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REVIEW

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An investigation of the impact of atenolol on the risk of all-cause mortality in Asian individuals with hypertension and cardiovascular conditions

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Abstract

Background Despite several justifications for utilizing beta-blockers, such as atenolol, as the initial treatment for hypertension in the presence of cardiovascular disease, some studies have demonstrated that calcium channel blockers were more effective than beta-blockers in decreasing mortality. This review intended to determine the efficacy of atenolol in reducing all-cause mortality in Asian individuals with hypertension, coronary artery disease, atrial fibrillation, and heart failure.

Main body of the abstract Studies published before March 31, 2023, were searched using Trip, Google Scholar, Cochrane, and EMBASE databases. We only considered studies that compared atenolol with other medications in terms of all-cause mortality rates in Asian individuals diagnosed with hypertension and cardiovascular diseases. Therefore, we only considered three trials with a total of 79,603 participants. The results indicated a statistically significant higher all-cause death rate among non-atenolol users compared to atenolol users ($p < 0.001$). The all-cause death rate was considerably greater in individuals who consumed metoprolol tartrate compared to those who consumed atenolol (OR = 0.50, $p < 0.0001$). Although the included publications were deemed to have a low risk of bias, significant heterogeneity was observed ($p = 0.001$).

Short conclusion Due to the limited studies included, this analysis concluded that atenolol, in comparison with non-users of atenolol or especially metoprolol tartrate, significantly reduces the overall death rate in East Asian and Southeast Asian patients with hypertension, coronary artery disease, atrial fibrillation, and heart failure. Yet, the current study cannot finalize this conclusion for other Asian ethnic groups, such as South Asians, Central Asians, and West Asians. Additional systematic reviews and meta-analyses with low heterogeneity and high-quality evidence are suggested to validate our findings and explore the efficacy of atenolol in various ethnic populations.

Keywords Atenolol, Mortality, Asians, Hypertension, Cardiovascular disease

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Background

Individuals with cardiovascular diseases (CVDs) are advised to take beta-blockers in combination with other medications to decrease overall and cardiovascular morbidity and mortality. Beta-blockers are indicated as the initial treatment for hypertensive patients with cardiovascular conditions such as heart failure and coronary artery disease (Chrysant and Chrysant 2022). Despite controversies, beta-blocker agents are recommended to reduce overall mortality in patients undergoing non-cardiac surgery with two or more specific conditions such as coronary artery disease, diabetes mellitus, renal insufficiency, and cerebrovascular disease (Vivas and Raposeiras 2022; Nan et al. 2020). Multiple studies have assessed beta-blocker medicines and compared their effectiveness in lowering all-cause mortality in individuals with chronic illnesses. Assimon et al. showed that carvedilol is linked to a 1.08-fold increased risk of all-cause death in end-stage renal disease (ESRD) patients compared to metoprolol (Hundemer et al. 2021). Another study among patients with end-stage renal disease (ESRD) found that bisoprolol was significantly linked to decreased rates of all-cause mortality compared to carvedilol, as reported by Wu et al. (2021). Schupp et al. observed that carvedilol was not superior to metoprolol in reducing the all-cause death rate among patients with ventricular tachyarrhythmia (Schupp et al. 2022). The all-cause death rate was greater among patients with advanced stages of heart failure who used nebivolol compared to those who used bisoprolol, with no meaningful difference (Alhabeeb et al. 2022). Shin et al.'s study found a reduced mortality rate among individuals using bisoprolol compared to those using atenolol. No substantial difference was seen (Shin et al. 2012). As to the American Heart Association (AHA) guidelines, atenolol is contraindicated for patients with stable ischemic heart disease (SIHR). This guideline is derived from multiple studies that examined the cardiovascular event risk in Caucasian people taking 25–100 mg of atenolol once daily (Aronow et al. 2011).

The recommendations against using atenolol are based on factors such as dosing potency, frequency, and pharmacokinetic interactions. Research indicates that atenolol doses of 100 to 200 mg daily were more helpful than doses of 25 and 50 mg daily in patients with angina (Leopold 2022; Katsukunya et al. 2023).

