Review Article

Antihypertensive Treatment and Cancer: Umbrella Review of Meta-Analyses of Randomized Controlled Trials and Observational Studies

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Highlights

- These findings support the continued use of antihypertensive drugs for cardiovascular benefits while highlighting the need for long-term studies to clarify any potential cancer risks.

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ABSTRACT

Background: Data on the link between use of antihypertensive medications and the risk of developing or dying from cancer have uncertain credibility and certainty.

Objectives: We sought to evaluate the credibility of evidence from observational studies and the certainty of evidence from randomized controlled trials (RCTs) on the association between antihypertensive medication use and cancer risk, mortality, or survival outcomes.

Methods: Comprehensive searches were performed in PubMed, Embase, Scopus, and the Cochrane Database of Systematic Reviews from their creation through July 2024. The study included systematic reviews and meta-analyses of epidemiological research investigating the relationships between antihypertensive therapies and cancer risk, mortality, or survival outcomes. The credibility of evidence from observational studies was categorized as convincing, highly suggestive, suggestive, weak, or nonsignificant. Through the GRADE framework, the certainty of evidence from RCTs was categorized as high, moderate, low, or very low.

Results: A total of 109 meta-analyses were identified, with 90 originating from observational studies and 23 from RCTs. The observational studies provided highly suggestive evidence that calcium channel blockers (CCBs) and diuretics were associated with an increased cancer risk (equivalent odds ratio [eOR], 1.07; 95% CI, 1.04 to 1.10; and eOR, 1.15; 95% CI, 1.10 to 1.20, respectively). Evidence suggests that β-blockers are associated with an increase in cancer-specific survival (eOR, 0.78; 95% CI, 0.69 to 0.89). No association satisfied the standards for convincing evidence. Pooled analyses of RCTs determined that CCB use was associated with an increased cancer risk (eOR, 1.06; 95% CI, 1.01 to 1.12; moderate certainty).

Conclusions: No strong or consistent evidence was found to support a causal relationship between antihypertensive medications and cancer outcomes. The observed associations were of very small magnitude, suggesting limited clinical relevance.

Keywords: Hypertension; Cancer; Risk; Mortality; Survival; Review

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Introduction

Hypertension is a major worldwide health issue, affecting more than 1.4 billion people and contributing considerably to cardiovascular morbidity and death,[1] yet fewer than 1 in 5 people has the condition adequately controlled.[2] Antihypertensive medicines, which are necessary for controlling high blood pressure, are among the most widely prescribed treatments worldwide.[3,4] While their usefulness in lowering cardiovascular risks is well known,[5] concerns regarding their possible link to cancer have generated decades of discussion and research.[6–8] Several pathways have been hypothesized to explain the possible association between elevated blood pressure and cancer risk, but findings are inconsistent.[7, 9, 10] Most of the concern is related to the ARB drug class; blocking of angiotensin receptors by this class of drugs may increase cell proliferation, angiogenesis, and tumor progression, and they may also have possible carcinogenic effects on lung tissue.[11] In 2018, regulatory agencies identified a possibly carcinogenic nitrosamine compound in valsartan, which was subsequently identified in losartan and irbesartan.[9] As a consequence of these findings, the Food and Drug Administration (FDA) initiated testing of all angiotensin receptor blockers (ARBs) to detect nitrosamine compounds.[12] Thiazide diuretics are also considered drugs with the highest sensitivity to light,[13] potentially increasing skin sensitivity to sunlight exposure[14] and leading to free radical reactions with lipids, proteins, and DNA.[13] Reported associations may indicate a causal link, but they may also be affected by intrinsic study flaws, such as selective reporting of positive findings and residual confounding, which might overstate the effect of antihypertensive medication on cancer.[15–17] The association between antihypertensive medications and cancer outcomes is complex. Several meta-analyses of observational studies and randomized controlled trials (RCTs) have examined the association between antihypertensive therapy and cancer. Nonetheless, results have been variable and occasionally conflicting,[18–20] contributing to uncertainty in clinical decision-making and public health policy.[17] Given the substantial global burden of hypertension and cancer, it is important to investigate potential associations between antihypertensive therapies and cancer.[21, 22]

This study provides a comprehensive evaluation of the available evidence to clarify these uncertainties and assess the extent of potential biases. A systematic approach was used to evaluate the quality, credibility, and certainty of the evidence and to identify patterns of association between antihypertensive drug classes and cancer outcomes. This umbrella review provides clinicians and policymakers with evidence to support informed decision-making in the management of participants with hypertension.

