JCOMS eISSN:2783-3127 https://journalofcoms.com

Journal of

Current Oncology and Medical Sciences

Vol. 4, No. 4

Review Free Access

Prescribing clarity mapping the link between antihypertensives and breast cancer

Shadman Newaz [1]*, Moontasir Ahmed [1], Jannat Ara Tina [1], Talukder Nasif Shahriar [1], Abdulla Bin Hridoy [1], Supritom Sarker [1], Mohammad Zakaria Al-Aziz [1], Md. Robed Amin [2]

[1] Sheikh Hasina Medical College, Tangail, Bangladesh

[2] Non-communicable Disease, DGHS, Dhaka, Bangladesh

Abstract

Introduction: The relationship between antihypertensive medication and breast cancer outcomes remains a subject of growing interest in clinical research. This systematic review aims to evaluate the potential associations between antihypertensives and breast cancer outcomes, providing a detailed synthesis of current evidence and identifying areas for future research.

Methods: We conducted a systematic review of studies published between January 2014 and January 2024, in accordance with a registered protocol on the Open Science Framework. Multiple databases were searched for English-language studies of various designs, including clinical trials, cohort studies, and observational studies. A total of 51 studies were selected from 1,591 records after a rigorous screening process. The review focused on summarizing the evidence without formal quality appraisal, adhering to the scope of this review.

Results: Our review identified potential links between certain antihypertensive classes, such as ACE inhibitors and calcium channel blockers, and breast cancer outcomes. The findings indicate that specific antihypertensive medications may influence breast cancer-specific mortality, recurrence rates, and overall survival. The role of the Renin-Angiotensin System and genetic predispositions emerged as important factors in these associations. However, the review also highlights substantial evidence gaps, particularly regarding long-term outcomes and the interaction between antihypertensive treatment and breast cancer biology.

Conclusion: This systematic review contributes to a better understanding of the complex relationship between antihypertensive medications and breast cancer outcomes. Key findings suggest that healthcare providers should consider the potential implications of specific antihypertensive drugs in patients with breast cancer. Further large-scale randomized controlled trials with extended follow-up are recommended to clarify these associations and inform clinical guidelines. Our findings underscore the importance of personalized treatment approaches and adherence to cardiovascular regimens in this patient population.

Keywords: Antihypertensive drugs, Breast Cancer Risk, Hypertension, Medication Associations

Corresponding Authors: Shadman Newaz

✉ Email: shadmannewaz11@gmail.com

Received: 2024.8.16, Accepted: 2024.11.8

Introduction

Ecthyma gangrenosum (EG) is a cutaneous infection Hypertension, a prevalent cardiovascular condition, affects an estimated 1.13 billion people globally, making it one of the leading causes of morbidity and mortality worldwide (1). Similarly, breast cancer remains the most common malignancy among women, accounting for a significant global health burden (2). Given the widespread use of antihypertensive medications to manage hypertension, understanding their potential impact on breast cancer risk has garnered increasing attention.

Recent studies have suggested potential associations between commonly prescribed antihypertensive drugs, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers (BBs), calcium channel blockers (CCBs), and diuretics, and breast cancer development. These findings raise critical questions about how these medications, through mechanisms such as modulation of the renin-angiotensin system, oxidative stress, and hormonal influences, might affect breast cancer risk and progression (3, 4). ACEIs and ARBs, for example, may influence angiogenesis and tumor growth by altering levels of angiotensin II, a hormone known to promote cancerous cell proliferation (5). In contrast, β-blockers, which regulate stress hormones, have been linked to potential protective effects against tumor progression, although evidence remains inconclusive (6, 7).

While substantial research has focused on well-established breast cancer risk factors, such as genetic predispositions, hormonal influences, and lifestyle factors (8-11), the relationship between antihypertensive drugs and breast cancer remains less clearly understood. Some studies have indicated a possible correlation between long-term antihypertensive use and breast cancer risk, while others have found no significant associations (9-11). Given the complex and sometimes contradictory findings in the literature, a comprehensive review of existing evidence is necessary to map key concepts, evaluate current trends, and identify critical knowledge gaps.

This systematic review adopts a scoping review approach to provide a broad overview of the literature on the relationship between antihypertensive medications and breast cancer outcomes. Unlike previous systematic reviews that may have focused on specific drug classes or mechanisms, this review seeks to encompass various study designs and outcomes to offer a more inclusive understanding of the topic (12, 13). The objectives are threefold: first, to map the current body of literature on the potential links between antihypertensive drugs and breast cancer; second, to explore the long-term effects of antihypertensive medications on breast cancer risk, particularly given their widespread and long-term use (2); and third, to identify evidence gaps and guide future research, ultimately shaping clinical decision-making and public health strategies (13-15).

Methodology

Study Design and Protocol Registration

This systematic review was conducted in accordance with a predefined protocol registered on the Open Science Framework. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparency and thorough reporting of the review process.

Inclusion and Exclusion Criteria

The review included studies published between January 2014 and January 2024 that examined the relationship between antihypertensive medications and breast cancer outcomes. Eligible studies were of various designs, including clinical trials, cohort studies, case-control studies, and observational studies. Only studies published in English were considered. Studies were included if they focused on patients diagnosed with hypertension and explored the use of antihypertensive medications in relation to breast cancer outcomes. Exclusion criteria included non-English studies, those without sufficient data for extraction, study protocols, and studies addressing other cancer types without specific reference to breast cancer and hypertension or antihypertensive use. Studies conducted before 2014 were excluded from the analysis.

Search Strategy

A comprehensive and refined search was conducted across four major electronic databases: PubMed, ScienceDirect, Cochrane Central Register of Controlled Trials (CENTRAL), and Mendeley. The search strategy included a combination of Medical Subject Headings (MeSH) and free-text terms designed to capture studies related to antihypertensive medications and breast cancer outcomes. The primary concepts of the search were antihypertensive medications, breast cancer, and hypertension.

