort study, Taylor et al. 2006 was evaluated using the Newcastle–Ottawa Scale (NOS) (**Figure 19**). The summary plot indicates generally high quality in terms of cohort representativeness and ascertainment of exposure. However, limitations included reliance on self-reported medication use and potential residual confounding despite adjustments for multiple variables. The overall risk of bias was moderate but acceptable, providing useful long-term observational insights complementary to the randomized evidence.

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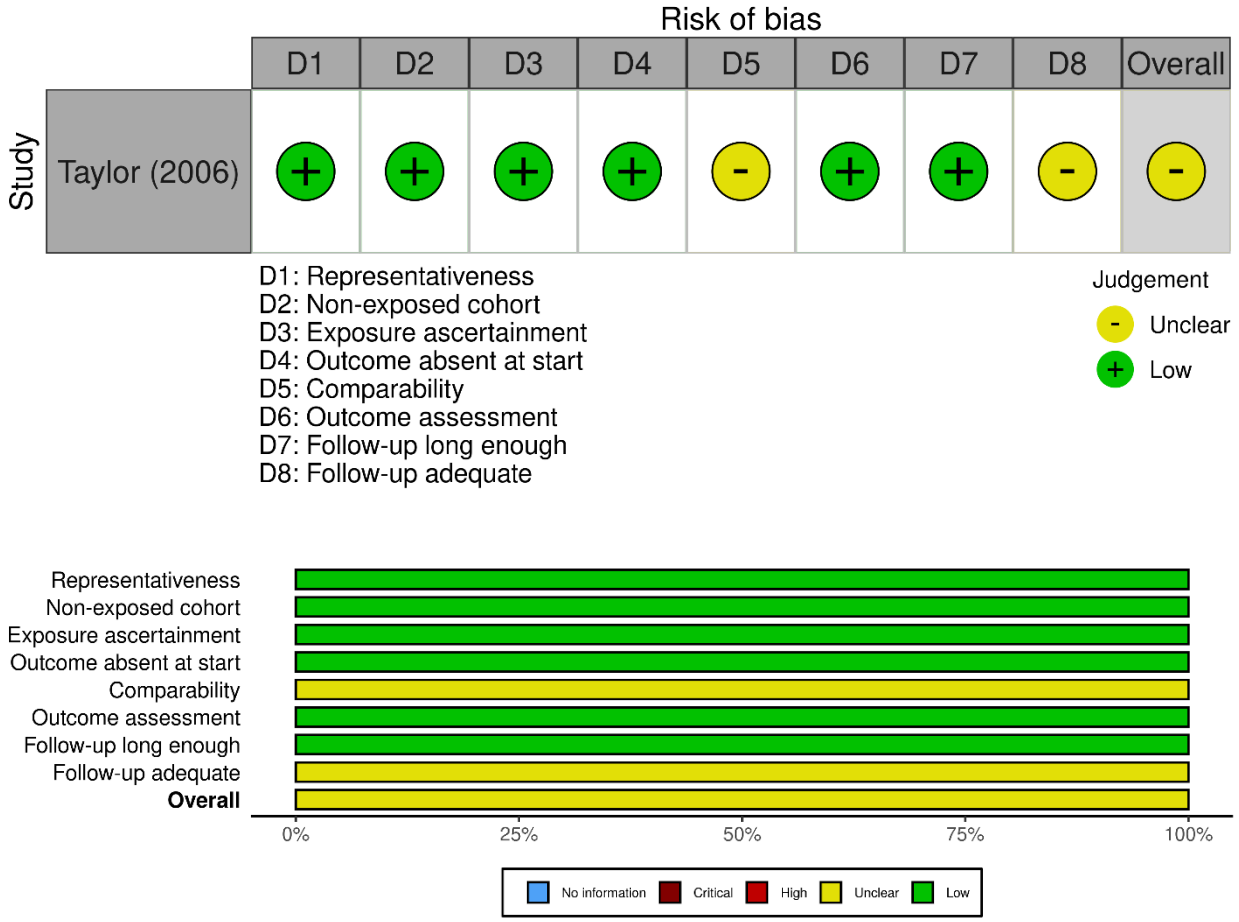

Figure 19: a. Risk of bias traffic plot for cohort study assessed using the NOS tool across eight domains. b. Summary plot showing the distribution of judgments (high, low, or some concerns) across all included cohort studies

DISCUSSION

The primary finding of this meta-analysis is that thiazide diuretic therapy was not at statistically significant risk of new-onset diabetes mellitus (NODM) compared with non-thiazide antihypertensive therapy regimens (overall OR 1.21, 95% CI 0.91–1.59, p = 0.19). Overall, however, this masks considerable heterogeneity and subtle but important nuances as uncovered by subgroup and secondary analyses.

