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Review Article

Pharmacology Section

Hypotensive Effects of Statins: A Rapid Review

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ABSTRACT

Introduction: Recently, hypertension has become a major global health concern that plays a substantial role in morbidity and mortality related to Cardiovascular Disease (CVD). Although statins primarily reduce cholesterol levels, they have also been shown to possess Blood Pressure (BP)-lowering properties that may provide further cardiovascular protection.

Aim: To explore the hypotensive effects of statins on BP and to determine whether they can serve as an adjunct to antihypertensive drugs.

Materials and Methods: This study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Statement (PRISMA-S) guidelines. Databases such as PubMed, MEDLINE and Web of Science were employed to conduct a thorough literature search, focusing on research studies published between 2004 and 2024. Search terms such as "antihypertensive effect," "hypertension," and "statins" were used to identify relevant studies. The articles included observational studies, pooled analyses, clinical trials, Randomised Controlled Trials (RCTs) and literature syntheses that demonstrated the impact of statins on BP. All three authors contributed equally to this study and independently extracted the data in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-S) standards to ensure accuracy and consistency.

Results: Eleven studies met the inclusion criteria. The results indicated that statins, particularly lipophilic statins such as simvastatin and atorvastatin, have a slight but noteworthy impact on decreasing BP in individuals with dyslipidaemia and hypertension. Statins exhibit a stronger BP-lowering effect when used in conjunction with other antihypertensive medications, particularly those that target the Renin-Angiotensin-Aldosterone System (RAAS). Additionally, the study emphasised that the effects of statins vary depending on the type and dosage and that the combination of statins and RAAS inhibitors may lower BP more effectively.

Conclusion: Statins have a moderate effect on BP, especially when combined with other antihypertensive drugs. Although there is evidence to support their use in improving cardiovascular protection, further studies are required to determine whether statins qualify as antihypertensive medications. These results highlight the potential for statins to be used as an adjuvant treatment to help hypertensive individuals better regulate their BP and reduce their overall cardiovascular risk.

Keywords: Antihypertensive agents, Hydroxymethylglutaryl-CoA reductase inhibitors, Hypotension

INTRODUCTION

Hypertension, a major global public health concern and a significant risk factor for CVD is often referred to as a 'silent killer.' In metropolitan regions, the prevalence of hypertension ranges between 24% and 30%, whereas in rural areas, it falls between 12% and 14%. It is associated with 13.5% of premature deaths, 54% of strokes and 47% of cases of ischaemic heart disease globally [1]. By 2025, it is projected that 1.56 billion people worldwide will have high BP, with an increase in chronic non communicable diseases such as CVD and hypertension, particularly in regions like Southeast Asia [2]. Furthermore, it is estimated that hypertension will cause 12.5 million deaths by 2030. Currently, one in six people is obese and one in three people has hypertension. Due to its asymptomatic nature, hypertension is especially difficult to diagnose early [3].

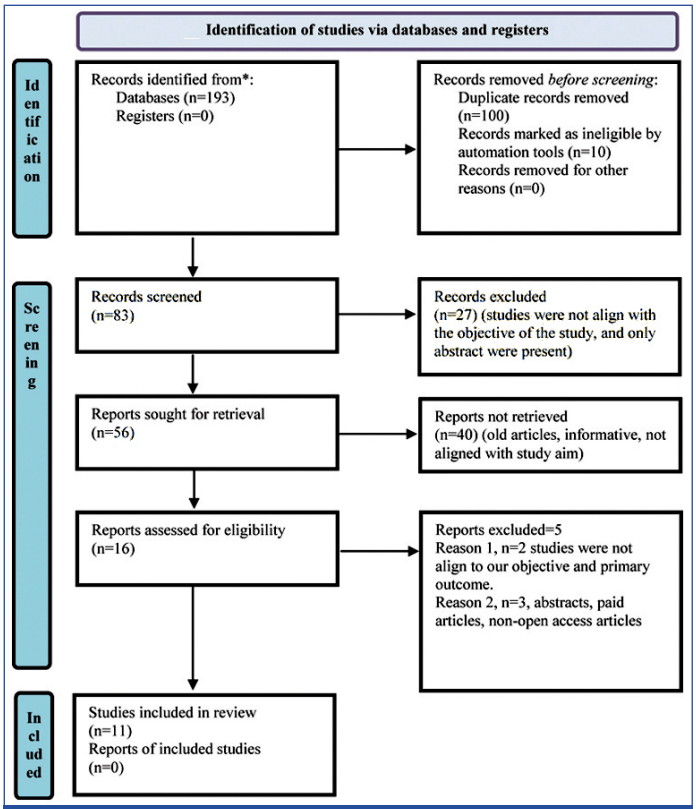
Statins, which are Hydroxy Methyl Glutaryl CoA Reductase Enzyme Inhibitors (HMG-CoA reductase inhibitors), are primarily administered to reduce high cholesterol levels. They are recommended as a preventative therapy for individuals over 40 years of age with diabetes and CVD risk, regardless of their baseline Low-Density Lipoprotein Cholesterol (LDL-C) levels, as endorsed by various international guidelines. This is particularly important for patients with dyslipidaemia and Type 2 Diabetes Mellitus (T2DM) to help lower their risk of CVD [4,5]. Substantial evidence links dyslipidaemia to hypertension in terms of metabolism, epidemiology and clinical manifestations [6]. Endothelial dysfunction is a significant factor that contributes to the early onset and persistence of arterial hypertension [7].