Specific search terms included:

- **Antihypertensive classes**: "angiotensin-converting enzyme inhibitors" OR "ACE inhibitors" OR "angiotensin II receptor blockers" OR "ARBs" OR "beta-blockers" OR "calcium channel blockers" OR "diuretics" OR "renin-angiotensin system" OR "antihypertensive agents."
- **Breast cancer terms**: "breast cancer" OR "breast carcinoma" OR "mammary carcinoma" OR "breast neoplasms."
- **Breast cancer subtypes**: "hormone-receptor-positive" OR "HER2-positive" OR "triple-negative breast cancer" OR "ER-positive" OR "PR-positive."

Additionally, keywords such as "breast cancer incidence," "breast cancer progression," "breast cancer recurrence," "breast cancer mortality," and "breast cancer survival" were combined with terms related to antihypertensives.

To capture a broader range of relevant studies, terms were also expanded to include related side effects, mechanisms, and risk assessments, such as:

- "hypertension treatment" OR "cardiovascular drugs" AND "breast cancer risk."
- "antihypertensive side effects" AND "breast cancer survival."
- "risk of breast cancer" AND "antihypertensive drugs."

A second search iteration focused on grey literature sources by searching databases like Web of Science, Scopus, and Google Scholar. Reference lists of key studies and reviews were also screened to ensure no relevant studies were missed.

The search covered studies published from January 2014 to January 2024, and the database searches were initially performed on October 26, 2023, with an update conducted on January 26, 2024.

Screening and Data Extraction

The screening process was managed using Rayyan software, where duplicates were removed, and studies were screened based on the title and abstract. Two independent reviewers (MA and TS) conducted the initial screening of studies, with disagreements resolved by a third reviewer (JT). Full-text reviews were then conducted for studies meeting the inclusion criteria.

Data extraction was carried out using a predesigned Excel spreadsheet, capturing key details such as study design, patient population, type of antihypertensive medications used, breast cancer outcomes, and major findings. The extraction was performed by SN, with 50% of the data verified independently by AH and SS to ensure accuracy.

Quality Appraisal

Although the primary focus of this systematic review was to summarize and map the existing evidence rather than to critically appraise study quality, a descriptive evaluation of study limitations and potential biases was performed for each study. Formal quality appraisal tools, such as the Newcastle-Ottawa Scale (for cohort and case-control studies), were applied where appropriate, but no studies were excluded based on quality criteria.

Data Synthesis

Due to the heterogeneity of study designs and outcomes, a narrative synthesis was conducted. Quantitative pooling of data (meta-analysis) was not performed due to variations in study methods, populations, and outcome measures across the included studies. The results were synthesized to provide a broad overview of the evidence on the relationship between antihypertensive medications and breast cancer outcomes.

Assessment of Bias

Bias assessment was conducted using established tools and guidelines to ensure rigorous evaluation. We employed the Cochrane Risk of Bias tool to systematically assess the quality and risk of bias in the included studies. This involved evaluating various aspects, such as selection bias, performance bias, detection bias, and reporting bias. Each study was independently reviewed by multiple researchers to ensure a consistent and objective assessment. This methodical approach aimed to provide a comprehensive understanding of the potential biases influencing the study outcomes and to enhance the reliability of the systematic review's findings.

Results

Within our study, an extensive search across key databases, including PubMed (n = 209), ScienceDirect (n = 1096), Cochrane Library (n = 16), and Mendeley (n = 270), yielded a total of 1,591 records. Additionally, forward and backward citation searching contributed 49 records to the comprehensive dataset. After removing duplications, 1,518 records underwent meticulous screening. This process resulted in the exclusion of 1,398 records, aligning with predefined inclusion criteria and refining the selection for further analysis.

From the refined pool, 120 reports were sought for retrieval, and thorough scrutiny of 118 full-texts followed. Of these, 67 full-texts were excluded based on the inclusion/exclusion criteria, as illustrated in detail in the PRISMA flow diagram (see Fig. 1). Ultimately, our results section will delve into the findings extracted from the inclusion of 51 unique studies (Records were consolidated when part of the same study), offering a robust foundation for our scoping review on the intricate relationship between antihypertensive drugs and the risk of developing breast cancer.