Methods

According to the Preferred Reporting Items for Overviews of Reviews (PRIOR) guideline,[23] we conducted and reported a tertiary study, which is also known as an umbrella review (Table 1 in S1 Appendix).

Literature Search

Comprehensive searches were performed in PubMed, Embase, Scopus, and the Cochrane Database of Systematic Reviews from their creation through July 2024, without language constraints. The study included systematic reviews and meta-analyses of epidemiological research investigating the relationships between antihypertensive therapies and cancer risk, mortality, or survival outcomes. The search strategy used MeSH terms and keywords pertinent to the subject and study design.[24] The comprehensive search techniques for each database are included in S1 Appendix.

Eligibility Criteria

The study included systematic reviews and meta-analyses of observational studies and RCTs that documented links between antihypertensive therapies and human cancer. Excluded studies were those in which antihypertensive medications or classes were not the principal intervention of interest and those lacking outcomes related to cancer incidence, mortality, or survival. Systematic reviews devoid of meta-analyses or missing study-specific data, including relative risks (RR), odds ratios (ORs), hazard ratio (HRs), or 95% confidence intervals (95% CIs), were eliminated. Laboratory studies were ineligible. Data were

retrieved and evaluated independently for each outcome in studies reporting multiple outcomes.

Interventions and Outcomes

The major intervention of interest included the 5 main kinds of antihypertensive medications: ARBs, angiotensin-converting enzyme inhibitors (ACEIs), β-blockers, calcium channel blockers (CCBs), and diuretics. Secondary interventions included additional pharmaceuticals or categories of antihypertensive medicines documented in meta-analyses of observational studies and RCTs. The main outcomes were cancer incidence and cancer-specific mortality. In a pilot search, supplementary outcomes were considered, encompassing all-cause mortality, overall survival, disease-free survival, cancer-specific survival, progression-free survival, and recurrence-free survival.

Data Extraction

The following information was taken from meta-analyses and the original studies that were part of them: first author, publication year, number and design of included studies (eg, cohort, case-control, and RCT), population characteristics (eg, hypertensive patients, patients with atrial fibrillation or heart failure), interventions (drugs or drug classes), comparison, evaluated outcomes, cancer type(s), follow-up duration, participant and event numbers, estimated summary effect with 95% CI, effect metric (RR, OR, and HR), effect model (random or fixed), heterogeneity metrics (I^2 statistic, τ^2 statistic, Cochran Q test *P* value), publication bias assessments (*P* value of the Egger or Begg test), and risk of bias assessment scores.

Quality Assessment of Meta-Analyses

The AMSTAR 2 tool (A Measurement Tool to Assess Systematic Reviews, second edition) was used to evaluate the quality of papers that qualified for inclusion in this umbrella review[25] (Table 7 in S1 Appendix). The eligibility of retrieved articles, the data extraction process, and the methodological quality of the included meta-analyses were independently evaluated by 2 researchers (AR and HM). Disagreements were resolved by consulting with a third researcher (NF).

Data Analysis

Pooled associations were re-analyzed using random-effects meta-analysis. For pooled analyses with 10 or more studies, the DerSimonian-Laird random-effects model[26] was applied; for pooled analyses with fewer than 10 studies, the Hartung-Knapp-Sidik-Jonkman method[27] was employed. Relative measures (HR, RR, and OR) were converted to an equivalent odds ratio (eOR) to harmonize effect measures across meta-analyses.[28–30] Heterogeneity was assessed using I^2, and 95% prediction intervals were calculated to reflect the range of effects expected in new studies.[31–33] Small-study effects were assessed using the Egger test, and excess significance was tested where applicable.[34–36] The credibility of evidence from observational meta-analyses was classified into 5 categories (convincing → nonsignificant), and RCT meta-analyses were appraised using GRADE.[37-39] Comprehensive methodological rationale, formulas, and classification criteria are detailed in the Supplemental Methods (Table 2 and 3 in S1 Appendix). A schematic representation of the methodological workflow used in this umbrella review is provided in (Figure 1).