Specific gene mutations, which may be prevalent in certain ethnic groups, can impact the way atenolol is effective. Gene polymorphisms associated with *TBX2* and *GNB3* genes have been shown to notably diminish the antihypertensive impact of atenolol (McDonough et al. 2013; Pharmacogenomics Knowledge Base (PharmGKB). rs8068318 variant (TBX2 gene)). The alleles rs3213619 and rs2144300 linked to *ABCB1* and *GALNT2* genes have been strongly correlated with decreased levels of high-density lipoprotein cholesterol (HDL-C) (Pharmacogenomics Knowledge Base (PharmGKB). rs2144300 variant (GALNT2 gene)). The *TBX2* mutation associated with the reduced effectiveness of atenolol is prevalent in more than 69% of Finnish, non-Finnish European, Amish, and Ashkenazi Jewish ethnic populations. Nevertheless, this mutation is less commonly found in Africans, African Americans, and Asians (Moskalewicz and Oremus 2020). The rs2144300 allele associated with the *GALNT2* gene is present in up to 21% of Asians, Africans, and African Americans, whereas more than 60% of non-Finish Europeans carry this mutant allele (Santesso et al. 2020). The alterations in the above genes may provide a rationale for excluding Asians, Africans, and African Americans from the AHA recommendations advising against the use of atenolol. Additionally, atenolol, along with other beta-blockers, may have clinical effectiveness in reducing overall mortality in certain ethnic populations.

Rationale

Asians may respond differently to atenolol due to their distinct genetic traits, potentially affecting its efficacy in reducing overall mortality.

Objective

This review intended to determine the efficacy of atenolol in reducing all-cause mortality in Asian individuals with cardiovascular disease (CVD) and hypertension.

Materials and methods

The review comprised cohort studies conducted in English. The studies analyzed the impact of atenolol compared to other beta-blockers and non-beta-blockers on overall mortality in Asian patients with hypertension, coronary artery disease, atrial fibrillation, and heart failure. We omitted trials including non-Asian patients, non-Asian patients taking atenolol, and Asian patients without diagnoses of hypertension and cardiovascular diseases. Furthermore, studies that fulfilled the inclusion criteria but omitted the specific number of atenolol users were also eliminated.

The studies published before March 31, 2023, were searched using Trip, Google Scholar, Cochrane, and EMBASE databases. We exclusively analyzed trials that compared atenolol with other medications in terms of all-cause mortality rates in Asian individuals diagnosed with hypertension and cardiovascular disease. The search terms used were: atenolol, OR beta-blockers, AND Asians, OR Chinese, OR Korean, OR Taiwanese, OR Japanese, OR Vietnamese, OR Mongols, OR Thais, OR Cambodians, OR Indonesians, OR Malays, OR Bengalis, OR Nepalese, OR Pakistanis, OR Singaporeans, OR Burmese,

OR Filipinos, OR Indians, AND hypertension, OR cardiovascular disease, OR angina, OR ischemic heart disease, OR ischemia, OR myocardial infarction, AND all-cause death.

Two researchers independently edited the summaries of the selected papers. Acquire eligible articles and extract their features. The authors resolved any disputes through discussion.

The main objective was to establish the overall mortality rate in those using atenolol compared to those who did not take it. The secondary objective was to compare the all-cause mortality rate between individuals using metoprolol tartrate and those using atenolol.

The publications were assessed for bias using the Newcastle–Ottawa scale for cohort studies, which graded the risk as ambiguous, low, or high. The scale delineates the domains as follows: selective reporting, adequate case definition, consecutive representativeness of cases, selection of community controls, adequate control definition, independent blind assessment of outcome, all subjects complete the follow-up period (Hacke and Nunan 2020).

Data analysis was conducted using a random effect model in Review Manager version 5.3. The findings were presented as odds ratios (OR) along with 95% confidence intervals (CI).