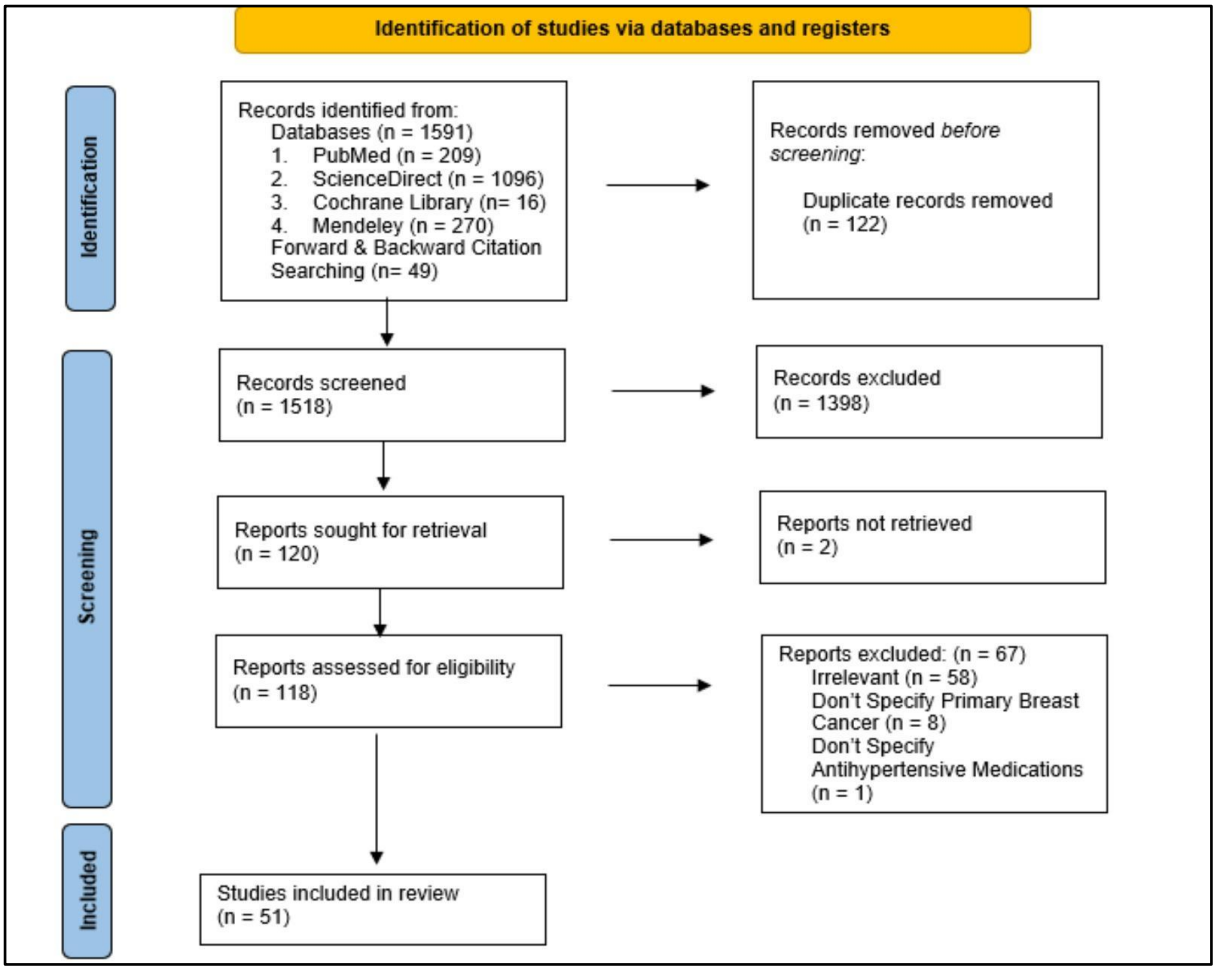

Figure 1. Prisma Flow Diagram.

Most studies were conducted in the US (n = 8) followed by UK, China, Thailand, Taiwan having 2 studies each, and one each from Bangladesh, South Africa, South Korea, Spain, Mexico, Israel, Australia, Switzerland, Israel and Indonesia; 13 were multi-country studies (see Fig. 2).

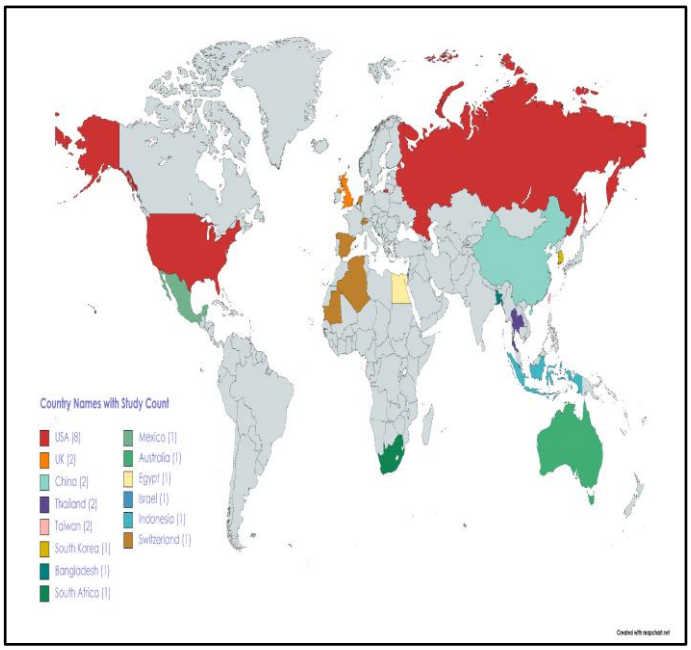

Figure 2. World Map Showing Regions (Countries) of Included Study.

The studies varied in their methodological designs (Table 1) which included mostly observational studies (n=30), experimental studies (n = 9), systematic reviews with or without meta-analysis (n = 6), literature reviews (n= 4) followed by one randomised controlled trial and one reply article. We did not perform a quality appraisal of the included studies as our objective was to summarise the extent and full range of evidence on the topic.

Table 1. Methodological Designs of Included Studies.

Study Method	Study Count(s)
Cohort/Case-control/Observation study	30
Systematic Review & Meta-Analysis	6
Experimental study/Animal study/In vitro study	9
Literature Review	4
Randomised Controlled Trial	1
Reply Article	1

Summarization of Key Findings of Each Study

Here, we present a succinct summary of the key findings extracted from each study included in our scoping review (Table 2). This summary captures essential insights into the nuanced relationship between antihypertensives and breast cancer outcomes, highlighting specific medications, genetic factors, and the role of the Renin-Angiotensin System. The diverse array of studies contributes to a comprehensive understanding of this complex association, informing healthcare decisions and guiding future research endeavors (9,16-63).

Table 2. Summarization of Key Findings of Each Study.