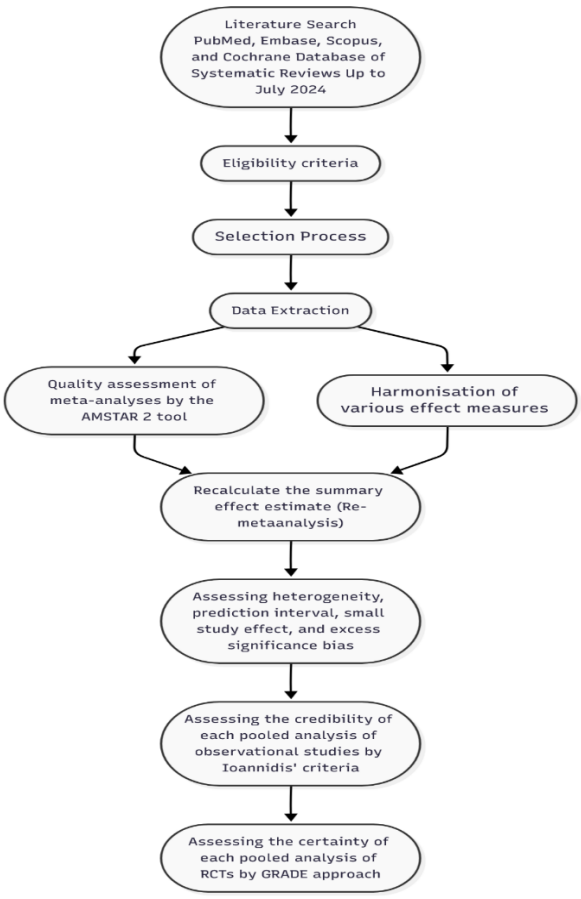

Figure 1. Schematic workflow of the umbrella review methodology

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Results

Literature Search

The flowchart of the literature search and selection process is depicted in Figure 2. A systematic literature search yielded 10 028 distinct articles. Of these, 2950 were duplicates, 6872 were excluded during the title and abstract screening, and 97 were excluded during the full-text review (Table 4 in S1 Appendix). Ultimately, 109 studies met the inclusion criteria.

Characteristics of Meta-Analyses

Among 109 papers considered, 90 were meta-analyses of observational studies, including 313 meta-analytical associations, while 23 were meta-analyses of RCTs, yielding 75 meta-analytical associations. Meta-analytical relationships denote the pooled effects reported in each included meta-analysis.

Meta-Analyses of Observational Studies

According to AMSTAR 2, 7 meta-analyses were graded as high quality, 12 as moderate, 33 as low, and 37 as critically low. Because only 1 study was included in the investigation by Harewood et al,[40] no quality evaluation was conducted. The meta-analyses had a median of 28 934 cases (range, 3518 to 252 559), 2 918 587 participants (range, 2364 to 43 210 409), and a median of 16 separate studies (range, 1 to 57).

A total of 313 distinct meta-analytical relationships were found, 145 of which reached a significance level of *P* less than .05 and were considered statistically significant. Among the 313 meta-analytical relationships that were reported, β-blockers and incidence were the most commonly examined intervention and outcome, with 85 and 195 associations, respectively (Table 5 in S1 Appendix).

Meta-Analyses of RCTs

Four studies received a high-quality rating for RCTs, 1 received a moderate rating, 6 received a low rating, and 12 received a critically low rating. Each meta-analysis had an average of 23 original research articles (range, 4 to 90). The range of participants was 394 to 390,750, with 79,776 being the median.

Only 9 of 75 distinct meta-analytical associations that were found were statistically significant at a significance threshold of *P* less than .05. ARBs were the most researched intervention (25 relationships) out of the 75 published meta-analytical associations, whereas diuretics with 8 associations were the least examined intervention (Table 6 in S1 Appendix).

Credibility and Certainty of Evidence on Antihypertensive Treatments and Outcomes

Incidence

Pooled Effect Estimates from Observational Studies

Data from 335 observational studies were used to evaluate the increased risk of cancer associated with the use of antihypertensive pharmaceuticals. The development of cancer was not significantly associated with the use of 2 drug classes: ARBs and ACEIs. A weak association was discovered between the use of β-blockers and an elevated risk of cancer (eOR, 1.06; 95% CI, 1.01 to 1.12). Based on pooled analyses of 73 and 85 studies, respectively, modest statistically significant associations were identified for CCBs and diuretics (eOR, 1.07; 95% CI, 1.04 to 1.10; and eOR, 1.15; 95% CI, 1.10 to 1.20) (Figure 3, Table 8 in S2 Appendix).