Outcome measures were assessed for quality using the GRADE technique, which categorizes them as high, moderate, low, or very low based on research constraints such as risk of bias, directness of evidence, consistency across trials, and precision of the pooled estimate (Wong et al. 2014). The I^2 test was utilized to assess heterogeneity among the papers included (Chen et al. 2017).

Results

A total of 174 studies were retained after eliminating duplicates from a pool of 380 studies. After eliminating irrelevant submissions throughout the screening process, 108 papers were assessed for eligibility. Three studies fulfilled our inclusion criteria. The search specifics are outlined in the PRISMA flow diagram (Fig. 1).

Three cohort studies were included in the review (Wongpraparut et al. 2020; Sharma et al. 2022; Chan et al. 2021). Table 1 provides an explanation of the features of the studies that were considered. The characteristics encompassed study setting, duration, design, participant age and sex, and outcome measures.

The research analyzed 79,865 Asian patients, with 43,819 not using atenolol and 36,046 using atenolol. Patients were over 46 years old. Wongpraparut et al.'s study involved individuals with cardiovascular disorders, including coronary artery disease, heart failure, and atrial fibrillation. Yet, Chen et al. and Wong et al.'s studies mainly included patients with hypertension. 68.5% ($N=30,001$) of patients in the non-atenolol group used metoprolol tartrate (Wongpraparut et al. 2020; Chan et al. 2021), whereas the remaining non-atenolol users (31.5%) utilized a variety of beta-blockers such as carvedilol, metoprolol succinate, nebivolol, bisoprolol, and propranolol, totaling $N=262$ (Chan et al. 2021), or non-beta-blocker medicines, totaling $N=13,556$ (Sharma et al. 2022).

The research included generally had a low risk of bias across most areas, with no instances of significant bias observed. Reporting bias was identified as low risk among the three articles. Some ambiguous risk of bias was identified in the three articles included, relating to various aspects such as selection of community controls, definition of controls, follow-up period, blind assessment of outcome, and independent assessment of outcome (Fig. 2).

Figure 3 displays a forest plot illustrating the all-cause death rate comparison between 36,046 atenolol users and 43,819 non-users from the three studies considered. Atenolol non-users had a higher all-cause death rate of 10.50% compared to atenolol users with a rate of 5.57% (OR = 0.58, CI = 0.44–0.76, $p < 0.0001$). Significant heterogeneity was detected with an I2 value of 88% and a p value of less than 0.001.

Figure 4 displays a forest plot comparing the all-cause death rate between 30,001 metoprolol tartrate users and 22,490 atenolol users from two out of the three relevant papers (Wongpraparut et al. 2020; Chan et al. 2021). Metoprolol tartrate users had a higher all-cause death rate of 13.15% compared to atenolol users with a rate of 7.02% (OR = 0.50, CI = 0.47–0.53, $p < 0.0001$). There was no heterogeneity seen (I2 = 0%, $p = 0.97$).

The studies included had a low risk of bias, which reduced the quality of evidence for each study. Outcome measure increased by one level. We assessed the evidence quality as low for the all-cause mortality rate in non-atenolol users compared to atenolol users. We reduced the level of evidence by two levels due to the observational nature of the studies involved and the significant heterogeneity ($I2 = 88\%$). Minor variability was identified in the study of secondary outcome.

Discussion

The present study assessed the overall mortality rate among Asians ($N=79,865$) with hypertension and cardiovascular diseases. Among them, 36,046 were using atenolol, whereas 43,819 were not. The primary result suggests that the usage of atenolol was linked to reduced rates of overall mortality. Recent studies have shown a decline in research on atenolol, whereas novel beta-blocker medications are being extensively examined employing modern research techniques and materials across diverse