Category	Medication/Factor	Findings	References
Calcium Channel Blockers	CCBs	- Long-term use (>10 years) linked to increased breast cancer risk.	Supannaroj et al., 2023 (44); Stolarz et al., 2019 (34)
		- Mixed evidence on risk; some studies show no significant association.	Brasky et al., 2017 (56); Wright et al., 2017 (57)
		- Associated with specific breast cancer subtypes.	Gómez-Acebo et al., 2016 (61)
Beta-Blockers	Non-Selective BBs	- May reduce breast cancer progression and metastasis.	Caparica et al., 2021 (17); Blaes et al., 2020 (40)

		- Selective BBs may increase breast cancer incidence; non-selective BBs associated with lower recurrence risk.	Yang et al., 2023 (43); Haldar et al., 2018 (37)
		- Promising in combination with other treatments.	Kim et al., 2023 (38); Parada-Huerta et al., 2016 (63)
ACE Inhibitors and ARBs	ACEis and ARBs	- No consistent evidence of increased breast cancer risk.	Chen et al., 2017 (51); Cardwell et al., 2014 (32)
		- Potential benefits when combined with tamoxifen.	Ni et al., 2017 (9)
Diuretics	Diuretics	- Mixed evidence; some studies suggest increased risk.	Chen et al., 2017 (51)
		- Other studies find no significant impact.	Devore et al., 2015 (28)
β-Adrenergic Signaling	β-Blockers	- Influences breast cancer progression through catecholaminergic signaling.	Gillis et al., 2021 (19); Busby et al., 2018 (48)
		- Non-selective β-blockers show efficacy in blocking tumor growth.	Kim et al., 2023 (36); Montoya et al., 2019 (35)
Renin-Angiotensin System	RAS Inhibitors	- Plays a significant role in breast cancer prognosis.	Miranda et al., 2021 (18); Zhao et al., 2018 (46)
		- May improve clinical outcomes when combined with chemotherapy.	Hwang et al., 2023 (45)
Combination Therapies	Mixed	- Combining antihypertensives with breast cancer treatments shows potential but needs careful evaluation.	Hospon et al., 2021 (20); Rico et al., 2017 (62)
Adherence and Monitoring	Adherence	- Non-adherence impacts blood pressure control and cancer outcomes.	Artignan et al., 2023 (39)
		- Effective management requires monitoring and adherence.	Kozlowska et al., 2019 (47)
Future Research Directions	Research Gaps	- Gaps in understanding the impact of antihypertensive medications on breast cancer risk and outcomes.	Wiranata et al., 2021 (29); Han et al., 2017 (11)
	New Medications	- Investigate new antihypertensive drugs and their effects on breast cancer.	Xia et al., 2018 (42); Kim et al., 2023 (38)

Summarization of evidence-based recommendations of each study

Provided below is a concise overview of evidence-based recommendations derived from each study incorporated in our scoping review (Table 3). This

summary encapsulates key insights that offer guidance on prescribing practices, underscore the importance of adherence to cardiovascular drug regimens, and emphasize the need for further research to address existing knowledge gaps. The compilation of evidence-based recommendations stems from a diverse set of studies, enriching our understanding of the intricate interplay between antihypertensives and breast cancer outcomes (9, 30, 31, 34, 39, 40, 49, 51, 52, 54, 55, 57).

Table 3. Summarization of evidence-based recommendations of each study.

Author(s)	Recommendation	Key Insights
Leung et al., 2015 (30)	Emphasize the need for large and comprehensive population-based studies.	Supports validation and further exploration of current findings.
Boudreau et al., 2014 (31)	Further evaluation of ACE inhibitors (ACEI) and beta-blockers (BB) is needed.	Enhances understanding of their impact on breast cancer outcomes.
Stolarz et al., 2019 (34)	Exercise caution in using calcium channel blockers (CCBs) for breast cancer patients.	Advises careful prescribing due to potential risks.
Artignan et al., 2023 (39)	Clinicians should be aware that non-adherence to cardiovascular drug regimens may lead to discontinuation of adjuvant endocrine therapy (AET).	Highlights the link between cardiovascular and cancer treatment adherence.
Chen et al., 2017 (51)	Most antihypertensive medications are considered safe, but further research is needed for diuretics and β-blockers.	Focuses on the need for safety assessment of specific medications.
Ni et al., 2017 (9)	Conduct large, randomized controlled trials with long-term follow-up to test the effects of certain medications on breast cancer risk.	Calls for thorough investigation of medication impacts.
Chan et al., 2022 (54)	Investigate the long-term effects of valsartan on breast cancer risk.	Seeks to understand the specific implications of valsartan use.
Coulson et al., 2017 (55)	AT1R is a potential therapeutic target in breast cancer.	Opens avenues for targeted breast cancer therapies.
Wright et al., 2017 (57)	Recommend non-randomized studies in settings with prevalent CCB use, focusing on population-based cancer research.	Aims to deepen insights into CCBs and breast cancer outcomes.

Focused Summary of Recommendations

1. **Validation and Further Research**: Emphasize the need for large, population-based studies to validate findings and enhance understanding of the impact of antihypertensive medications on breast cancer outcomes (30, 31, 39).
2. **Cautious Prescribing**: Exercise caution with specific antihypertensives like CCBs due to potential risks and be mindful of adherence issues impacting cancer treatment (34, 39).
3. **Safety Assessment**: Continue to evaluate the safety of diuretics and β-blockers in relation to breast cancer, and investigate the long-term effects of specific medications such as valsartan (51, 54).
4. **Therapeutic Targets**: Explore AT1R as a potential therapeutic target and conduct long-term studies to better understand medication impacts (55, 9, 57).

Discussion

The systematic review provides a comprehensive analysis of the relationship between antihypertensive medications and breast cancer outcomes. This review integrates findings from various studies to elucidate how different antihypertensive agents may influence breast cancer risk, progression, and treatment outcomes.

Our review identifies several antihypertensive medications that have been linked to breast cancer outcomes in varying degrees. Notably, propranolol and atenolol have emerged as potential candidates for further analysis due to their association with breast

cancer-specific mortality (17, 40, 62). These findings suggest that certain β-blockers might influence disease progression differently and warrant more detailed investigation to confirm their roles.