Pooled Effect Estimates from RCTs

In 123 RCTs, the association between cancer risk and antihypertensive drugs was investigated. Among 5 pooled analyses, only CCBs exhibited a small but statistically significant association with cancer risk, supported by moderate certainty (eOR, 1.06; 95% CI, 1.01 to 1.12). For the remaining 4 drug classes, no significant relationships were observed (Figure 4, Table 9 in S2 Appendix).

Cancer-Specific Mortality

Pooled Effect Estimates from Observational Studies

Antihypertensive drug usage did not appear to

lower cancer-specific mortality, according to pooled analyses of data from 45 original studies (Figure 3, Table 8 in S2 Appendix).

Pooled Effect Estimates from RCTs

Data from 84 original studies showed no indication of a significant association between antihypertensive medication usage and cancer-specific mortality (Figure 3, Table 9 in S2 Appendix).

All-Cause Mortality

Pooled Effect Estimates from Observational Studies

Only the β-blocker drug class has been used to assess the association between antihypertensive medication usage and all-cause mortality in the literature. There was no significant association between the use of β-blockers and all-cause mortality, according to the effect estimates from the pooled studies (Figure 3, Table 8 in S2 Appendix).

Pooled Effect Estimates from RCTs

Antihypertensive drug usage and all-cause mortality were not found to be significantly associated in an analysis of 2 pharmacological classes, β-blockers and ARBs (Figure 4, Table 9 in S2 Appendix).

Overall Survival

Pooled Effect Estimates from Observational Studies

In total, 130 observational studies evaluated increased survival of patients with cancer taking antihypertensive drugs. Weak evidence of better overall survival with ARBs and β-blockers was found in summary effect estimates of 91 observational studies (eOR, 0.83; 95% CI, 0.74 to 0.93; and eOR, 0.92; 95% CI, 0.87 to 0.97, respectively) (Figure 3, Table 8 in S2 Appendix).

Pooled Effect Estimates from RCTs

Only 6 studies examined the association between antihypertensive medication use and overall survival in patients with cancer. The use of CCBs significantly improved survival among patients with cancer with very low certainty (eOR, 0.77; 95% CI, 0.63 to 0.94) (Figure 4, Table 9 in S2 Appendix).

Disease-Free Survival

Pooled Effect Estimates from Observational Studies

Only observational studies have examined the association between antihypertensive medication usage and disease-free survival. The use of β-blockers and ACEIs was not significantly associated with disease-free survival, according to synthesized analyses from 13 original studies (Figure 3, Table 8 in S2 Appendix).

Cancer-Specific Survival

Pooled Effect Estimates from Observational Studies

Use of β-blockers was significantly associated with higher cancer-specific survival, according to a pooled analysis of data from 26 observational studies (eOR, 0.78; 95% CI, 0.69 to 0.89) (Figure 3, Table 8 in S2 Appendix).

Progression-Free Survival

Pooled Effect Estimates from Observational Studies

A pooled analysis of data from 25 observational studies showed no significant association between the use of antihypertensive medications and improved progression-free survival (Figure 3, Table 8 in S2 Appendix).

Pooled Effect Estimates from RCTs

Synthesizing the effect estimates from 4 studies, we examined the increase in progression-free survival and found no significant association with the use of β-blockers (Figure 4, Table 9 in S2 Appendix).

Recurrence-Free Survival

Pooled Effect Estimates from Observational Studies

The use of β-blockers and recurrence-free

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survival were not significantly associated, according to a pooled analysis of data from 7 observational studies (Figure 3, Table 8 in S2 Appendix).

Other Antihypertensive Drugs

Pooled Effect Estimates from Observational Studies

Use of α-blockers was not significantly associated with increased risk of cancer, according to a pooled analysis of 6 studies; however, summary estimates based on data from 11 original studies showed that use of phosphodiesterase 5 inhibitors (PDE5Is) was associated with a higher incidence of cancer (eOR, 1.07; 95% CI, 1.00 to 1.14). The association between α-blocker use and all-cause and cancer-specific mortality was investigated in 10 studies. Use of α-blockers was not significantly associated with either cancer-specific or all-cause mortality according to synthesized analyses of these 10 studies (Table 10 in S2 Appendix).

Pooled Effect Estimates from RCTs

There is no significant association between the use of finerenone and the risk of cancer, with moderate certainty (Table 10 in S2 Appendix).