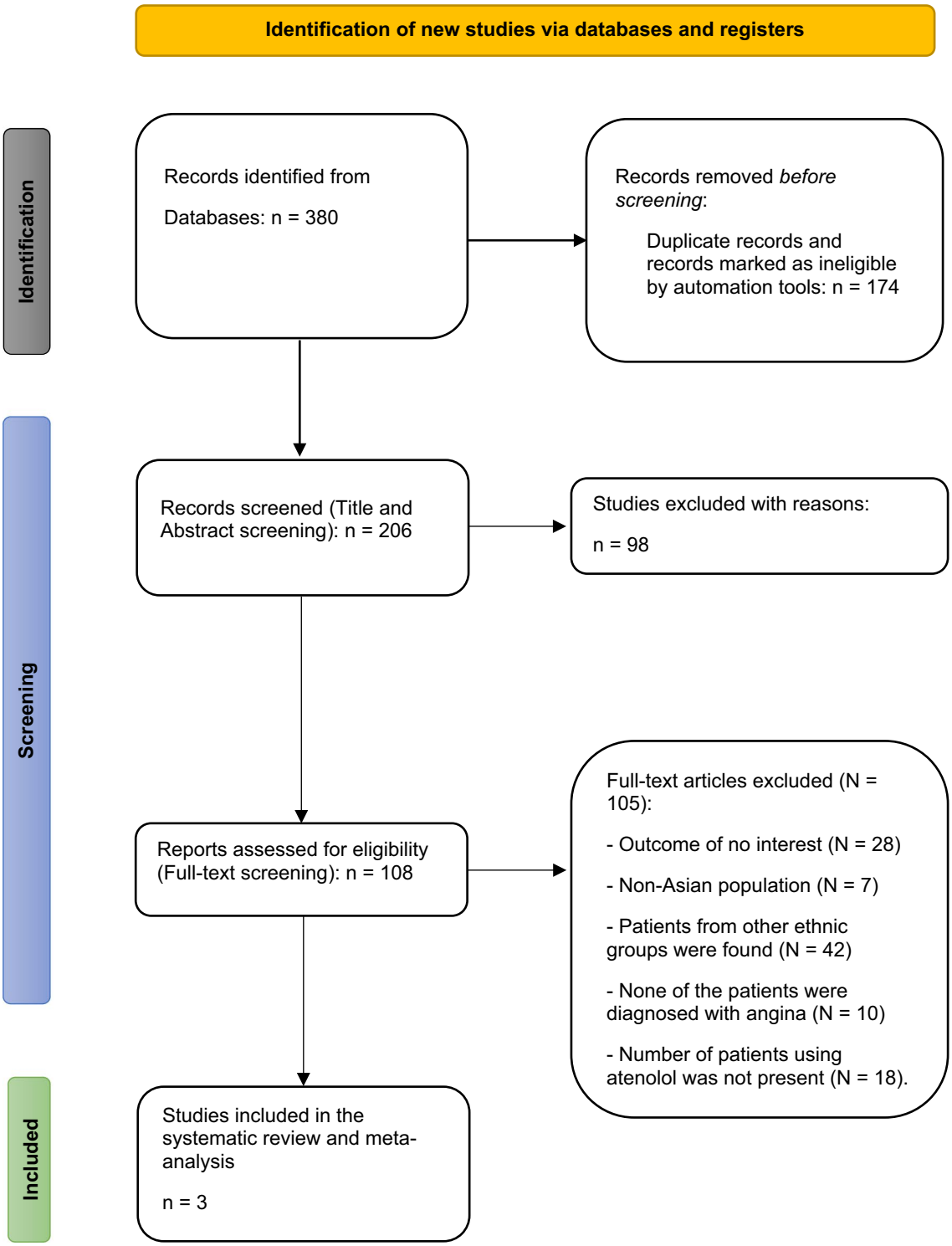

Fig. 1 PRISMA flow diagram of studies in systematic review

ethnic populations (Sharma et al. 2022; Chan et al. 2021; Marques et al. 2022; Glezer 2021). Only three studies were included in the current analysis, focusing on the effectiveness of atenolol in reducing all-cause mortality in East and Southeast Asian patients with hypertension, coronary artery disease, atrial fibrillation, and heart failure.