Statins exhibit a number of pleiotropic effects beyond their cholesterol-lowering mechanism [8]. They demonstrate BP-lowering effects through both direct and indirect processes. The direct effects include enhancing vasodilation and endothelial function, decreasing angiotensin type 1 receptor activity, increasing the bioavailability of nitric oxide and ultimately reducing BP [8,9]. Indirect effects may arise from their lipid-lowering properties, anti-inflammatory effects and potential enhancement of antihypertensive drug efficacy [10]. A previous study on cholesterol-lowering regimens provided indirect evidence suggesting that statin use can decrease BP by 2-5 mmHg [11]. The notion that statins may exert effects independent of cholesterol is further supported by the rapid and substantial reduction in cardiovascular events associated with statin therapy [12]. However, the extent to which these mechanisms synergistically or independently contribute to BP reduction remains uncertain [13]. These findings, however, remain inconclusive and underexplored in routine care settings. Given the global rise in hypertension and its associated co-morbid conditions, further investigation into the ability of statins to manage BP is warranted. This review aims to evaluate the hypotensive effects of statins and their potential as adjunctive therapy in hypertension management by addressing the aforementioned knowledge gap.

MATERIALS AND METHODS

This study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Statement (PRISMA-S)

guidelines. A comprehensive search was conducted using Medical Subject Headings (MeSH) terms such as "Antihypertensive effect," "hypertension" and "statins," with the Boolean operator "AND" applied between keywords, across databases such as PubMed, MEDLINE and Web of Science. Additional criteria or filters were implemented, including full-text availability, English language, RCTs, clinical studies and publication years ranging from 2004 to 2024. To identify further research pertinent to the study objective, the reference lists of the screened publications were manually examined [Table/Fig-1].



[Table/Fig-1]: This flowchart outlines the systematic search and selection process for relevant studies on statins and blood pressure control, following PRISMA guidelines.
*Databases: PubMed, MEDLINE, WoS (Web of science)

To ensure complete reporting of the study's design, search strategy and data analysis, this study was conducted in accordance with the PRISMA-2 standards [14].

Inclusion criteria: To ensure consistency and accuracy in the selection process of this study, the three authors adopted a standardised technique to evaluate eligibility criteria, extract data and review each study. This study primarily focused on published papers that assessed the effects of statins on BP, specifically studies which aimed at determining the changes in BP associated with statin medication. Trials where the intervention group received statins, while the control groups consisted of non pharmacological methods, conventional medication, or placebo, were also considered. The study types included in the evaluation comprised clinical trials, observational studies, RCTs, pooled analyses and literature syntheses.

Exclusion criteria: Studies in which statins were used for informational purposes and where the relevant outcomes were not assessed were excluded from this analysis. Additionally, studies with titles and materials that did not align with the objectives of this research were also excluded. Articles published in languages other than English, as well as paid articles or abstracts, were likewise omitted from consideration.

Data Extraction and Analysis

All three authors carefully performed data extraction to ensure the accuracy and reliability of the collection of pertinent study details. Using a predetermined data extraction form designed to capture important information thoroughly- such as study characteristics (e.g., study design, author, publication year and sample size), disease diagnosis, intervention details, control group and study outcomes- each reviewer independently extracted data from the selected studies. To facilitate organisation and transfer, the collected data were initially saved as Comma-Separated Value (CSV) files in a standardised format. Once all the data had been extracted, the CSV files were compiled and imported into a Microsoft Excel spreadsheet. This process allowed for advanced data mining, sorting and filtering to identify trends and primary assessments, thereby ensuring the accuracy of all pertinent data. The authors cross-checked the extracted data to resolve any inconsistencies, further enhancing the reliability of the process. In cases of dispute or uncertainty, a third senior author was consulted to make decisions and reach a consensus. This meticulous methodology enabled the study's conclusions to be supported by a thorough and rigorous synthesis of the available data.

Study Quality Summary Table

This review assessed study design, sample size, potential sources of bias and study limitations to evaluate the reliability of the included studies. All authors critically evaluated the methodological quality according to research type, confounding variables and study heterogeneity. The likelihood of selection bias was found to be higher in observational research, while study heterogeneity contributed to variability in the meta-analyses.