Marginal Structural Models for Estimating the Intended Causal Effect. While the large cohort study of Taylor et al. [14] showed a slightly increased risk (OR 1.15, 95% CI 1.03–1.28), randomized controlled trial (RCT) results were conflicting. Bakris et al.'s [13] PROBE trial exhibited much higher rates of NODM for combination losartan/HCTZ (26.6% vs. 11.0%), whereas the more realistic RCTs of Ueda et al. [16] and Ogihara et al. [15] exhibited essentially the same rates between groups (~4.6% vs. ~4.9% and 3.4% vs. 3.1%, respectively). This clinical heterogeneity is reflected in the moderate statistical heterogeneity of the pooled analysis (I^2 = 48%).

Our meta-analysis also confirms a very high risk of hypokalemia in thiazide users (OR 6.58, 95% CI 5.49–7.89, p < 0.00001) without any heterogeneity (I^2 = 0%). This provides a reasonable explanation for the diabetogenic effect in certain studies since hypokalemia may increase insulin secretion and cause dysglycemia. To be effective, our results firmly demonstrate that thiazides are as effective as non-thiazide regimens in reducing blood pressure, with no difference in ultimate systolic blood pressure (mean difference –0.67 mmHg, 95% CI –1.54 to 0.19) or diastolic blood pressure (mean difference –0.25 mmHg, 95% CI –0.93 to 0.42). Most critically, thiazide treatment was not linked with an increased risk of MACE (OR 0.78, 95% CI 0.56–1.09)

or heart failure (OR 0.84, 95% CI 0.35–2.02) compared with other antihypertensive drug classes. In total, these findings suggest that while thiazides are undoubtedly linked with some metabolic risk, this is not echoed in cardiovascular excess risk.

This heterogeneity in our review is also characteristic of the wider literature. The ALLHAT trial, for instance one of the largest RCT to compare thiazides

demonstrated a greater incidence of diabetes in chlorthalidone compared to amlodipine or lisinopril use [12,17]. Interestingly, though, this greater incidence of diabetes did not equate to worse cardiovascular outcomes on follow-up, providing additional support for the observation that metabolic effects of drug-induced thiazides may have little clinical impact. Conversely, smaller RCTs conducted in Japan, such as those by Ueda et al. and Ogihara et al., did not find any difference in diabetes incidence between thiazide and comparison groups. Such differences emphasize the importance of considering population differences, such as ethnicity, baseline risk factors, and diet, in interpreting the thiazide risk-benefit profile [14,15]

Compared to the literature, our findings are consistent with several past systematic reviews and meta-analyses comparing the cardiovascular and metabolic consequences of thiazide treatment. In a meta-analysis in 2004, Zillich et al. [18] discovered thiazides caused a small increase in fasting plasma glucose but by an extent too small to significantly heighten clinically significant NODM risk, a result in agreement with our combined estimate. In the same way, Elliott and Meyer (2007) [19] stated that although thiazide diuretics were associated with mild derangements in potassium and glucose homeostasis, they were not associated with excess cardiovascular morbidity and mortality. Our findings contribute to the strength of this evidence by showing that thiazide treatment was not associated with an increased risk of MACE or heart failure, indicating that the mild metabolic effects may not have long-term clinical implications.

For the blood pressure response, our findings are consistent with the present consensus that thiazides are among the most potent antihypertensive drug classes, with blood pressure lowering being as effective as with calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers. Our findings also validate the hypokalemia as a mechanistic pathway for the thiazide-glycemic effect. This result is powerfully supported by previous mechanistic studies and provides a biologically plausible explanation of the trial-to-trial heterogeneous diabetogenic effect. Overall, our analysis adds to the evidence base by providing a novel synthesis of both large observational cohorts and also more recent RCTs and concludes that thiazides remain an acceptable first-line treatment for hypertension despite ongoing uncertainty about metabolic side effects.

There are several strengths of this systematic review and meta-analysis. It incorporates evidence from RCTs and large observational cohorts, which allows for a thorough evaluation of efficacy and safety. Our analysis, based on over 22,000 participants, has heightened statistical power and external validity of findings. Subgroup analyses allowed effect modifiers, such as comparator class and study design, to be examined, allowing for greater insight into heterogeneity. Moreover, the homogenous and consistent finding of an increased risk of hypokalemia with thiazides across studies with no heterogeneity speaks for this side effect.