Heterogeneity Patterns

Across the re-analyzed pooled associations, heterogeneity varied substantially between outcomes and study designs. Several observational pooled analyses showed substantial or considerable heterogeneity (I^2 >50%), for instance: ARBs—incidence (I^2=95.4%), ACEIs—incidence (I^2=83.3%), diuretics—incidence (I^2=88.5%), and CCBs—incidence (I^2=51.8%). High heterogeneity was also evident for several survival outcomes in observational analyses (eg, ARBs overall survival I^2=81.4%). By contrast, most pooled analyses of RCTs displayed low heterogeneity (for example, CCBs incidence I^2=9.5% and several RCT pooled estimates with I^2 close to 0%). The full list of I^2 values for each pooled analysis is provided in S2 Appendix (Supplemental Tables 8–10).

Characteristics of the Individual Studies

S2 Appendix (Tables 11 and 12) details the characteristics of the individual studies included in each of the pooled analyses. Of the 834 individual papers included in the current meta-analytical combinations, 596 were observational studies and 238 were RCTs. Of 596 observational studies (421 cohort, 126 case-control, and 49 nested case-control), 73 focused on ARBs, 105 on ACEIs, 254 on β-blockers, 95 on CCBs, and 42 on diuretics. Among the 238 RCTs, 60 focused on ARBs, 51 on ACEIs, 45 on β-blockers, 52 on CCBs, and 26 on diuretics.

Discussion

Principal Findings

According to this umbrella review, the links between antihypertensive medicines and cancer outcomes differ depending on drug type and study design. We investigated 5 main antihypertensive medication classes and 8 cancer-related outcomes (cancer risk, mortality, and survival) in 41 pooled analyses (26 from observational studies and 15 from RCTs).

In terms of cancer risk, RCTs ruled out 2 of 3 significant links observed in observational studies with moderate certainty. These differences highlight the possibility of reporting bias, selection bias, and other inherent biases in observational studies, which might overestimate relationships.[15–17] While observational studies usually yield stronger associations than RCTs,[41] such biases are especially common in the cancer epidemiology literature.[42–44]

For survival outcomes, 3 relationships were statistically significant in observational studies; 1 was contradicted by RCTs (very low certainty), and the other 2 lacked RCT data. When interpreting studies on cancer mortality and survival, various methodological issues must be addressed.[44,45] These studies are frequently more biased than those evaluating cancer incidence. Cancer mortality studies typically do not account for cancer stage at diagnosis or treatment regimens, and oncologists may modify anticancer treatments in patients with cancer due to potential complications and side effects.[44,46] In addition,

only a handful of these associations produced highly significant findings without bias, as demonstrated by large heterogeneity, small-study effects, and excess significance bias. Two of the 3 survival-related relationships were not significant ($P < .001$), further limiting the evidence for a substantial link between antihypertensive medications and cancer survival. In contrast, the link between CCBs and overall survival was statistically significant in a pooled analysis of RCTs but not in observational studies. Two essential aspects should be addressed when evaluating this finding. First, meta-analyses of RCTs may be inconclusive, especially when sample sizes are small[47]; only 3 RCTs were included in this pooled analysis. Second, the included RCTs were of poor quality, and previous research has shown that low-quality trials might overstate treatment benefits by about 34%.[48]

The link between CCB use and cancer risk was the only statistically significant finding validated by both observational studies (highly suggestive credibility) and RCTs (moderate certainty). Nevertheless, while both research designs yielded nominally significant findings, the associations were not very strong. The 95% CIs for both pooled analyses ranged from 1.01 to 1.12, indicating minimal clinical importance.[24,49] Validating relative risks below 1.20 requires large datasets, long-term follow-up, rigorous study designs, and precautions against selective reporting and other biases.[24]

Effect of Heterogeneity on Interpretation

The presence of substantial heterogeneity in numerous pooled observational analyses reduces confidence in pooled point estimates and suggests that true effects may vary across populations, settings, or study methods. Heterogeneity may arise from clinical diversity (differences in participant populations, treatment duration, drug dose, or co-medication), methodological diversity (study design, confounder adjustment, and outcome definitions), or selective reporting. When heterogeneity was high, prediction intervals frequently included the null value or spanned clinically meaningful benefit and harm, indicating that the average effect may not be generalizable to individual settings. Therefore, pooled estimates with I^2 above 50% should be interpreted cautiously, and small statistically significant effect sizes in highly heterogeneous syntheses are unlikely to indicate consistent or causal effects. Accordingly, the certainty of evidence was downgraded where appropriate according to prespecified rules (S1 Appendix).