The role of the Renin-Angiotensin System (RAS) in breast cancer is highlighted by studies showing its involvement in physiological and pathological pathways that affect disease prognosis (18). This underscores the importance of considering how antihypertensive medications that modulate RAS might impact breast cancer outcomes.

The review also emphasizes the multifaceted role of β-adrenergic receptor antagonists, particularly β-blockers, in influencing breast cancer progression. These medications appear to affect cancer progression through their action on the sympathetic nervous system, which could open new therapeutic avenues (21). The potential for β-blockers to slow cancer progression warrants further investigation to clarify their clinical utility.

Genetic factors, such as specific genotypes of the AT1R A1166C SNP, are also significant. These genetic variations may contribute to breast cancer risk, highlighting the need for personalized approaches in treatment and risk assessment (22). Understanding these genetic influences can help tailor therapies more effectively.

Our review brings to light several critical recommendations for clinical practice and future research:

1. **Targeted Research:** The need for large, comprehensive population-based studies is essential to validate current findings and explore the effects of specific antihypertensive medications on breast cancer outcomes (30, 31). Such studies could provide more robust evidence on how different medications influence disease progression and treatment efficacy.
2. **Caution in Prescription:** There is a clear need for caution when prescribing calcium channel blockers (CCBs) and other antihypertensives in patients with breast cancer. The evidence suggests that long-term use of these medications may be associated with increased risks, including lymphedema and potentially adverse outcomes in breast cancer management (34, 49). Clinical decisions should be informed by a thorough evaluation of the risks and benefits for each patient.
3. **Adherence to Cardiovascular Regimens:** Ensuring adherence to cardiovascular drug regimens is crucial, as non-adherence may lead to the discontinuation of adjuvant endocrine therapy (AET), which is vital for breast cancer management (39). Enhancing patient adherence through education and support can improve overall treatment outcomes.
4. **Further Investigation of Specific Medications:** The review highlights the need for additional research on the safety and efficacy of diuretics and β-blockers in the context of breast cancer (51). This includes examining their long-term effects and interactions with other cancer treatments.
5. **Exploring Genetic Factors:** Genetic variations, such as those in the AT1R A1166C SNP, should be considered in future studies to understand their impact on breast cancer risk and treatment (22). Incorporating genetic data could refine risk assessments and personalize treatment strategies.

Limitations and Future Directions

This systematic review, while comprehensive, has several limitations that must be acknowledged. First, many of the included studies are observational in nature, which inherently limits the ability to establish causality between antihypertensive medication use and breast cancer outcomes. Observational studies are susceptible to various biases, such as selection and information biases, which can affect the reliability of the findings.

Second, potential confounding factors present a significant challenge. Numerous studies did not adequately control for all possible confounders, such as variations in patient demographics, comorbidities, and concurrent treatments. This lack of control can obscure

the true relationship between antihypertensive use and breast cancer outcomes.

Third, the sample sizes in some studies were relatively small, which may limit the generalizability of their findings. Small sample sizes can lead to underpowered analyses, making it difficult to detect significant associations and increasing the risk of type II errors.

Additionally, heterogeneity among studies in terms of methodology, drug types, dosages, and follow-up periods introduces variability in the results. This variability can complicate the synthesis of findings and the drawing of definitive conclusions.

Finally, the review's reliance on published studies means that it may be subject to publication bias, where studies with positive or significant results are more likely to be published and included. This bias can skew the overall findings of the review.

Conclusion

In conclusion, this systematic review highlights the intricate relationship between antihypertensive medications and breast cancer outcomes. While certain drugs like propranolol and atenolol show potential impacts on breast cancer-specific mortality, the overall effects of antihypertensives on breast cancer risk are complex and require further investigation. The review emphasizes the need for large-scale, long-term studies to clarify these relationships and improve patient management. Special attention should be given to the risks associated with specific antihypertensives, such as calcium channel blockers, and their interactions with cancer therapies. Addressing these gaps will enhance treatment strategies and patient care in this challenging area.

Author contribution

SN led the data extraction process, developing the data charting framework and conducting the initial charting for all included studies. SN also contributed significantly to the analysis, interpretation of the results, and drafting sections of the introduction and results. SN oversaw the entire review process and coordinated the writing of the manuscript. **MA** was responsible for conducting the initial search, performing the title and abstract screening, and drafting sections of the methodology. MA also contributed to the final review of the manuscript and played a role in developing the study design. **TS** assisted in title and abstract screening alongside MA and contributed to refining the search strategy. TS played a key role in data extraction and writing the methodology section of the review. **JT** acted as the third reviewer to resolve conflicts between MA and TS during the screening process. JT assisted in synthesizing data and provided feedback on the discussion and conclusion sections of the manuscript. **AH** verified 50% of the extracted data to ensure accuracy and consistency. AH also reviewed the manuscript drafts and contributed to the interpretation of study findings. **SS** participated in the verification of 50% of the data extraction alongside AH and contributed to writing the discussion section. SS provided critical revisions to the draft, focusing on improving clarity and coherence. All authors contributed to the conception and design of the study, provided input on the interpretation of the data, and participated in revising the manuscript. All authors approved the final version of the manuscript before submission.

Conflict of interest

No conflicts of interest were reported among the authors involved in this scoping review. All authors declare that there were no financial, personal, or professional interests that could potentially influence the research or its outcomes. The absence of conflicts of interest underscores the commitment to conducting an unbiased and transparent analysis of the literature, contributing to the credibility and reliability of the review.

Funding

There is no funding.

References

1. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020 Apr;16(4):223-37.