Risk of Bias Assessment

The first author evaluated each study for risk of bias using appropriate tools specific to each study type. The second author reviewed the judgments made by the first author, while the third senior author addressed any discrepancies through mutual discussions. The Cochrane Risk of Bias Tool-2 was used to assess RCTs [15], the Newcastle-Ottawa Scale [16] was applied to observational studies (cross-sectional and retrospective), the ROBINS-I tool was employed for non randomised studies [17] and the AMSTAR tool [18] (A measurement tool to assess systematic reviews) evaluated systematic reviews and meta-analyses. Literature analyses or non systematic reviews were classified as high-risk based on subjective selection criteria and a lack of standardised methodology.

RESULTS

Of the 193 articles retrieved from the three databases, 11 met all the criteria for inclusion in this study [Table/Fig-2] [7-9,11,12,19-24]. This review explains the effect of statins on BP in a range of patient groups, including those with hypertension and dyslipidaemia.

The majority of the RCTs included in this review are regarded as the gold standard in clinical research. RCTs provide a more transparent evaluation of the direct effect of statins on BP by reducing bias and establishing cause-and-effect relationships, regardless of confounding variables [7,12,19,21]. In addition to RCTs, cross-sectional studies, which gather data from various patient groups at a specific moment in time, were also included in the review. These studies enhance our understanding of statin usage across a range of patient profiles, particularly those with hypertension and dyslipidaemia, by identifying patterns and correlations that may not be observed in carefully monitored clinical settings.

This review offers a thorough examination of the effects of statins on BP by integrating data from both cross-sectional and RCT studies and comparing them with control groups. This comprehensive approach provides a more nuanced understanding of the advantages and drawbacks of statins, assisting researchers and clinicians in making well-informed decisions regarding their application in various patient populations.

Two studies employed survey methods to compare statin users with non users, utilising information from the computerised databases of the National Health and Nutrition Examination Survey (NHANES)

Author	Study design	Drugs used	Disease diagnosed	Clinical outcome
Kanbay M et al., [19] **2005**	Randomised Controlled Trial (RCT)	**Intervention (I) group:** Atorvastatin **Control group (C):** Diet	Hypertensive dyslipidaemia	Atorvastatin therapy significantly improves BP control, as compared to diet alone.
King DE et al., [20] **2007**	Cross-sectional survey	**I:** Atorvastatin, Fluvastatin, Pravastatin, Simavastatin **C:** Antihypertensive drug	Hypertension	Statins use associated with BP levels below 140/90 mmHg.
Golomb BA et al., [21] **2008**	RCT	**I:** Simavastatin or Pravastatin **C:** Placebo	Hypertension	Statins modestly but significantly reduced BP relative to placebo by 2.2 mmHg for SBP and 2.4 mmHg for DBP.
Bautista LE [8] **2008**	Cross-sectional study	**I:** Statins user **C:** Antihypertensive drugs	Hypertension	In statin users statins lowers SBP and DBP significantly compared to statin non user. Along with antihypertensive drug, statins lowered SBP significantly with SBP at least 140 mmHg.
Tycinska AM et al., [7] **2011**	RCT	**I:** Atorvastatin **C:** Antihypertensive drug	Normolipidaemic hypertension	Atorvastatin demonstrate the hypotensive effect and is associated with flow mediated dilation improvement.
Bawa S et al., [12] **2016**	RCT	**I:** Atorvastatin **C:** Antihypertensive drug	Essential hypertension	Patient with statins and ACE inhibitors had more significant fall in SBP that patients who received only ACE inhibitor.
You T et al., [22] **2017**	Pooled analysis	Atorvastatin, Simavastatin, Rosuvastatin	Hypertension	Atorvastatin and simvastatin can be regarded as positive drugs with significant BP lowering effect.
Drapala A et al., [23] **2014**	Review article	Statins and drugs acting via RAAS	Hypertension	Statins given either alone or together with antihypertensive drug acting via the RAAS may lower arterial BP.
Koh KK et al., [9] **2008**	Literature synthesis	Statins	Dyslipidaemia and hypertension	From the RCT studies, statins modestly lower BP in patients with high, but not normal BP regardless of cholesterol level.
Lee S et al., [11] **2021**	Systematic review and meta-analysis	**I:** Rosuvastatin **C:** Antihypertensive drug	Hypertension and dyslipidaemia	Rosuvastatin treated patients with antihypertensive agents significantly reduced DBP as compared to antihypertensive agent alone.
Abebe RB et al., [24] **2023**	Retrospective comparative cohort study	**I:** Atorvastatin **C:** Antihypertensive drug	Hypertension	BP control was higher among statin user.