Overall, some observed associations between antihypertensive medications and cancer outcomes may reflect limitations inherent in pharmacoepidemiologic investigations. These include insufficient control over treatment dosage and duration, recall bias from self-reported data, short follow-up periods, confounding by indication and illness duration, detection bias, and selective reporting.[15] In settings with a large number of unexplained comparisons, such biases may lead to false-positive findings.[50,51] Our findings indicate that most antihypertensive medications are not associated with a substantial or consistent relationship with cancer incidence or mortality. Given the small magnitude of effect (eOR values typically <1.15) and high heterogeneity across multiple analyses, these associations should not be considered clinically meaningful without further large-scale prospective investigation.

Newly Published Articles Related to Antihypertensive Treatment and Cancer

Several large cohort and review studies have been conducted since the date of our study search that align with our conclusion, indicating no clear, clinically meaningful overall cancer risk attributable to antihypertensive therapy as a class. Still, recent studies underscore ongoing class-specific concerns—most notably, repeated findings linking prolonged hydrochlorothiazide exposure with nonmelanoma skin cancer in primarily White populations, along with selected analyses suggesting modest associations between CCBs and certain outcomes. These findings highlight the need for continued pharmacovigilance, subgroup-specific research, and caution in translating small relative risks into practice changes.[52–54]

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risk attributable to antihypertensive therapy as a class; nevertheless, recent studies underscore ongoing class-specific concerns—most notably, repeated findings linking prolonged hydrochlorothiazide exposure with non-melanoma skin cancer in primarily White populations, and selected analyses suggesting modest associations with CCBs for certain outcomes. These findings highlight the need for continued pharmacovigilance, subgroup-specific research, and caution in translating small relative risks into practice changes.[52-54]

Strengths and Limitations

This umbrella review presents the most comprehensive synthesis of meta-analytical data to date on the association between antihypertensive therapy and cancer. Its primary strength lies in its rigorous approach, which includes a thorough search strategy, systematic evaluation of research quality, and the inclusion of credibility and certainty assessments. Moreover, this review adheres to the Preferred Reporting Items for Overviews of Reviews (PRIOR) 2022 statement to ensure methodological rigor and transparency.[23] By integrating data from both observational studies and RCTs, this evaluation provides a balanced viewpoint that accounts for the inherent limitations of each study design, offering a nuanced perspective for clinical decision-making.

Nonetheless, several limitations must be acknowledged. First, despite attempts to minimize bias, observational studies remain subject to confounding, selection bias, and measurement errors, which may have influenced the observed associations.[15,17,55] Second, many pooled analyses, particularly those from observational studies, have shown substantial heterogeneity (I^2 > 50%), which limits the interpretability and generalizability of the pooled effect estimates. Heterogeneity increases uncertainty and may reflect residual confounding, differences in exposure or outcome measurement, or other biases that meta-analysis cannot resolve. For these reasons, we emphasize caution when interpreting small pooled effect sizes from heterogeneous analyses. Third, even statistically significant findings should be interpreted with caution, as they may not reflect clinically relevant risk differences. Finally, although RCTs provide more credible data, they may be insufficient to identify rare cancer events, and follow-up periods may be inadequate to capture long-term carcinogenic effects.[24] Further, a primary disadvantage of umbrella reviews is their broad scope; consequently, this review could not account for specific confounder or mediator adjustments or individual sensitivity analyses, which may be essential to fully understand the results.

Clinical Implications

Given the high prevalence of hypertension and the widespread use of antihypertensive medications,[1–3] the absence of strong evidence supporting an association between these drugs and cancer should reassure both clinicians and patients. For clinicians, these data reinforce that the cardiovascular benefits of antihypertensive therapy outweigh potential cancer risks. Be that as it may, given the significant association between CCBs and cancer risk in RCTs, continued pharmacovigilance is warranted. Given the small effect size and moderate certainty of evidence, however, changes in antihypertensive prescribing patterns should be made cautiously.

