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Systematic Review and Meta-Analysis in Randomized Controlled Trials of Anti-Hypertensive Drugs and the Risk of Cancer

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Abstract

This paper evaluates the potential carcinogenicity of anti-hypertensive medications by performing a meta-analysis on the risk of cancer associated with their use. The analysis incorporated data from 12 studies, encompassing a total of 16,711,997 observations, and focused on randomized controlled trials of anti-hypertensive drugs. The primary objective was to compare the cancer risk across different classes of these medications while considering their blood pressure-lowering effects. The meta-analysis employed a random-effects model to synthesize the results. The mean effect size was found to be 1.178, with a 95% confidence interval ranging from 1.027 to 1.351. A Z-test conducted to test the null hypothesis that the mean effect size equals 1 yielded a Z-value of 2.343 and a p-value of less than 0.019, leading to the rejection of the null hypothesis. This indicates a statistically significant association between the use of anti-hypertensive drugs and an increased risk of cancer. The heterogeneity among the included studies was significant, as evidenced by a Q-statistic of 85.118 with 11 degrees of freedom and a p-value of less than 0.001. The I-squared statistic was 87%, suggesting that 87% of the variance in observed effects was due to differences in true effects rather than sampling error. The tau-squared value, representing the variance of true effect sizes, was 0.040 in log units, while tau, the standard deviation of true effect sizes, was 0.201 in log units. Assuming a normal distribution of true effects, the prediction interval for the true effect size was estimated to be between 0.733 and 1.894, meaning that the true effect size in 95% of all studies would fall within this range. Overall, the findings suggest a potential risk of cancer associated with anti-hypertensive drugs, which warrants careful consideration when weighing their benefits and risks. The computations for the analysis were conducted using Comprehensive Meta-Analysis.

Keywords: Meta-Analysis, Odds Ratio, Risk of Cancer, Anti-Hypertensive Medication, Cancer, Hypertension.

Introduction

Systematic review (SR) and Meta-analysis (MA) are new methodological terms and have been added to the research encyclopedia three decades ago, nowadays they are common

terms for their decisive applications. Briefly, SR introduces simple but critical methodology to review and select the best available research findings on a specific topic to minimize the selection bias in picking up the best accurate evidences. MA, however, uses statistical techniques to help us to combine the findings of comparable studies, present the aggregated statistics and check how significant the differences between the findings of studies are (i.e., their heterogeneity). There is a deep controversy surrounding the eligible type of studies for a MA. Some experts only recommend Randomized Clinical Trials (RCTs) (Haghdoost, et al., 2007)., while others include evidences from a diversity of sources. In fact, SR and MA are much more applicable to those studies that share a similar methodology and address comparable research questions. Therefore, the principles of the SR and MA are more applicable to the findings of comparable RCTs. Nevertheless, observational studies are very common type of studies that either describe variables (descriptive studies) or explore the relationship between variables (analytical studies). Considering the limitations, using SR and MA, we may explore the findings of observational studies conclusively. The concepts of the SA and MA may not be easily applicable to the findings of observational studies; nonetheless, we believe that the SA and MA techniques have some additional advantages which may help to propose more appropriate conclusions through combining the findings of observational studies (Haghdoost, et al., 2007).

The development of cell accumulation can migrate to other tissues and metastasize to distant sites, resulting in significant morbidity, eventually causing the death of a patient, this is known as cancer (Valavanidis, 2018) A subset of cardiovascular disorders that account for the largest percentage of deaths from illnesses, including acute myocardial infarction and cerebrovascular accident (stroke), which affect roughly two-fifths of adults in wealthy nations (Ferreira JS A. R., 2010). In this way, there is a need to evaluate the risk factors that contribute to this clinical situation and its prevalence, because the identification of groups at higher risk of being affected by arterial hypertension signifies an important contribution to the prevention of morbidities and the effectiveness of the treatment (Selem et al., 2013). Antihypertensive medication such as thaizide, beta blockers, calcium channel blockers and alpha blockers, widely used to treat hypertension as well as other conditions, such as heart disease, heart failure, and stroke, and lowers morbidity and mortality (Mukete, et al., 2015). Thiazide diuretics are considered first-line agents for the treatment of hypertension (H. Esh, 2023).