[Table/Fig-2]: Details about the study included for the review [7-9,11,12,19-24].
ACE: Angiotensin converting enzyme; I: Intervention group; C: Control group; RCT: Randomised controlled trial; RAAS: Renin-angiotensin-aldosterone system
Note: In some studies, particular drug name and type were specified, but in remaining studies it was documented as statin user and antihypertensive drug

[8,20]. The specific types of statins, doses and other relevant details were not provided in these studies. Furthermore, they relied on self-reported data concerning food intake, exercise and medication usage, which may have introduced errors into the study conclusions. Notwithstanding these drawbacks, statin treatment was associated with a slight reduction in BP to below 140/90 mmHg in both investigations when compared with non users. Participants who were also taking antihypertensive medications demonstrated a significant correlation between statin usage and reduced BP [8,20].

In individuals with both dyslipidaemia and hypertension, statins exhibited a two-fold effect by slightly lowering BP and cholesterol levels. Additionally, the study observed a noteworthy improvement in Flow-Mediated Dilatation (FMD) among statin-treated individuals, indicating that the hypotensive effects of statins may be linked to enhanced endothelial function. Furthermore, it was shown that the use of statins in conjunction with medications targeting the RAAS further reduced BP, suggesting a potential synergistic effect [23].

A pooled analysis of 5.9 million clinical reports submitted to the FDA Adverse Event Reporting System (FAERS) revealed that simvastatin and atorvastatin were significantly associated with decreased BP, whereas rosuvastatin was not associated with hypotension [22]. This suggests that lipophilic statins may have a more favourable impact on BP compared to hydrophilic statins.

Moreover, a meta-analysis of antihypertensive regimens indicated that triple combination therapy (rosuvastatin plus two antihypertensive medications) significantly decreased Diastolic Blood Pressure (DBP) compared to dual therapy (rosuvastatin plus one antihypertensive medication). However, Systolic Blood Pressure (SBP) was not significantly reduced with triple therapy [11].

Based on the evaluation of all trials, atorvastatin was the medication most commonly prescribed for the treatment of both dyslipidaemia and hypertension. When compared with dietary management alone or in conjunction with antihypertensive medications, it demonstrated notable reductions in BP. Prescription trends indicate that atorvastatin is most frequently prescribed at low and moderate intensities, suggesting that even at lower doses, it can effectively improve BP control while minimising the risk of adverse effects. In clinical practice, moderate-intensity statin therapy is increasingly preferred due to its balance of patient safety and efficacy. Depending on findings, statins may lower BP, especially when used alongside antihypertensive medications. However, the effects of statins could vary based on the type of statin prescribed and the duration of therapy [8,12,19,21,24].

Study Quality Summary Table

The study quality assessment evaluated the study's design, sample size, methodological limitations and potential biases, such as selection bias, measurement bias and confounding factors. It was found that selection bias was prevalent in studies with small sample sizes or non randomised designs, while measurement and detection biases were observed in studies with self-reported outcomes or limited follow-up durations [Table/Fig-3].

Risk of Bias Assessment of the included Studies

Based on the evaluation of each study's limitations, every study was categorised according to its risk level as either low, moderate, or high [Table/Fig-4-8]. The results showed that 54.55% of the studies

Author	Study type	Limitations	Potential bias
Kanbay M et al., [19] **2005**	RCT	Short follow-up and limited sample size	Selection bias.
King DE et al., [20] **2007**	Cross-sectional survey	Self-reported data	Selection bias, recall bias.
Golomb BA et al., [21] **2008**	RCT	Placebo controlled, no blinding, short duration	Performance bias.
Bautista LE [8] **2008**	Cross-sectional study	No control for confounding variables	Confounding bias due to adjustment for demographic factor-lifestyle factor.
Tycinska AM et al., [7] **2011**	RCT	Small sample size, variability in endothelial function assessment	Measurement bias.
Bawa S et al., [12] **2016**	RCT	No long-term BP monitoring, no dose response analysis	Detection bias due to lack of BP monitoring over time.
You T et al., [22] **2017**	Pooled analysis	Different study doses, heterogeneity, large sample pool	Selection bias due to variation in the included study.
Drapala A et al., [23] **2014**	Review article	Narrative review lacks systematic analysis	Publication bias due to selective reporting of positive findings.
Koh KK et al., [9] **2008**	Literature synthesis	Inconsistent inclusion criteria	Selection bias from non uniform study selection.
Lee S et al., [11] **2021**	Systematic review and meta-analysis	Heterogeneity of included studies, variation in BP measurement techniques	Heterogeneity bias.
Abebe RB et al., [24] **2023**	Retrospective comparative cohort study	Potential confounding variables were present	Confounding bias due to lack of randomisation.

[Table/Fig-3]: Study quality summary table.