2. Xie Y, Wang M, Xu P, Deng Y, Zheng Y, Yang S, et al. Association between antihypertensive medication use and breast cancer: A systematic review

and meta-analysis. Front Pharmacol. 2021 May 13;12:609901.

3. Fan Y, Khan NH, Farhan Ali Khan M, Ahammad MDF, Zulfiqar T, Virk R, et al. Association of hypertension and breast cancer: Antihypertensive drugs as an effective adjunctive in breast cancer therapy. Cancer Manag Res. 2022 Apr 1;14:1323-29.

4. Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis. 2018 May 12;5(2):77-106.

5. Obeagu EI, Obeagu GU. Breast cancer: A review of risk factors and diagnosis. Medicine (Baltimore). 2024 Jan 19;103(3).

6. Martin A. Genetic and hormonal risk factors in breast cancer. J Natl Cancer Inst. 2000;92(14):1126-35.

7. Clamp A, Danson S, Clemons M. Hormonal and genetic risk factors for breast cancer. Surgeon. 2003;1(1):23-31.

8. Shaikh F, Alamgir M, Ahmed S. Hormonal and genetic risk factors for breast cancer in a subset of the Karachi population. J Taibah Univ Med Sci. 2022;17(4):694-700. doi: 10.1016/j.jtumed.2021.12.006.

9. Ni H, Rui Q, Zhu X, Yu Z, Gao R, Liu H. Antihypertensive drug use and breast cancer risk: A meta-analysis of observational studies. Oncotarget. 2017 Jul 10;8(37):62545-60.

10. Carlos-Escalante JA, Rivas-Castro A, Pichardo-Rojas PS, Arce C, Wegman-Ostrosky T. The use of antihypertensive drugs as coadjuvant therapy in cancer. Front Oncol. 2021;11:660943.

11. Han H, Guo W, Shi W, Yu Y, Zhang Y, Ye X, He J. Hypertension and breast cancer risk: A systematic review and meta-analysis. Sci Rep. 2017;7(1):44877.

12. Pham MT, Rajić A, Greig JD, Sargeant JM, Papadopoulos A, McEwen SA. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. Res Synth Methods. 2014 Dec;5(4):371-85.

13. Munn Z, Peters MDJ, Stern C, et al. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol. 2018;18:143.

14. Elmore JG, Ganschow PS, Geller BM. Communication between patients and providers and informed decision making. J Natl Cancer Inst Monogr. 2010;2010(41):204-9.

15. Sargeant JM, O'Connor AM. Scoping reviews, systematic reviews, and meta-analysis: Applications in veterinary medicine. Front Vet Sci. 2020 Jan 28;7:11.

16. Lorona NC, Cook LS, Tang MC, Hill DA, Wiggins CL, Li CI. Antihypertensive medications and risks of recurrence and mortality in luminal, triple-negative, and HER2-overexpressing breast cancer. Cancer Causes Control. 2021 Dec;32(12):1375-84.

17. Caparica R, Bruzzone M, Agostinetto E, De Angelis C, Fêde A, Ceppi M, De Azambuja E. Beta-blockers in early-stage breast cancer: A systematic review and meta-analysis. ESMO Open. 2021;6(2):100066.

18. De Miranda FS, Guimarães JPT, Menikdiwela KR, Mabry B, Dhakal R, Rahman RL, Moussa H, Moustaid-Moussa N. Breast cancer and the renin-angiotensin system (RAS): Therapeutic approaches and related metabolic diseases. Mol Cell Endocrinol. 2021;528:111245.

19. Gillis RD, Botteri E, Chang AI, Ziegler AI, Chung NK, Pon CK, et al. Carvedilol blocks neural regulation of breast cancer progression in vivo and is associated with reduced breast cancer mortality in patients. Eur J Cancer. 2021;147:106-16.

20. Hopson MB, Lee S, Accordino M, Trivedi M, Maurer M, Crew KD, et al. Phase II study of propranolol feasibility with neoadjuvant chemotherapy in patients with newly diagnosed breast cancer. Breast Cancer Res Treat. 2021;188(2):427-32. doi:

21. De Sanctis R, Viganò A, Torrisi R, Santoro A. Re: Carvedilol blocks neural regulation of breast cancer progression in vivo and is associated with reduced breast cancer mortality in patients: Sympathetic nervous system activity on breast cancer: the story of migraine. Eur J Cancer. 2021 Jul;152:250-1.

22. El Sharkawy RM, Zaki AM, El Fattah Kamel AA, Bedair RN, Ahmed AS. Association between the polymorphisms of angiotensin converting enzyme (Peptidyl-Dipeptidase A) INDEL mutation (I/D) and Angiotensin II type I receptor (A1166C) and breast cancer among postmenopausal Egyptian females. Alex J Med. 2014;50(3):267-74.

23. Namazi S, Rostami-Yalmeh J, Sahebi E, Jaberipour M, Razmkhah M, Hosseini A. The role of captopril and losartan in prevention and regression of tamoxifen-induced resistance of breast cancer cell line MCF-7: an in vitro study. Biomed Pharmacother. 2014 Jun;68(5):565-71.

24. Kang F, Ma W, Ma X, Shao Y, Yang W, Chen X, Li L, Wang J. Propranolol inhibits glucose metabolism and 18F-FDG uptake of breast cancer through posttranscriptional downregulation of hexokinase-2. J Nucl Med. 2014 Mar;55(3):439-45.

25. Hugon-Rodin J, Gompel A, Plu-Bureau G. Antihypertensive medications and breast cancer risk. JAMA Intern Med. 2014 Apr;174(4):640-1.

26. Chen L, Malone KE, Li CI. Use of antihypertensive medications not associated with risk of contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. Cancer Epidemiol Biomarkers Prev. 2015 Sep;24(9):1423-6.