Research Gap

A series of meta-analyses of randomized controlled trials, based on aggregate data, have investigated the association between class-specific antihypertensive treatment and risk of cancer, but findings have been conflicting. One study has suggested that using ARBs increases the risk of cancer, (Yujiao Deng, 2022) whereas two subsequent meta-analyses showed no such association. In a study that found no consistent evidence that antihypertensive medication use had any effect on cancer risk. Although such findings are

reassuring, evidence for some comparisons was insufficient to entirely rule out excess risk, in particular for calcium channel blockers (Copland et al., 2021). Another meta-analysis of randomized controlled trials found no evidence linking any drug class with the incidence of any cancer, (Bangalore et al., 2012) but an increased risk of cancer with the use of angiotensin-converting enzyme inhibitors (ACEIs) in combination with ARBs could not be ruled out.

However, findings from existing meta-analyses based on summary statistics are limited by the study design, because such methods could not account for competing risks. Therefore, this study's aim in systemic review and meta-analysis of randomized controlled trials of anti-hypertensive drugs and the risk of cancer to address a gap in the evidence for the safety of antihypertensive medication.

Objectives

The main Objectives are to:

i. Estimate a summary of the random effect model for the risk of cancer in the use of anti-hypertensive medication
ii. Evaluate the presence of publication bias and assess the robustness of the findings through sensitivity analyses and examination of funnel plots.

Methodology

Research Design

Relevant parameters from the included studies were recorded in a standardized form via pooling data across the included studies. This started with extracting and appropriately recording mathematical requirements for the Meta-Analysis. These include SE (which in this case is the anti-hypertensive drugs and their trials concerning the risk of cancer), 95% confidence interval (CI) of the impact, log of the impact, and the standard error (SE) of the log of the impact. The quality of the articles that met the outlined inclusion criteria as such, satisfying the recommendations of the Preferred Reporting Items for and Meta-analysis (PRISMA) as it is provided (DerSimonian, et al., 2015).

Data Source

The systematic literature search on the controlled trial of anti-hypertensive drugs and the risk of cancer using both fixed and random effect model was carried out from 10th August, 2023 to 12th September, 2024 using the following databases, Google Scholar, Pubmed, Medline Scopus, Embase and relevant journal of pharmaceutical, annals of cardiovascular and journal of therapeutic and pharmacology.

Study selection

The titles and abstracts of the search results were independently screened according to the following inclusion criteria:

1. Observational epidemiological studies (i.e., The burden of hypertension in Nigeria)
2. Controlled trial of anti-hypertensive drugs in Relation to cancer
3. Controlled trials on the use of Losatarn, and Amlodipine and their potential association with the risk of cancer
4. The outcome data reported the effect size with 95% confidence interval (CI).

Data extraction and quality assessment

Data extraction was independently performed using the standardized data extraction sheet. The detailed data extraction sheet included the following items: first author, year of publication, sample size, effect sizes, and 95% CIs.

Model specification

In this Meta-analysis estimates were pooled via Random Effect Model using DerSimonian and Lea method when heterogeneity is significant, and Fixed Effect Model was carried out through IV method where the level of heterogeneity is not significant in line with (Lee,, et al., 2016,). To compute the study's variance under the REM, there was the need to calculate both the within-study variance, Yi V and between-study variance τ^2, since the study's total variance is the sum of the two values. One method for estimating τ^2 is the method of moments, or the DerSimonian and Laird method (DerSimonian, et al., 2015). The parameter τ^2 (tau-squared) is the between studies variance (The variance of the effect size parameters across the population of studies). The estimate of τ^2 is denoted by T^2

$$T^2=\frac{Q-df}{C} \quad (3.1)$$

$$Q=\sum_{[=]}^{k} W_i Y_i^2 - \frac{(\sum_{i=l}^{k} W_i Y_i)2}{\sum_{i=l}^{k} W_i} \quad (3.2)$$

df=k-l

where k is the number of studies, and

$$C=\sum_{i=l}^{k} W_i - \frac{\sum_{i=l}^{k} W_i^2}{\sum_{i=l}^{k} W_i} \quad (3.3)$$