Table 1 Characteristics of included studies

Author	Title	Study design	Setting/duration	Aim	Participants	Outcome
Wong et al. (2014)	The effectiveness of metoprolol versus atenolol on prevention of all-cause and cardiovascular mortality in a large Chinese population: a cohort study	Retrospective cohort study	The study conducted in Hong Kong between 2001 and 2010	Compared the incidence of all-cause death and cardiovascular mortality between patients newly prescribed atenolol versus metoprolol tartrate users	Hypertensive patients using atenolol ($N=22,479$) or metoprolol tartrate ($N=29,972$). About 34% of the participants from both groups had cardiovascular risk factors and medical conditions which could potentially confound the choice of antihypertensive drug class	7.0% and 13.1% died of any causes among atenolol and metoprolol users, respectively ($p<0.005$). The incidence of cardiovascular mortality among atenolol users was lower than metoprolol users (1.4% vs. 3.7%, $p<0.001$)
Chen et al. (2017)	Impact of beta-blocker initiation timing on mortality risk in patients with diabetes mellitus undergoing non-cardiac surgery: a nationwide population-based cohort study	Retrospective cohort study	The study conducted using the Taiwan's National Health Insurance Research Database between 2000 and 2011	To explore the role of perioperative initiation of beta-blockers, including atenolol, in patients with diabetes mellitus undergoing non-cardiac surgery	Diabetic patients with hypertension undergoing non-cardiac surgery using atenolol ($N=13,556$) or non-atenolol matched controls ($N=13,556$). Nearby 92% of the participants from both groups were hypertensive, 65% have dyslipidemia, 16% have cancer, 15% valvular heart disease, 7% have peripheral vascular disease, and 5% have atrial fibrillation	Beta-blocker users were associated with lower risks of in-hospital (odds ratio 0.75, 95% CI 0.68–0.82) and 30-day (odds ratio 0.75, 95% CI 0.70–0.81) mortality
Wongpraparut et al. (2020)	Impact of guideline-recommended versus non-guideline-recommended β-blocker and Doppler echocardiographic parameters on 1-year mortality in Thai ischemic cardiomyopathy patients: a prospective multicenter registry	Prospective cohort study	The study conducted in 9 medical centers located across Thailand from December 2014 to November 2015	To determine and to identify factors that significantly predicts 1-year mortality of Thai patients with ischemic cardiomyopathy	Patients with coronary artery disease using atenolol ($N=11$), metoprolol tartrate ($N=29$), or non-atenolol beta-blocker agent ($N=291$)	The use of non-guideline-recommended beta-blockers (atenolol, metoprolol tartrate, and propranolol) rather than guideline recommended beta-blockers (Carvedilol, metoprolol succinate, nebivolol, and bisoprolol) were associated with increased with 1-year mortality