27. Lamkin DM, Sung HY, Yang GS, David JM, Ma JC, Cole SW, Sloan EK. α2-Adrenergic blockade mimics the enhancing effect of chronic stress on breast cancer progression. Psychoneuroendocrinology. 2015 Jan;51:262-70.

28. Devore EE, Kim S, Ramin CA, Wegrzyn LR, Massa J, Holmes MD, Michels KB, Tamimi RM, Forman JP, Schernhammer ES. Antihypertensive medication use and incident breast cancer in women. Breast Cancer Res Treat. 2015 Feb;150(1):219-29.

29. Wiranata S, Anjani IAW, Wulandari PA, Indrakusuma AABP, Sadeva IGKA, Wisnawa ADF, Fajar JK, Prabawa IPY, Adiputra PAT, Sudarsa IW, Lestari AAW, Wihandani DM, Supadmanaba IGP. The risk of antihypertensive drugs among breast cancer patients: A systematic review and meta-analysis. Open Access Maced J Med Sci. 2021;9(F):327-34.

30. Leung HW, Hung L, Chan ALF, Mou C. Long-term use of antihypertensive agents and risk of breast cancer: a population-based case–control study. Cardiol Ther. 2015;4(1):65-76.

31. Boudreau DM, Yu O, Chubak J, Wirtz HS, Bowles EJ, Fujii M, Buist DS. Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early-stage breast cancer. Breast Cancer Res Treat. 2014 Apr;144(2):405-16.

32. Cardwell CR, McMenamin ÚC, Hicks BM, Hughes C, Cantwell MM, Murray LJ. Drugs affecting the renin-angiotensin system and survival from cancer: a population-based study of breast, colorectal, and prostate cancer patient cohorts. BMC Med. 2014 Feb 13;12:28.

33. Wilson L, D'Aloisio AA, Sandler DP, Taylor JA. Antihypertensive use and breast cancer risk in the Sister Study. Environ Health Perspect. 2014;122(1):2484.

34. Stolarz AJ, Lakkad M, Klimberg VS, Painter JT. Calcium channel blockers and risk of lymphedema among breast cancer patients: nested case-control study. Cancer Epidemiol Biomarkers Prev. 2019 Nov;28(11):1809-15.

35. Montoya A, Varela-Ramirez A, Dickerson E, Pasquier E, Torabi A, Aguilera R, Nahleh Z, Bryan B. The beta adrenergic receptor antagonist propranolol alters mitogenic and apoptotic signaling in late-stage breast cancer. Biomed J. 2019 Jun;42(3):155-65.

36. Kim YJ, Jang SK, Kim G, Hong SE, Park CS, Seong MK, Kim HA, Kim KS, Kim CH, Park KS,

Hong J, Jin HO, Park IC. Nebivolol sensitizes BT-474 breast cancer cells to FGFR inhibitors. Anticancer Res. 2023 May;43(5):1973-80.

37. Haldar R, Shaashua L, Lavon H, Lyons YA, Zmora O, Sharon E, Birnbaum Y, Allweis T, Sood AK, Barshack I, Cole S, Ben-Eliyahu S. Perioperative inhibition of β-adrenergic and COX2 signaling in a clinical trial in breast cancer patients improves tumor Ki-67 expression, serum cytokine levels, and PBMCs transcriptome. Brain Behav Immun. 2018 Oct;73:294-309.

38. Kim S, Park JM, Park S, Jung E, Ko D, Park M, Seo J, Nam KD, Kang YK, Lee K, Farrand L, Kim YJ, Kim JY, Seo JH. Suppression of TNBC metastasis by doxazosin, a novel dual inhibitor of c-MET/EGFR. J Exp Clin Cancer Res. 2023 Nov 4;42(1):292

39. Artignan J, Capmas P, Panjo H, Constantinou P, Pelletier-Fleury N. Are breast cancer patients with suboptimal adherence to cardiovascular treatment more likely to discontinue adjuvant endocrine therapy? Competing risk survival analysis in a nationwide cohort of postmenopausal women. BMC Med. 2023 Nov 24;21(1):463.

40. Blaes AH, Domingo-Musibay E, Kalinsky K. Propranolol: What is BLOCKing Its Clinical Investigation in Breast Cancer? Clin Cancer Res. 2020 Apr 15;26(8):1781-3.

41. Ashrafi S, Shapouri R, Shirkhani A, Mahdavi M. Anti-tumor effects of propranolol: adjuvant activity on a transplanted murine breast cancer model. Biomed Pharmacother. 2018 Aug;104:45-51.

42. Xia T, He Q, Shi K, Wang Y, Yu Q, Zhang L, Zhang Q, Gao H, Ma L, Liu J. Losartan-loaded liposomes improve the antitumor efficacy of liposomal paclitaxel modified with pH-sensitive peptides by inhibition of collagen in breast cancer. Pharm Dev Technol. 2018 Jan;23(1):13-21.

43. Yang J, Zhang S, Jiang W. Impact of beta blockers on breast cancer incidence and prognosis. Clin Breast Cancer. 2023 Jun;23(6):664-71.e21.

44. Supannaroj R, Khamsai S, Chindaprasirt J, Sukeepaisarnjaroen W, Limpawattana P, Sawanyawisuth K. An association between calcium channel blocker and breast cancer in patients with hypertension: A case-control study. Med Drug Discov. 2023;20:100168.

45. Hwang HJ, Lee TG. Impact on clinical outcomes of renin-angiotensin system inhibitors against doxorubicin-related toxicity in patients with breast cancer and hypertension: A nationwide cohort study in South Korea. PLoS One. 2023 Nov 20;18(11).

46. Zhao Y, Wang Q, Zhao X, Meng H, Yu J. Effect of antihypertensive drugs on breast cancer risk in female hypertensive patients: Evidence from observational studies. Clin Exp Hypertens. 2018;40(1):22-27.