Under the random-effect, model the weight assigned to each study is

$$W_i={}^1/_{\mathrm{Var}(Y_i)} \quad (3.4)$$

Where $\mathrm{Var}(Y_i) = V_{y_i}^*$ is the within-study variance from study I plus the between-study variance, $r^{2.}$

$$V_{y_i}^* = V_{y_i+T^2}$$

The weighted mean, M^*, is

$$M^* = \frac{\sum_{i=l}^{k} W_i W_i}{\sum_{i=l}^{k} W_i^*} \quad (3.5)$$

That is the sum of the products (effect size multiplied by weight) divided by the sum of weights.

The variance of the summary effect is estimated as the reciprocal of the sum of the weight, or

$$VM^{*} = \frac{1}{\sum_{i=1}^{k} w_i^*} \quad (3.6)$$

$$\text{SE}M^* = \sqrt{V}M^* \quad (3.7)$$

The (1-a)% lower and upper limits for the summary

$$\text{LL}M^* = M^* - Za/_2 x\, SEm^*\} \quad (3.8)$$

$$\text{UL}M^* = M^* + Za/_2\, xSEm^*\}$$

a Z-value to test the null hypothesis mean effect μ is zero is computed as

$$P^* = 1 - \emptyset\left(\pm \int Z^*\right)$$

where we choose '+' if the difference is in the expected direction or '- 'otherwise. For a two-tailed test by

$$P^* = 2 - \emptyset\left(\pm \int Z^*\right)$$

and Ø(/ Z^* /) is the standard normal cumulative distribution. The I 2 - Statistic is an alternative and stronger measure compared to the Q- measure in (3.2)

$$l^2 = \left(\frac{Q-df}{Q}\right) x\ 100\% \quad (3.9)$$

use value of Q from (3.2). Heterogeneity in the I^2 – Statistics may be termed low, moderate, or high based on the intervals 2 0 25% ≤ < I, 2 25% 50% ≤ < I, or 2 I ≥ 50% respectively. For subgroup analysis, the z-test method of the DerSimonian and Laird process was used thus: - Let ϑA and ϑB be the true effects of group A and B respectively, and let M A and M B be the estimated effects, and let M A V and M B V be their variances. If we use 'Diff' to refer to the difference between the two effects, and choose to subtract the mean of A from the mean of B,

$$Diff = M_B - M_A$$

$$Z_{Diff} = \frac{Diff}{SE_{Diff}}$$

Where

$$SE_{Diff} = \sqrt{V_{M\,A} + V_{M\,B}}$$

under the null hypothesis that the true effect size ϑ is the same for both groups,

H_o :

and ϕ (Z) is the standard normal cumulative distribution. For meta-regression analysis, to assess the impact of covariates and to predict effect size in studies with specific characteristics, assess the impact of the slope using the Z-test statistics to test the significance of the slope. The test statistics is based on the Z-distribution.

$$Z = \frac{B}{SE_B}$$

Under the null hypothesis that B = 0, Z would follow the normal distribution. The Z-test can be used to test the statistical significance of any single coefficient but when it is required to assess the impact of several covariates simultaneously, the Q-test is useful. In which case, we obtain Q, Q_{model},$Q_{residual}$ and consider the degrees of freedom. From the model, fit a model of the form

$$Ln(Y) = B_0 + B_i X_i \qquad i = 1,2,3, \ldots \ldots \ldots, n.$$

While quantifying the magnitude of the relationship by computing the (1–α)% confidence interval for B, using,

$$LL_B = B - Z_{\frac{a}{2}}\, x\, SE_B$$

And

$$UL_B = B + Z_{\frac{a}{2}}\, x\, SE_B$$

Data Analysis

In the meta-analyses, the effect estimates were pooled from original studies reported meeting the criteria set in the Data section The effect size and 95% CI were used as the primary measures to assess the relationship between antihypertensive drugs and risk of cancer. The summary effect size was collected base previous studies on both controlled trials on the use of Losatarn, and Amlodipine and their potential association with the risk of cancer.