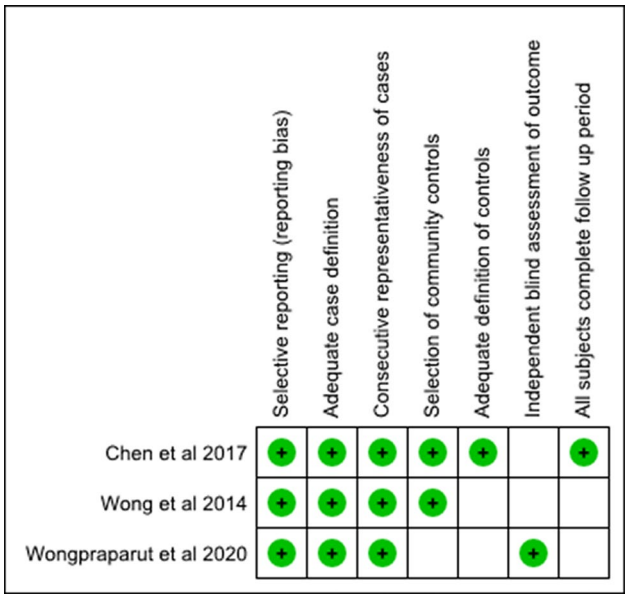

Fig. 2 Risk of bias summary according to authors' judgment

The new review results, which mainly involves East and Southeast Asian patients, go against a current suggestion (Virani et al. 2023). The current advice was derived from the Carlberg et al. review, which concluded that atenolol is equally effective as the control group in reducing all-cause mortality (Virani et al. 2023). Carlberg et al. did not examine research that compared atenolol with other beta-blockers in terms of all-cause mortality (Virani et al. 2023). Therefore, atenolol may still considered a good beta-blocker therapeutic choice for treating hypertension with cardiovascular comorbidities, including coronary artery disease, atrial fibrillation, and heart failure diseases, particularly among certain ethnic groups like East and Southeast Asians. Besides, the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization did not distinguish between different beta-blocker drugs for treating certain medical disorders. However, it may suggest utilizing certain beta-blockers for patients with distinct genetic variations (Lawton et al. 2022). Won et al. demonstrated a decrease in overall mortality among Asians with acute myocardial infarction who used any beta-blocker medicine compared to those who did not take them (Won et al. 2020).

Furthermore, beta-1 receptor-selective blockers, such as atenolol, metoprolol, and bisoprolol, are beneficial for patients with coronary artery disease. These medications lower heart rate and blood pressure, which reduces the strain on the heart muscle. By decreasing the oxygen demand of the heart muscle, they also lower the risk of future heart attacks (Zhang et al. 2022; Santucci et al. 2020; Bajraktari et al. 2021). A previous study conducted a comparison between individuals treated with atenolol and nebivolol, a new beta-blocker, to assess the advancement of coronary artery disease. The study found no notable disparities in endothelial function, oxidative stress indicators, or coronary plaque volume between those on nebivolol and atenolol. The previous study showed that specific parameters in individuals, such as

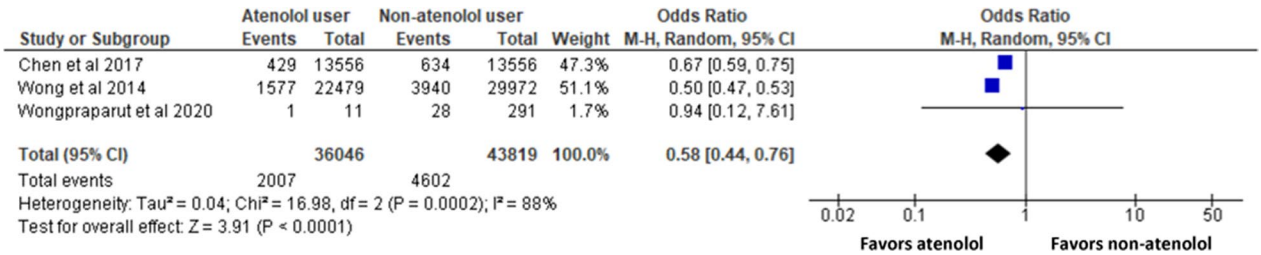

Fig. 3 Forest plot of the all-cause mortality rate among atenolol versus non-atenolol users

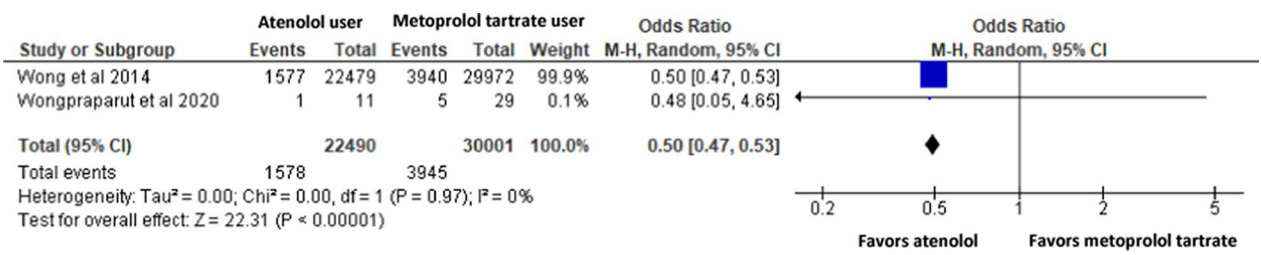

Fig. 4 Forest plot of the all-cause mortality rate among atenolol versus metoprolol tartrate users

wall shear stress of arteries, can greatly impact plaque development and the prognosis of coronary artery disease, irrespective of the beta-blocker medication utilized. The trials found that certain beta-blockers were more effective in reducing overall mortality compared to other beta-blocker medications. Yet, this explanation may be constrained by the absence of perfect group alignment (Dawson et al. 2022).