Study	Randomisation process	Missing outcome data	Deviations from intended interventions	Selective reporting	Outcome measurement	Overall risk
Kanbay M et al., (2005) [19]	Some concerns	Low	Low	Low	Low	Some concerns
Golomb BA et al., (2008) [21]	Some concerns	Low	Some concerns	Some concerns	Low	High-risk
Tycinska AM et al., (2011) [7]	High	Low	Some concerns	Some concerns	Some concerns	High-risk
Bawa S et al., (2016) [12]	Some concerns	Low	Low	Low	Low	Some concerns

[Table/Fig-4]: Cochrane risk of bias 2 for RCTs [15].

Study	Selection (4)	Comparability (2)	Outcome (3)	Total stars	Quality (Risk)
King DE et al., (2007) [20]	**	*	*	04/09	Poor (high-risk)
Bautista LE (2008) [8]	**	*	**	05/09	Fair (moderate-risk)

[Table/Fig-5]: Newcastle-Ottawa Scale (NOS) for observational studies [16].

Study	Selection	Confounding	Intervention classification	Missing data	Outcome measurement	Deviation from intended intervention	Selection of the reported result
You T et al., (2017) [22]	Moderate	Serious	Serious	Low	Moderate	Not reported	Not reported
Abebe RB et al., (2023) [24]	Serious	Serious	Moderate	Moderate	Moderate	Not reported	Not reported

[Table/Fig-6]: ROBINS-I (Non-randomised studies) [17].

Study	Protocol registered	Comprehensive search	Justified exclusions	Risk of bias assessed	Meta-analysis methods	Interpretation	Publication bias
Lee S et al., (2021) [11]	Yes	Yes	Yes	Yes	Yes	Yes	Not reported

[Table/Fig-7]: AMSTAR 2 (Systematic review/Meta-analysis) [18]

Author	Study design/type	Tool used	Risk of bias	Justification
Kanbay M et al., [19] **2005**	RCT	Cochrane RoB 2 [15]	Moderate	Short duration, high baseline values, missing synergistic effects of concomitant antihypertensive drugs.
King DE et al., [20] **2007**	Cross-sectional survey	Newcastle Ottawa Scale (NoS) [16]	High	Potential confounding, misclassification bias (self-reported data) and inability to establish causality.
Golomb BA et al., [21] 2008	RCT	Cochrane RoB 2 [15]	Moderate	Exclusion of CVD and DM patients may limit generalisability; potential selection bias.
Bautista LE [8] **2008**	Cross-sectional study	Newcastle Ottawa Scale (NoS) [16]	High	Confounding due to demographic factors, cross-sectional nature limits causal inference, potential bias in effect estimation.
Tycinska AM et al., [7] **2011**	RCT	Cochrane RoB 2 [15]	Moderate to high	Short duration, small sample size, variations in baseline BP not accounted for, differences in medication regimes.
Bawa S et al., [12] **2016**	RCT	Cochrane RoB 2 [15]	Moderate	Small sample size, single centre, follow-up for only 16 weeks.
You T et al., [22] **2017**	Pooled analysis	ROBINS-I [17]	High	No healthy control group, classification issues (cases vs. controls). Potential publication bias.
Drapala A et al., [23] **2014**	Review article	Not applicable	High	Inclusion of heterogeneous studies with different populations and treatments; selection bias possible.

Koh KK et al., [9] 2008	Literature synthesis	Not applicable	High	Small sample size, variation in BP measurement techniques, confounding effects from antihypertensive drugs.
Lee S et al., [11] 2021	Systematic review and meta-analysis	AMSTAR [18]	Moderate	Only included rosuvastatin 20 mg/day, limiting generalisability to other doses.
Abebe RB et al., [24] 2023	Retrospective comparative cohort study	ROBINS-I [17]	High	Relied on retrospective data, did not account for the effects of antihypertensive drugs, lack of detailed dosage/statin regimen data.

[Table/Fig-8]: Risk of bias assessment.

had a high-risk of bias, 36.36% had a moderate-risk and 9.09% had a moderate-to-high risk. These findings indicate variability in study quality, which was taken into account when interpreting the overall results.

DISCUSSION

Previous research indicates that statins significantly reduce both SBP and DBP [11,12,21,24]. In individuals with hypertension and no history of CVD, BP was found to be below 140/90 mm Hg among statin users, but only when they were also taking antihypertensive medications. This could be attributed to physiological effects, a potential marker of improved medication adherence, or other factors such as the pleiotropic effects of statins. The relationship remained consistent after adjusting for possible confounding factors, including age, race, gender, Body Mass Index (BMI), smoking, diabetes, exercise, a low-salt diet and the use of antihypertensive drugs [8,11,20]. Even after incorporating C-reactive Protein (CRP) into the model, the association between statin use and lower BP persisted to a similar extent, suggesting that this effect may be independent of the anti-inflammatory properties of statins [20].