Cochran *Q* and I^2 statistics were used to evaluate the possible heterogeneity among the included studies, and $P < 0.10$ and $I^2 > 50\%$ represent a significant level of heterogeneity (Higgins et al., 2003; Coory, 2010). A fixed-effect model was performed when the overall summary OR revealed no obvious heterogeneity. Otherwise, a random-effect model was used. Publication bias among the included studies was assessed with Egger test and Begg tests (Egger et al., 1997; Begg et al., 1994). The statistical analyses were performed using Comprehensive Meta-analysis (version 4.0), and the statistical significance was determined when $P < 0.05$ (two-sided).

Result

The result has been divided into four sections such as outcome of the Data extraction presentation of data searched, forest plot and funnel plot.

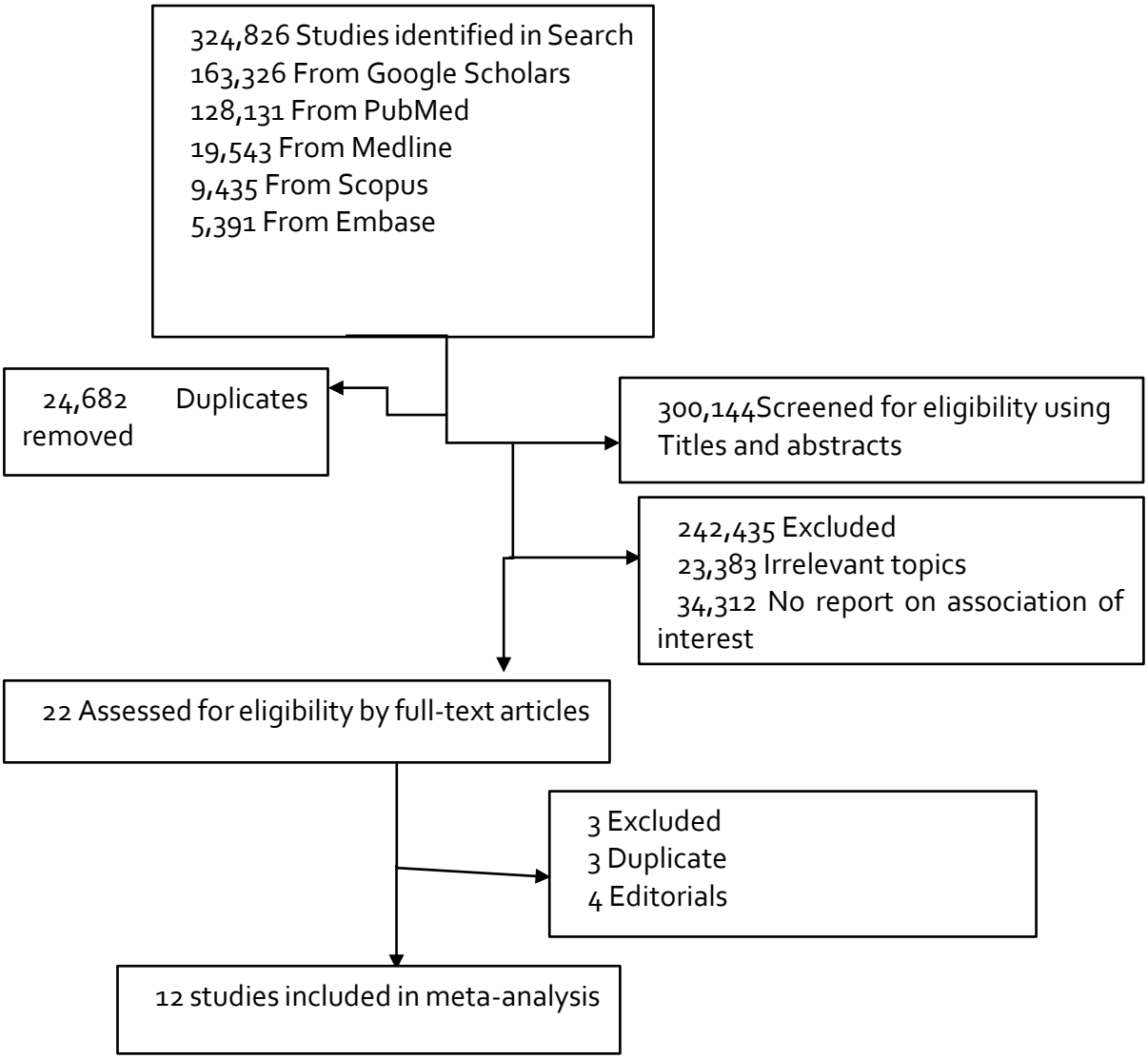

Figure 1: Flow Chart Showing outcome of Data Extraction on both Fixed and Random Effect Model of Randomized Controlled Trials of Antihypertensive Drugs and Risk of Cancer