Moreover, atenolol, along with other beta-1 receptor-selective blockers, also has beneficial outcomes when used for clients diagnosed with atrial fibrillation and heart failure by regulating heart rate, decreasing the strain on the heart muscle, preventing blood clots, and reducing the likelihood of stroke. According to the literature, the combination of atenolol and spironolactone was found to be helpful in minimizing remodeling of both the atria and ventricles (Koniari et al. 2023). In addition, the combination of atenolol and perindopril is effective in treating heart failure. It can alleviate clinical symptoms, enhance ventricular function, lower connective tissue growth factor (CTGF) and nexin levels, and is considered to be quite safe (Chen et al. 2021).

Over the past thirty years, multiple research and reviews have cautioned that atenolol does not improve survival rates compared to a placebo and may be linked to a greater overall death rate when compared to other medications including amlodipine, losartan, and metoprolol (Virani et al. 2023; Thomopoulos et al. 2020; Blonde et al. 2022; Al Ghorani et al. 2021; Ye et al. 2023). However, most of the investigations and evaluations focused on patients from non-Asian ethnic backgrounds (Virani et al. 2023; Thomopoulos et al. 2020; Blonde et al. 2022; Al Ghorani et al. 2021; Ye et al. 2023).

Ethnicity and culture-related lifestyle are significant factors that can impact the prognosis of many chronic diseases (Jin et al. 2021; García-González et al. 2023). Pharmacogenomics is a valuable tool in treating chronic progressive diseases by changing drug doses or seeking alternative treatment options. Several gene polymorphisms are linked to treatment failure (Cacabelos 2020; Tang et al. 2023). Calcium channel blockers (CCB), such amlodipine, may be more efficient at lowering blood pressure in Asians compared to Europeans and Africans (Pharmacogenomics Knowledge Base (PharmGKB). rs588076 variant (PICALM gene); Rysz et al. 2020). The increased effectiveness is attributed to the high frequency of the rs588076 allele associated with the *PICALM* gene in Eastern Asians (32.4%) and South Asians (26.7%), compared to 19.7% in Europeans and 13.2% in Africans (Rysz et al. 2020).

Furthermore, atenolol may offer more effective blood pressure management in Asians compared to Europeans, Africans, and Latinos based on the prevalence of three gene polymorphisms: *ALDH1A2* rs261316, *EDN1* rs5370, and *ZMAT4* rs1367094. These genetic polymorphisms are associated with low levels of aldehyde dehydrogenase, endothelin-1 protein, and zinc finger matrin-type protein 4 (Pharmacogenomics Knowledge Base (PharmGKB). rs261316 variant (ALDH1A2 gene); Zhou et al. 2016; Pharmacogenomics Knowledge Base (PharmGKB). rs5370 variant (EDN1 gene); Sethi et al. 2023; Pharmacogenomics Knowledge Base (PharmGKB). rs1367094 variant (ZMAT4 gene)). Although there is no established correlation between atenolol pharmacokinetics and the aforementioned gene polymorphisms, it is possible that these polymorphisms have an impact on the regulation of certain genes or pathways that ultimately affect blood pressure. Therefore, there may be a very indirect link to atenolol's ability to lower blood pressure.