Future Research

Several methodological issues should be addressed to strengthen future research. First, prospective cohort studies with rigorous control for confounding factors, such as lifestyle factors, socioeconomic status, and polypharmacy, are needed to evaluate findings from observational research. Second, large-scale RCTs with extended follow-up that assess cancer outcomes as prespecified end points, as well as advanced pharmacoepidemiologic investigations using the Mendelian randomization, may provide stronger causal inference. Third, data linkage studies combining clinical trial data with cancer registries may provide valuable insight into the long-term cancer outcomes associated with antihypertensive medication use. In addition, mechanistic studies examining the biological plausibility of antihypertensive-associated carcinogenesis are needed.

Conclusions

This umbrella review presents a thorough and therapeutically relevant summary of the evidence regarding antihypertensive treatment and cancer. The current data do not suggest a causal relationship between antihypertensive medication use and an increase in unfavorable cancer outcomes, and where associations existed, effect sizes were small (typically eOR <1.15), indicating minimal clinical impact. The documented cardiovascular advantages of antihypertensive medication significantly exceed the potential cancer risks, and existing prescription practices should be maintained. To improve knowledge of these connections, future research should include long-term RCTs, mechanistic investigations, and increased pharmacovigilance. When establishing firm conclusions regarding the cancer risks of drugs, it is important to consider the burden of multiple endpoints and analyses. In the meantime, clinicians should continue to emphasize blood pressure management and reassure patients that their antihypertensive medication remains safe and necessary for cardiovascular health.

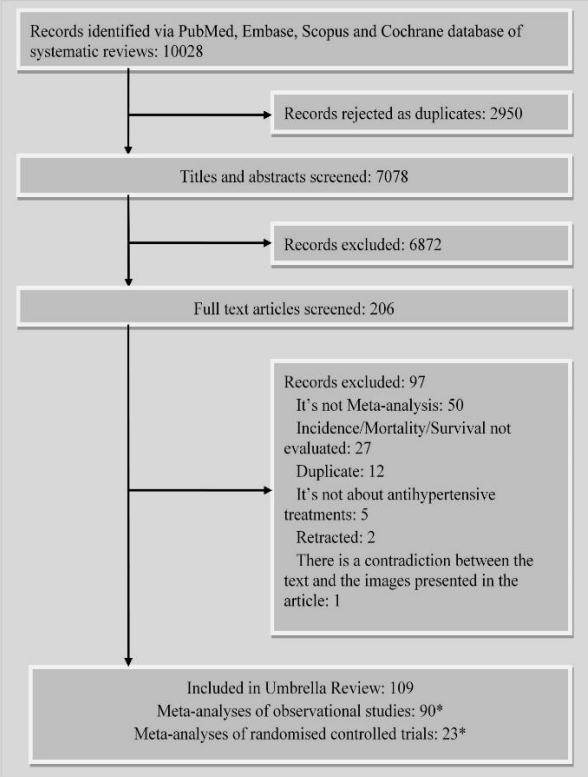

Figure 2. Flowchart of systematic search and selection process
* Four meta-analyses included both observational and randomized controlled trials.