Table 1: Data presentation on a fixed and random effect model for the risk of in the use of anti-hypertensive medication

Study Name	Effect Size	Sample Size	P – Value	Confidence interval 95%
Marco Pahor (2000)	OR = 1.26	27743	0.0003	1.11-1.43
Matthew F. Muldoon (2001)	OR = 1.32	19	0.6	0.98-1.77
Lina Chen (2008)	OR = 1.72	4,219	0.00005	2.18-6.31
Stocks T. (2008)	OR = 2.57	306	0.00021	1.20-5.52
Sripal Bangalore (2010)	OR = 1.01	76	0.004	0.93-1.09
Peter M. Rathwell (2012)	OR = 0.88	1021	0.003	0.78-0.96
Guiming Zang (2013)a	OR = 1.96	62		1.16-3.30
Guiming Zang (2013)b	RR = 8.42	62		3.112-2.272
Victoria Rotshild (2019)a	OR = 1.22	4174	0.001	1.07-1.40
Victoria Rotshild 2019b	OR = 1.33	4174	0.001	0.90-1.96
YuxiuXie (2020)a	RR = 1.45	31	0.061	1.20-1.75
YuxiuXie (2021)b	RR = 1.20	18	0.001	1.09-1.32
SintaWiranata (2021)	OR = 0.59	5	0.003	0.42-0.83
Annalen G.U Heisel (2023)a	OR = 1.27	16,670,045	0.001	1.09-1.47
Annalena G.U Heisel (2023)b	OR = 1.06	42	0.001	1.04-1.09