There are a few limitations that must be acknowledged, however. That there is moderate heterogeneity for the cumulative NODM risk decreases the confidence in this finding because it indicates heterogeneity between populations, diagnostic criteria, and duration of follow-up across studies. The majority of the RCTs were short-term, including assessments of cardiovascular and metabolic long-term outcomes. The observational trials, while similarly informative for the detection of rare outcomes, are subject to residual confounding as well as selection bias, particularly because thiazide prescribing differs from non-thiazide therapy. Moreover, variation in study thiazide dose and type limits the potential for direct comparison because chlorthalidone, hydrochlorothiazide, and indapamide cannot be assumed to have equivalent metabolic effects. Finally, the review did not capture patient-oriented outcomes such as treatment adherence, quality of life, and long-term renal outcomes that all bear importance in the determination of the net therapy effect.

The results from this meta-analysis are practice-relevant. Our findings suggest that calcium channel blockers and ACE inhibitors are suitable options in those at higher risk of metabolic side effects, i.e., the elderly or those with underlying diabetes or metabolic syndrome. In the meantime, the absence of cardiovascular excess risk when compared to thiazides reaffirms that they are still a cheap effective and widely available therapeutic agent in hypertension. Clinicians should weigh thiazides' proven antihypertensive efficacy and cardiovascular protection against the minimal but possible risk of dysglycemia, individualizing therapy according to patient characteristics, comorbidities, and electrolyte findings. Conservative surveillance of serum potassium and glucose levels, at least in susceptible populations, is a prudent measure.

Future research requirements include larger, better-designed RCTs with standardized outcomes and longer duration to explore moderate heterogeneity of NODM findings. Trials must also weigh patient-oriented outcomes such as quality of life, compliance, and metabolic adverse effects in various populations. Further studies on combination therapy with thiazides and drugs such as ACE inhibitors or ARBs can also establish whether the metabolic hazards can be minimized without compromise in antihypertensive effect. The examination of potential modifying factors such as age, comorbidities, genetic polymorphism of drug metabolism, and basal potassium level will also be relevant to the determination of which patients are at highest risk for adverse outcomes.

CONCLUSION

This Systematic Review demonstrates that thiazide diuretics are indeed a secure, effective, and indispensable part of the treatment of hypertension. Even though they were always related to hypokalemia and a possible but inconsistent risk of new diabetes mellitus type 2, these metabolic effects remained the same and therefore did not increase cardiovascular morbidity or mortality. The effect of blood pressure reduction and cardiovascular protection was on par with other antihypertensive drug groups, which supports their clinical efficacy. Close observation of potassium and glucose levels, especially in patients with high risks, is recommended as a precautionary measure, while more thorough long-term research is necessary to define metabolic risks and to create the best individualized treatment models.

Declarations

Ethics Approval and Consent to Participate
Not applicable. This article is a systematic review and meta-analysis based solely on previously published studies. No new human participants or animals were involved.

Consent for Publication
Not applicable.

Availability of Data and Materials
All data generated or analyzed during this study are included in this published article and its supplementary files. Additional datasets are available from the corresponding author upon reasonable request.

Competing Interests
The authors declare that they have no competing interests.

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This research received no external funding.

Authors' Contributions

ASD (Aya Sami Dahroug): Conceptualization, literature search, data curation, project administration, and writing original draft.

HIT (Husna Irfan Thalib): Conceptualization, study design and planning, data extraction, and critical revision of the manuscript.

SS (Sanha Sideeque): Data analysis, interpretation of results, and visualization.

AYJ (Ayesha Jamal): Data extraction, screening of studies, and methodology.

AAB (Alanood Abdullah Banafea): Data extraction and validation.

SMA (Sara Mohammed Alsharif): Risk of bias assessment and data verification.

MSD (Mahmoud Sami Dahroug): Literature screening, data organization, and reference management.

SAS (Shahed Abdul Samad): Literature screening, eligibility assessment, and data verification.

NMU (Nazib Mohammadnizam Uddin): Methodology review, quality assessment, and critical revision of the manuscript.

ARJ (Abdulrahman Jarousha): Data extraction, validation, and interpretation of findings.

AHU (Ahmad Hasib Uddin): Final review, critical revision of the manuscript, and approval of the final version.

All authors critically reviewed, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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Registration
The protocol for this systematic review was prospectively registered on PROSPERO (CRD420251132113).

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