However, the impact of statins on BP is inconsistent across studies. For instance, the use of simvastatin for 8-10 weeks and 10-80 mg of lovastatin daily over six months reported no impact on BP [25-27]. In a cohort of 85 individuals with both hypertension and hyperlipidaemia, there was no reduction in BP observed with pravastatin, fluvastatin, or simvastatin [28]. On the other hand, atorvastatin, at doses ranging from 10 mg to 80 mg, showed a significant reduction in BP [7,12,24]. Additionally, rosuvastatin demonstrated a greater reduction in DBP compared to the antihypertensive drug alone [11].

The study found that both simvastatin and pravastatin use led to suggestive but not statistically significant BP reductions after a month of treatment. However, by six months, these reductions became evident and significant. Two months after discontinuing statins, the difference in BP between the statin and placebo groups disappeared. The findings suggest that statins may decrease elevated BP but not normal BP. The observed effect cannot be solely attributed to interactions with existing antihypertensive drugs [21].

Combined therapy with simvastatin and ramipril or losartan may provide extra benefits through unique and interconnected mechanisms. While adding simvastatin did not improve the BP-lowering effects of losartan, ramipril, or valsartan, the use of these medications together could still offer complementary advantages [9]. Bautista LE, found that statin users showed lower SBP and DBP compared to non statin users [8]. These findings indicate a mixed outcome regarding the overall effect of statins on BP. It remains unclear whether the addition of statins consistently affects both SBP and DBP, or if the effects vary depending on the specific statin or concomitant drug used, or possibly other factors such as dosage, duration of treatment and patient characteristics.

It has also been found that the addition of statins to antihypertensive drugs can result in better BP control compared to using either drug alone, suggesting a possible additive effect between the two types of medication [7,12,19,20]. However, although Bautista LE, found that statins were associated with a significant reduction in SBP when used in combination with antihypertensive drugs, this does not necessarily imply a synergistic effect. It was further noted that statins alone can decrease both SBP and DBP across all levels of BP, with the effect being more pronounced at higher BP levels [8].

Hence, this represents a debatable outcome regarding whether the combined use of statins and antihypertensive drugs provides a true synergistic effect or if the observed benefits are merely additive. The conflicting findings highlight the need for further research to clarify whether statins enhance the effects of antihypertensive drugs beyond what would be expected from their individual effects, or if their combined use is primarily due to their separate contributions to BP reduction.

The significant hypotensive effect of statins is likely due to an interaction with the RAAS system, which may depend on the patient and drug selection. Disruption in the RAAS plays a crucial role in the development of hypertension and related CVD complications. Current treatments for CVD include RAAS-targeting drugs such as renin inhibitors, ACE inhibitors (ACE-Is), Angiotensin II Receptor Blockers (ARBs) and aldosterone antagonists [23]. According to the ACC/AHA guidelines on treating dyslipidaemia and preventing CVD, LDL-C levels are no longer the sole focus; instead, the guidelines emphasise assessing overall risk factors, including hypertension [23,29,30].

Statins interact with the RAAS in several ways that contribute to BP control. They decrease the expression of Angiotensin II type 1 Receptors (AT1Rs), inhibit angiotensin II-dependent oxidative stress and inflammation and reduce the synthesis of angiotensin II and aldosterone. These actions help mitigate the adverse effects associated with hypertension and further reduce the risk of CVD. Statins administered either alone or with antihypertensive drugs acting via the RAAS lower BP; for instance, statins enhance the hypotensive effect of ACE-Is and ARBs [23]. Such evidence suggests that concomitant treatment with statins and RAAS-targeting drugs exerts a synergistic effect on BP; however, the mechanisms and therapeutic potential of such interactions have not yet been clarified [9,23].

The hypothesis was evaluated using data from the FAERS. If a particular statin had antihypertensive effects, it would be expected to cause unexpected hypotension more frequently as an adverse effect. Indeed, hypotensive effects were significantly associated with atorvastatin and simvastatin, but not with rosuvastatin. Following the guilt-by-association principle, the study identified specific protein targets and signalling pathways that were disrupted by atorvastatin and simvastatin but not by rosuvastatin, highlighting the need for further studies to understand the biological nature of statin-induced BP reduction [22].

Since CVD is often accompanied by dyslipidaemia, many patients receive statins for primary and secondary prevention based on their risk profile. The cited study suggests that, in addition to lowering cholesterol levels, statins may also provide a modest benefit in lowering BP [8,11,31]. This “dual approach” of statins could offer additional advantages for patients with co-morbid conditions, potentially leading to broader use of statins in patients with both hypertension and dyslipidaemia.