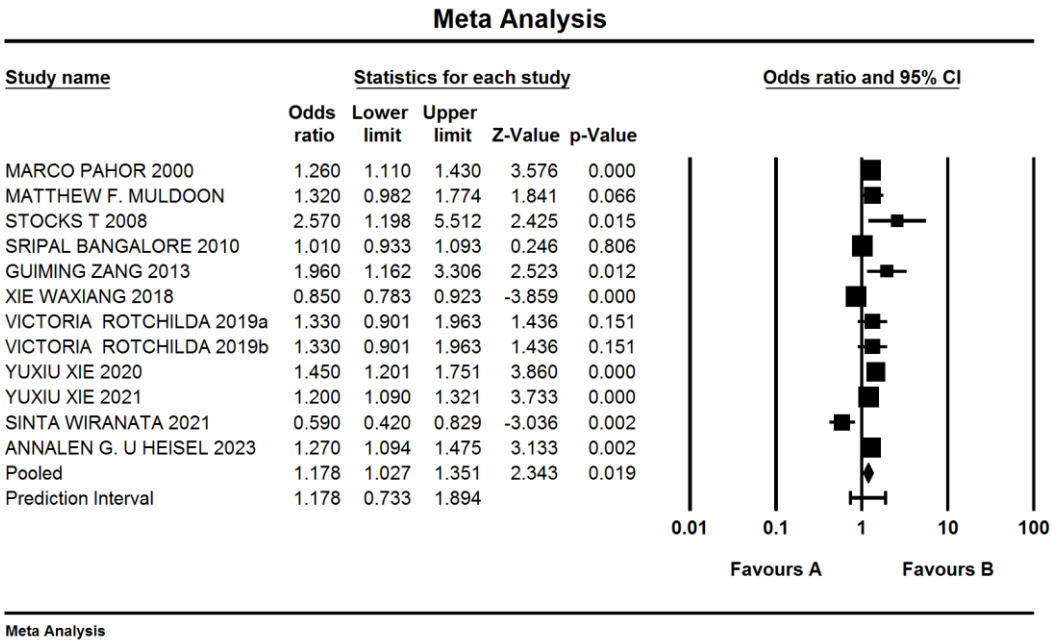

Figure 2: Forest Plot of Meta-analysis on Fixed and Random Effect Model for the Risk of in the use of Anti-hypertensive Medication

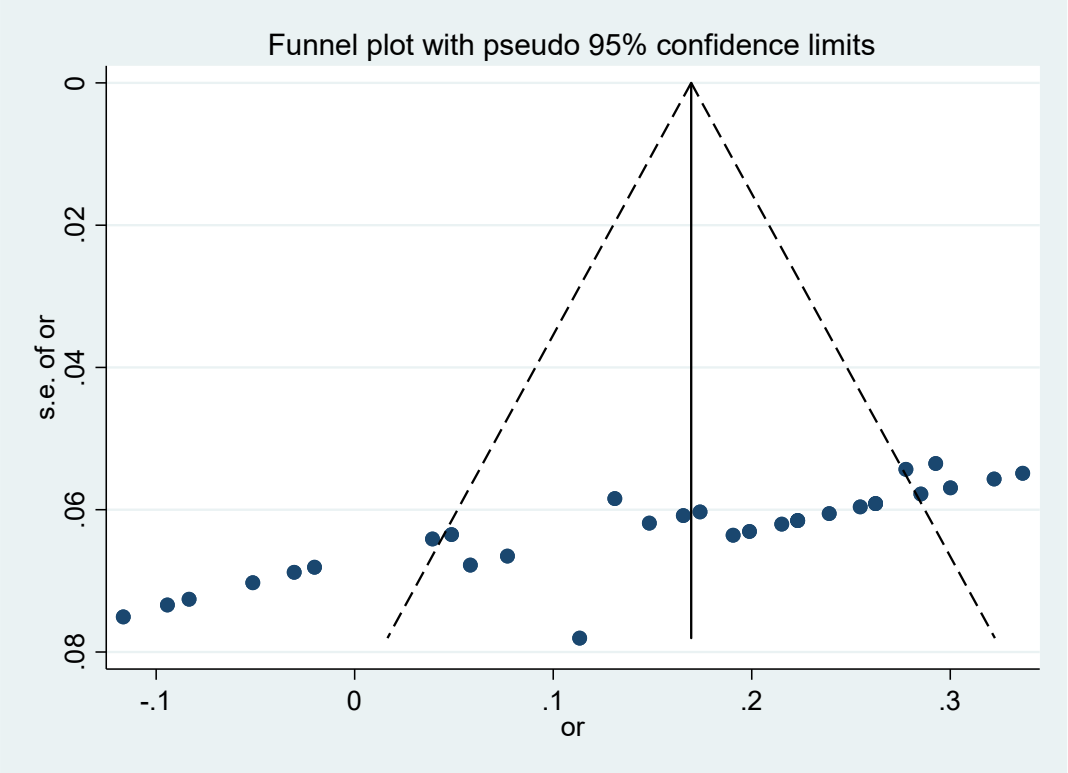

Figure 3: Funnel Plot of Meta-analysis on Fixed and Random Effect Model for the Risk of in the use of Anti-hypertensive Medication