Nevertheless, other genetic polymorphisms that are more prevalent in Asians than Europeans, such as *ACY3* rs2514036 and *GRK4* rs1024323, are probably associated with the poor efficacy of bisoprolol and metoprolol, respectively (Pharmacogenomics Knowledge Base (PharmGKB). Clinical Annotation for rs2514036 (ACY3); Pharmacogenomics Knowledge Base (PharmGKB). G-protein-coupled receptor kinase 4 polymorphisms and blood pressure response to metoprolol among African Americans: sex-specificity and interactions). Yet, *UGT2B7* rs12233719 gene polymorphism, which is very common among Asians, is linked to the better efficacy of carvedilol (Pharmacogenomics Knowledge Base (PharmGKB). Annotation of rs12233719). Hence, we suggest that the guidelines for using atenolol and other beta-blockers in people with high blood pressure, coronary artery disease, atrial fibrillation, and heart failure should be changed so that they are more appropriate for certain ethnic groups (Whelton et al. 2018). We recommend that researchers carry out clinical trials on overall mortality utilizing data from a sufficient number of individuals from diverse ethnic backgrounds (Vilcant et al. 2022).

Limitations

Limitations identified in this review include a small number of studies, possibly due to a paucity of cohort studies conducted with Asians using atenolol or the inability to determine the real number of atenolol users in some research. Furthermore, a significant weakness was the substantial heterogeneity among the studies considered. Also, while two of the studies included in the analysis were classified as long-term studies with mortality assessment conducted for over 1 year (Wong et al. 2014; Wongpraparut et al. 2020), one of the studies was categorized as short-term research with mortality assessment conducted for only 1 month (Chen et al. 2017).

Potential bias encountered during the review process

Bias is unlikely in our systematic review because we thoroughly searched the main database for suitable articles. Furthermore, two authors performed the screening and data extraction autonomously.

Conclusions

Due to the limited studies included, this analysis concluded that atenolol, in comparison with non-users of atenolol or especially metoprolol tartrate, significantly reduces the overall death rate in East Asian and Southeast Asian patients with hypertension, coronary artery disease, atrial fibrillation, and heart failure. Yet, the current study cannot finalize this conclusion for other Asian ethnic groups, such as South Asians, Central Asians, and West Asians. Additional systematic reviews and meta-analyses with low heterogeneity and high-quality evidence are suggested to validate our findings and explore the efficacy of atenolol in various ethnic populations.

Abbreviations

AHA	American Heart Association
ACC	American College of Cardiology
SCAI	Society for Cardiovascular Angiography and Interventions
OR	Odds ratio
CVDs	Cardiovascular diseases
SIHR	Stable ischemic heart disease
HDL-C	High-density lipoprotein cholesterol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
ESRD	End-stage renal disease
GRADE	Grading of Recommendations Assessment, Development, and Evaluation

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PROSPERO registration number

Registration and protocol

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and registered through the International Prospective Register of Systematic Reviews (PROSPERO) under the Registration Number CRD42023413623.

Preprint

The study was published as preprint, which can be found at the following link: https://www.preprints.org/manuscript/202309.1522/v1.

Author contributions

AK and NR contributed in conceptualization and extracted the study characteristics and judged the risk of bias among included studies. AK, EA and AH contributed in writing—original draft preparation. MNF, HQ, NM, AF, and MK contributed in writing—review and editing. AK, NR, HQ, NM, MAF, AF, and MK contributed in resources. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The data that support the findings of this study were derived from the following resources available in scientific journals:
Wong MC, Tam WW, Lao XQ, Wang HH, Kwan MW, Cheung CS, Tong EL, Cheung NT, Yan BP, Yu CM, Griffiths SM. The effectiveness of metoprolol versus atenolol on prevention of all-cause and cardiovascular mortality in a large Chinese population: a cohort study. International journal of cardiology. 2014 Aug 20;175(3):425–32. https://doi.org/10.1016/j.ijcard.2014.06.009.
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Declarations

Ethics approval and consent to participate

This review article is based on previously conducted studies and the clinical expertise of the authors. No new clinical studies were performed by the authors, and no patients were involved in the production of this article, beyond their involvement in the previously published studies we cite. Accordingly, no ethical approval is required for this article.

Consent for publication

This study was dependent on anonymous data; therefore, no consent for publication was required.

Competing interests

The authors have no significant relationships with or financial interests in any commercial companies related to this study or article.

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