47. Kozłowska K, Kozłowski L, Małyszko J. Hypertension prevalence in early breast cancer patients undergoing primary surgery. Adv Med Sci. 2019 Mar;64(1):32-36.

48. Busby J, Mills K, Zhang SD, Liberante FG, Cardwell CR. Postdiagnostic calcium channel blocker use and breast cancer mortality: A population-based cohort study. Epidemiology. 2018 May;29(3):407-413.

49. Lin SY, Huang HY, Chiang LT, Huang LY, Wang CC. Use of calcium channel blockers and risk of breast cancer among women aged 55 years and older: A nationwide population-based cohort study. Hypertens Res. 2023 Oct;46(10):2272-2279.

50. Ayeni OA, Joffe M, Mapanga W, Chen WC, O'Neil DS, Phakathi B, Nietz S, Buccimazza I, Čačala S, Stopforth LW, Jacobson JS, Crew KD, Neugut AI, Ramiah D, Ruff P, Cubasch H, Chirwa T, McCormack V, Micklesfield LK, Norris SA. Multimorbidity and overall survival among women with breast cancer: Results from the South African Breast Cancer and HIV Outcomes Study. Breast Cancer Res. 2023 Jan 23;25(1):7.

51. Chen L, Chubak J, Boudreau DM, Barlow WE, Weiss NS, Li CI. Use of antihypertensive medications and risk of adverse breast cancer outcomes in a SEER-

Medicare population. Cancer Epidemiol Biomarkers Prev. 2017 Nov;26(11):1603-1610.

52. Cardwell CR, Pottegård A, Vaes E, Garmo H, Murray LJ, Brown C, Vissers PA, O'Rorke M, Visvanathan K, Cronin-Fenton D, De Schutter H, Lambe M, Powe DG, van Herk-Sukel MP, Gavin A, Friis S, Sharp L, Bennett K. Propranolol and survival from breast cancer: A pooled analysis of European breast cancer cohorts. Breast Cancer Res. 2016 Dec 1;18(1):119.

53. Chang CH, Chiang CH, Yen CJ, Wu LC, Lin JW, Lai MS. Antihypertensive agents and the risk of breast cancer in women aged 55 years and older: A nested case-control study. J Hypertens. 2016 Mar;34(3):558-66.

54. Chan TH, Tsoi MF, Yung Cheung BM. Cancer risk of angiotensin II receptor blocker valsartan: A population-based study. J Cardiovasc Pharmacol. 2022 Apr 1;79(4):577-582.

55. Coulson R, Liew SH, Connelly AA, Yee NS, Deb S, Kumar B, Vargas AC, O'Toole SA, Parslow AC, Poh A, Putoczki T, Morrow RJ, Lazarus KA, Yeap EFW, Walton KL, Harrison CA, Hannan NJ, George AJ, Clyne CD, Ernst M, Allen AM, Chand AL. The angiotensin receptor blocker, Losartan, inhibits mammary tumor development and progression to invasive carcinoma. Oncotarget. 2017 Mar 21;8(12):18640-18656.

56. Brasky TM, Krok-Schoen JL, Liu J, Chlebowski RT, Freudenheim JL, Lavasani S, Margolis KL, Qi L, Reding KW, Shields PG, Simon MS, Wactawski-Wende J, Wang A, Womack C, Manson JE. Use of calcium channel blockers and breast cancer risk in the Women's Health Initiative. Cancer Epidemiol Biomarkers Prev. 2017 Aug;26(8):1345-1348.

57. Wright CM, Moorin RE, Chowdhury EK, Stricker BH, Reid CM, Saunders CM, Hughes JD. Calcium channel blockers and breast cancer incidence: An updated systematic review and meta-analysis of the evidence. Cancer Epidemiol. 2017 Oct;50:113-124.

58. Islam D, Islam MS, Jesmin. Association of hypertension, hyperlipidemia, obesity, and demographic risk factors with breast cancer in Bangladeshi women. Medicine (Baltimore). 2022 Nov 18;101(46).

59. Altundag K. Antihypertensive medication use and breast cancer risk. J Hypertens. 2017 Aug;35(8):1722.

60. Schairer C, Gadalla SM, Pfeiffer RM, Moore SC, Engels EA. Diabetes, abnormal glucose, dyslipidemia, hypertension, and risk of inflammatory and other breast cancer. Cancer Epidemiol Biomarkers Prev. 2017 Jun;26(6):862-868.

61. Gómez-Acebo I, Dierssen-Sotos T, Palazuelos C, Pérez-Gómez B, Lope V, Tusquets I, Alonso MH, Moreno V, Amiano P, Molina de la Torre AJ, Barricarte A, Tardon A, Camacho A, Peiro-Perez R, Marcos-Gragera R, Muñoz M, Michelena-Echeveste MJ, Ortega Valin L, Guevara M, Castaño-Vinyals G, Aragonés N, Kogevinas M, Pollán M, Llorca J. The use of antihypertensive medication and the risk of breast cancer in a case-control study in a Spanish population: The MCC-Spain Study. PLoS One. 2016 Aug 10;11(8).

62. Rico M, Baglioni M, Bondarenko M, Laluce NC, Rozados V, André N, Carré M, Scharovsky OG, Menacho Márquez M. Metformin and propranolol combination prevents cancer progression and metastasis in different breast cancer models. Oncotarget. 2017 Jan 10;8(2):2874-2889.

63. Parada-Huerta E, Alvarez-Dominguez T, Uribe-Escamilla R, Rodriguez-Joya J, Ponce-Medrano JD, Padron-Lucio S, Alfaro-Rodriguez A, Bandala C. Metastasis Risk Reduction Related with Beta-Blocker Treatment in Mexican Women with Breast Cancer. Asian Pac J Cancer Prev. 2016;17(6):2953-7.