This review suggests that the hypotensive effects of statins may be due to both direct and indirect mechanisms. While some studies have shown improvements in endothelial function and bioavailability of nitric oxide, indicating a direct effect [7-9,23], others have associated the effects with indirect mechanisms such as lipid

lowering and anti-inflammatory benefits [10,20]. The combination of RAAS inhibitors and statins has shown potential synergistic effects rather than solely independent hypotensive action [23]. These variations underscore the necessity for more focused studies to distinguish between secondary cardiovascular effects and direct pharmacological activities.

Understanding the long-term effects of statins on BP can guide safer prescribing decisions and help healthcare professionals develop comprehensive management strategies for chronic conditions. This knowledge enhances cardiovascular risk assessment, supports preventive strategies and leads to more cost-effective care by minimising the risk of adverse events and hospitalisations due to uncontrolled hypertension. Additionally, this review highlights statins' potential as an adjunctive treatment for hypertension, particularly in patients with dyslipidaemia and CVD risk factors, with moderate BP reductions that could be significant for those requiring additional BP control beyond antihypertensive drugs [10,11,22,23].

Moreover, the hypotensive effects of statins depend upon the type of statin- lipophilic statins show more significant effects compared to hydrophilic statins [20-22]- as well as the dosage; higher doses demonstrate more beneficial effects, suggestive of a dose-response relationship. However, future research is needed to confirm this effect [10-12,22]. While current guidelines do not recommend statins as primary antihypertensive therapy, their potential BP -lowering effects could be utilised in high-risk patients already on statin therapy and clinicians should monitor BP trends.

This review includes findings from various studies, including RCTs, observational studies, systematic reviews and meta-analyses. The reliability of these studies depends on their design, with RCTs being the gold standard for minimising confounding variables. Observational studies are prone to selection bias and confounding factors. Systematic reviews and meta-analyses depend on the quality of the studies, which may affect generalisability. The authors have critically examined these methodologies to ensure a rational interpretation of the results.

Limitation(s)

This review has demonstrated the potential hypotensive effect of statins, but it has several limitations. The heterogeneity of the included studies (RCTs, observational studies, retrospective studies) introduces variation in methodologies, population, sample size and outcome measures, which may affect the consistency of the findings. The lack of standardised BP measurement across studies makes direct comparison challenging and may influence the overall results. Additionally, confounding factors (such as diet, habits and concomitant drugs) were not adequately controlled, which could independently impact BP. While some studies suggested that higher statin doses may have stronger hypotensive effects, there were no standardised analyses of optimal dosing strategies, necessitating further exploration in future trials.

CONCLUSION(S)

Overall, statins may serve as an add-on drug to reduce BP, as the reviewed studies suggest that statins, particularly atorvastatin and simvastatin, have a modest but significant BP -lowering effect in patients with hypertension. The hypotensive effect of statins is more evident when used in combination with other antihypertensive medications, particularly those targeting the RAAS. Statins appear to provide an additional cardiovascular advantage beyond lipid lowering by modestly reducing BP, especially in hypertensive patients and those with dyslipidaemia, regardless of their cholesterol levels.

It is also suggested that lipophilic statins have more pronounced effects than hydrophilic statins and that higher doses have more beneficial effects on BP, indicating potential dose-response effects. This review supports the concept that statins have effects beyond lipid lowering and can serve as an additional or adjunctive treatment for managing BP in hypertensive patients, potentially improving cardiovascular protection. Therefore, to address the dilemma related to the effects of statins on BP, a large multicentre trial is needed to generate real-world evidence from routine clinical settings.

Authors' contribution: SB: Drafting the article or revising it critically for important intellectual content; SB, SJ, SSP: Substantial contributions to concept and design, acquisition of data or analysis and interpretation of data; SJ, SSP: Final approval of the version to be published.