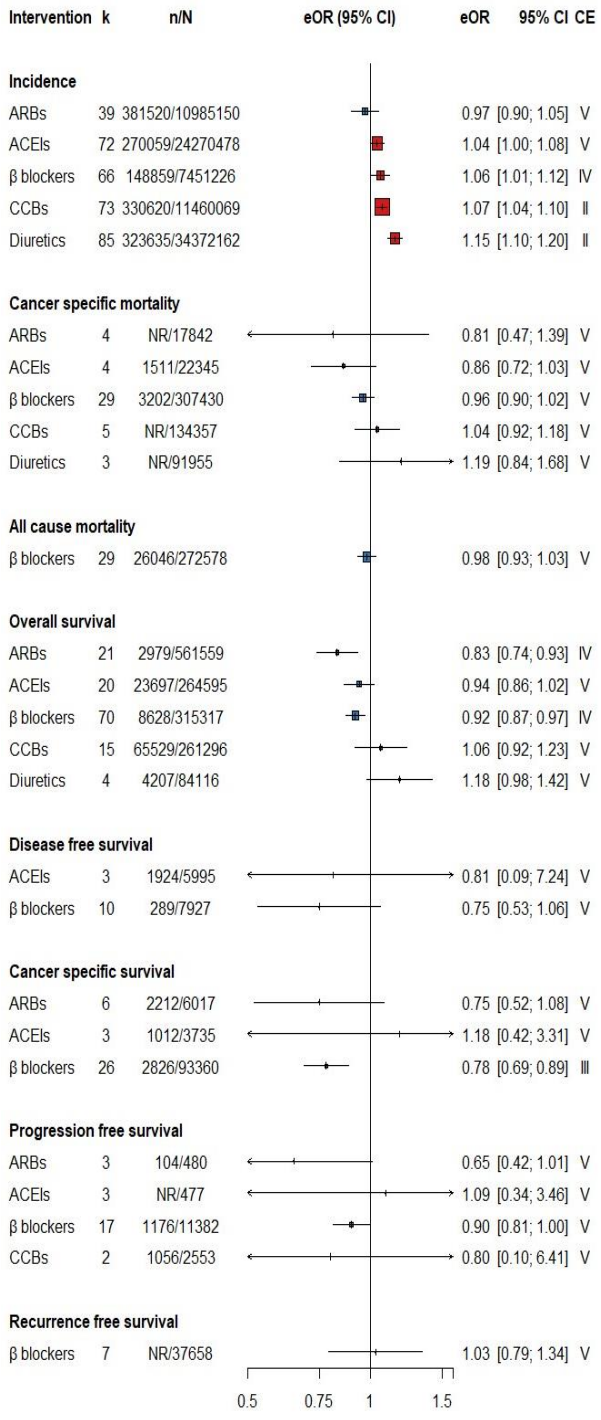

Figure 3. Summary of reanalyzed associations between antihypertensive treatments and cancer across observational studies
***K*:** number of studies; *n*: number of cases; *N*: total number of participants; eOR: equivalent odds ratio; CI: confidence interval; CE: class of evidence (convincing [I], highly suggestive [II], suggestive [III], weak [IV], nonsignificant association [V]); NR: not reported; ARBs: angiotensin receptor blockers; ACEIs: angiotensin-converting enzyme inhibitors; CCBs: calcium channel blockers

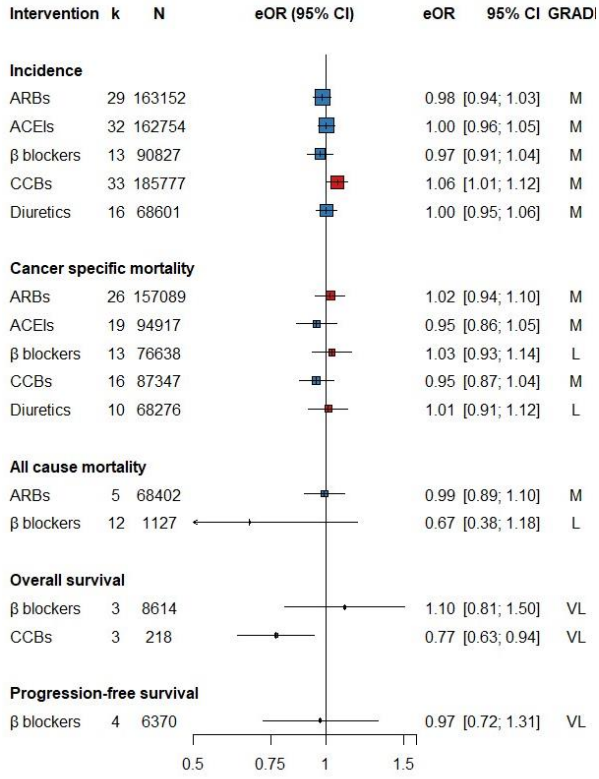

Figure 4. Summary of reanalyzed associations between antihypertensive treatments and cancer across randomized controlled trials

***K*:** number of studies; *N*: total number of participants; eOR: equivalent odds ratio; CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations (high [H], moderate [M], low [L], very low [VL]); ARBs: angiotensin receptor blockers; ACEIs: angiotensin-converting enzyme inhibitors; CCBs: calcium channel blockers

Supplemental Information

S1 Appendix. Search strategy, PRIOR checklist, evidence classification criteria, GRADE framework, excluded studies with reasons for exclusion, characteristics of included meta-analyses, quality assessment

S2 Appendix. Credibility and certainty assessment, characteristics of included original research articles

Declarations:

Ethical Approval

Ethical approval was taken from the Research Ethics Committee of Tehran University of Medical Sciences (Ethical approval ID: IR.TUMS.SPH.REC.1403.061, Approval date: 2024-07-02).

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Conflict of Interest

The Authors declare that there is no conflict of interest.

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