Discussion

Table 1 is an illustration of the literature search via Google Scholar to obtain the twelve studies that we used for the meta-analysis. Though we obtained studies at the first instance, further use of keywords as is shown in Figure 1, made us arrive at only 12 studies. It is important to include only similar content in one analysis, otherwise, results could be misleading. Figure 2 represents the random effect model meta-analysis; it is needed in the computation for the overall random effect model as can be seen in equations 11 and 15. This result shows controlled trial of antihypertensive drugs and risk of cancer confirmed in the random effects model illustrated in Figure 2 with a summary result of 1.178 with a 95% confidence interval of 1.027 to 1.351, the Z-value tested the null hypothesis that the mean effect size is 1, we found $Z = 2.343$ with $p = 0.019$ for $p = 0.050$ hence we rejected the null hypothesis and concluded that we reject the null hypothesis and conclude that in the universe of populations comparable to those in the analysis, the mean effect size is not precisely 1.000. Therefore, there is association between the anti-hypertensive drugs and risk of cancer which coincided with met-analysis conducted by (Yujiao Deng, 2022) and contradicted the meta-analysis studies conducted by Copland et al., (2021) and Bangalore et al., (2012). The Figure 3 shows the Funnel Plot which is a graphical tool used to assess publication bias in the meta-analysis of antihypertensive medication and cancer risk. A symmetric funnel shape suggests the absence of publication bias, indicating that studies of

various sizes, both positive and negative, were likely included in the analysis. This enhances the credibility of the conclusion that antihypertensive drugs do not significantly increase cancer risk.

Conclusion

The meta-analysis concludes that antihypertensive medications do not show a clear, significant increase in cancer risk, though slight variability exists, particularly with ACE inhibitors and ARBs.

Recommendation

Further research is recommended to clarify long-term risks for specific drug combinations. Clinicians should continue evidence-based prescriptions while monitoring high-risk patients. Future studies should utilize large databases, include subgroup analyses, and encourage the publication of all findings to minimize bias and strengthen the evidence.

References

Bangalore, S., Kumar, S., Kjeldsen, S. E., Makani, H., Grossman, E., Wetterslev, J., Gupta, A. K., Sever, P. S., Gluud, C., & Messerli, F. H. (2011). Antihypertensive drugs and risk of cancer: Network meta-analyses and trial sequential analyses of 324,168 participants from randomized trials. *The Lancet Oncology, 12*(1), 65–82. https://doi.org/10.1016/S1470-2045(10)70260-6

Chen, L., Smith, G. D., Harbord, R. M., & Lewis, S. J. (2008). Alcohol intake and blood pressure: A systematic review implementing a Mendelian randomization approach. *PLoS Medicine, 5*(3), e52. https://doi.org/10.1371/journal.pmed.0050052

Coory, M. D. (2010). Comment on: Heterogeneity in meta-analysis should be expected and appropriately quantified. *International Journal of Epidemiology, 39*(3), 932–933. https://doi.org/10.1093/ije/dyp157

Copland, E., Canoy, D., Nazarzadeh, M., Bidel, Z., Ramakrishnan, R., Woodward, M., Chalmers, J., Teo, K. K., Pepine, C. J., Davis, B. R., Kjeldsen, S., Sundström, J., Rahimi, K., & Blood Pressure Lowering Treatment Trialists' Collaboration. (2021). Antihypertensive treatment and risk of cancer: An individual participant data meta-analysis. *The Lancet Oncology, 22*(4), 558–570. https://doi.org/10.1016/S1470-2045(21)00033-4

DerSimonian, R., & Laird, N. (2015). Meta-analysis in clinical trials revisited. *Contemporary Clinical Trials, 45*(Pt A), 139–145. https://doi.org/10.1016/j.cct.2015.09.002

Deng, Y., & Xie, Y. (2022). Effects of antihypertensive drugs on risk and prognosis of colorectal cancer: A meta-analysis of 37 observational studies. *Frontiers in Pharmacology, 10,* 10.

Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ, 315*(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629

Ferreira, J. S., & Rocha, A. R. (2010). Prevalência de hipertensão arterial em crianças e adolescentes obesos. *Ciência & Saúde Coletiva, 15*(Suppl. 1), 97–104.

Haghdoost, A. A., Sadeghirad, B., Hajarizadeh, B., & Mirzazadeh, A. (2007). The application of systematic review and meta-analysis concepts in summarizing the findings of observational studies. *Iranian Journal of Psychiatry, 2,* 132–136.

Heisel, A. G. U., Vuurboom, M. D., Daams, J. G., de Rie, M. A., Vogt, L., van den Born, B. H., & Olde Engberink, R. H. G. (2023). The use of specific antihypertensive medication and skin cancer risk: A

systematic review of the literature and meta-analysis. *Vascular Pharmacology, 150,* 107173. https://doi.org/10.1016/j.vph.2023.107173

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557

Mukete, B. N., Cassidy, M., Ferdinand, K. C., & Le Jemtel, T. H. (2015). Long-term anti-hypertensive therapy and stroke prevention: A meta-analysis. *American Journal of Cardiovascular Drugs, 15*(4), 243–257. https://doi.org/10.1007/s40256-015-0129-0

Muldoon, M. F., Manuck, S. B., Mendelsohn, A. B., Kaplan, J. R., & Belle, S. H. (2001). Cholesterol reduction and non-illness mortality: Meta-analysis of randomized clinical trials. *BMJ, 322*(7277), 11–15. https://doi.org/10.1136/bmj.322.7277.11

Pahor, M., Psaty, B. M., Alderman, M. H., Applegate, W. B., Williamson, J. D., Cavazzini, C., & Furberg, C. D. (2000). Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: A meta-analysis of randomized controlled trials. *The Lancet, 356*(9246), 1949–1954. https://doi.org/10.1016/S0140-6736(00)03306-7

Rotshild, V., Hirsh-Raccah, B., Miskin, I., Muszkat, M., & Matok, I. (2021). Comparing the clinical efficacy of COVID-19 vaccines: A systematic review and network meta-analysis. *Scientific Reports, 11*(1), 22777. https://doi.org/10.1038/s41598-021-02321-z

Salem, M. A., Ezzat, S. M., Ahmed, K. A., Alseekh, S., Fernie, A. R., & Essam, R. M. (2022). A comparative study of the antihypertensive and cardioprotective potentials of hot and cold aqueous extracts of *Hibiscus sabdariffa L.* in relation to their metabolic profiles. *Frontiers in Pharmacology, 13,* 840478. https://doi.org/10.3389/fphar.2022.840478

Wiranata, S., Anjani, I., Wulandari, P., Indrakusuma, A., Sadeva, K., Wisnawa, A., Fajar, J., Adiputra, P. A. T., Sudarsa, I. W., Lestari, A., Desak Made, W., & Supadmanaba, I. G. P. (2021). The risk of antihypertensive drug among breast cancer patients: A systematic review and meta-analysis. *Open Access Macedonian Journal of Medical Sciences, 9,* 327–334. https://doi.org/10.3889/oamjms.2021.6841

Xie, Y., Deng, Y., & Xi, Y. (2021). Association between antihypertensive medication use and breast cancer: A systematic review and meta-analysis. *Frontiers in Pharmacology, 2,* 10.

Zang, G. (2013). Antihypertensive drugs and the risk of fall injuries: A systematic review and meta-analysis. *The Journal of International Medical Research, 41*(5), 1408–1417. https://doi.org/10.1177/0300060513497562