REFERENCES

[1] Worldwide prevalence of hypertension: A systematic review | Request PDF [Internet]. [cited 2024 Aug 27]. Available from: https://www.researchgate.net/publication/8597973_Worldwide_prevalence_of_hypertension_A_systematic_review.
[2] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of worldwide data. Lancet Lond Engl. 2005;365(9455):217-23.
[3] Hypertension management in developing countries | SpringerLink [Internet]. [cited 2024 Aug 27]. Available from: https://link.springer.com/referenceworkentry/10.1007/978-3-030-74786-2_2-1.
[4] Elnaem MH, Mohamed MHN, Huri HZ, Azarisman SM, Elkalmi RM. Statin therapy prescribing for patients with Type 2 diabetes mellitus: A review of current evidence and challenges. J Pharm Bioallied Sci. 2017;9(2):80-87.
[5] Mwita JC, Godman B, Esterhuizen TM. Statin prescription among patients with type 2 diabetes in Botswana: Findings and implications. BMC Endocr Disord. 2020;20(1):36.
[6] Dalal JJ, Padmanabhan TNC, Jain P, Patil S, Vasnawala H, Gulati A. LIPITENSION: Interplay between dyslipidemia and hypertension. Indian J Endocrinol Metab. 2012;16(2):240-45.
[7] Tycinska AM, Janica J, Mroczko B, Musial WJ, Sawicki R, Sobkowicz B, et al. Hypotensive effect of atorvastatin in hypertensive patients: The association among flow-mediated dilation, oxidative stress and endothelial dysfunction. Arch Med Sci AMS. 2011;7(6):955-62.
[8] Bautista LE. Blood pressure-lowering effects of statins: Who benefits? J Hypertens. 2009;27(7):1478-84.
[9] Koh KK, Quon MJ, Waclawiw MA. Are statins effective for simultaneously treating dyslipidemias and hypertension? Atherosclerosis. 2008;196(1):01-08.
[10] Morofuji Y, Nakagawa S, Ujifuku K, Fujimoto T, Otsuka K, Niwa M, et al. Beyond lipid-lowering: Effects of statins on cardiovascular and cerebrovascular diseases and cancer. Pharmaceuticals. 2022;15(2):151.
[11] Lee S, Yang S, Chang MJ. Antihypertensive effects of rosuvastatin in patients with hypertension and dyslipidemia: A systemic review and meta-analysis of randomized studies. PloS One. 2021;16(11):e0260391.
[12] Bawa S, Dutta S, Varma A, Kumar H, Beg MA, Anjoom M. Comparative evaluation of ACE inhibitors with or without statins in the treatment of essential hypertension in a tertiary care teaching hospital at Dehradun, Uttarakhand. Int J Med Sci Public Health. 2016;5(10):2036-36.
[13] Bonetti PO, Lerman LO, Napoli C, Lerman A. Statin effects beyond lipid lowering-are they clinically relevant? Eur Heart J. 2003;24(3):225-48.
[14] The PRISMA 2020 statement: An updated guideline for reporting systematic reviews | The BMJ [Internet]. [cited 2023 Sep 5]. Available from: https://www.bmj.com/content/372/bmj.n71.
[15] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
[16] Ottawa Hospital Research Institute [Internet]. [cited 2025 Apr 19]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[17] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
[18] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
[19] Kanbay M, Yildirir A, Bozbas H, Ulus T, Bilgi M, Muderrisoglu H, et al. Statin therapy helps to control blood pressure levels in hypertensive dyslipidemic patients. Ren Fail. 2005;27(3):297-303.
[20] King DE, Mainous AG, Egan BM, Player M, Gessy ME. Use of Statins and Blood Pressure. Am J Hypertens. 2007;20(9):937-41. Oxford Academic [Internet]. [cited 2024 Aug 27]. Available from: https://academic.oup.com/ajh/article/20/9/937/136274.
[21] Golomb BA, Dimsdale JE, White HL, Ritchie JB, Criqui MH. Reduction in blood pressure with statins. Arch Intern Med. 2008;168(7):721-27.
[22] You T, Liu XG, Hou XD, Wang XK, Xie HH, Ding F, et al. Effect of statins on blood pressure: Analysis on adverse events released by FDA. Clin Exp Hypertens. 2017;39(4):325-29.
[23] Drapala A, Sikora M, Ufnal M. Statins, the renin-angiotensin-aldosterone system and hypertension- a tale of another beneficial effect of statins. J Renin-Angiotensin-Aldosterone Syst JRAAS. 2014;15(3):250-58.
[24] Abebe RB, Kebede SA, Birarra MK. The association of lipid-lowering therapy and blood pressure control among outpatients with hypertension at the Felege Hiwot Comprehensive Specialized Hospital, Northwest Ethiopia. Front Cardiovasc Med. 2023;10:1071338.

[25] Sartor G, Katzman P, Eizyk E, Kalén J, Nilsson A, Ugander L, et al. Simvastatin treatment of hypercholesterolemia in patients with insulin dependent diabetes mellitus. Int J Clin Pharmacol Ther. 1995;33(1):03-06.
[26] Antonicelli R, Onorato G, Pagelli P, Pierazzoli L, Paciaroni E. Simvastatin in the treatment of hypercholesterolemia in elderly patients. Clin Ther. 1990;12(2):165-71.
[27] D'Agostino RB, Kannel WB, Stepanians MN, D'Agostino LC. Efficacy and tolerability of lovastatin in hypercholesterolemia in patients with systemic hypertension. Am J Cardiol. 1993;71(1):82-87.
[28] Ichihara A, Hayashi M, Koura Y, Tada Y, Kaneshiro Y, Saruta T. Long-term effects of statins on arterial pressure and stiffness of hypertensives. J Hum Hypertens. 2005;19(2):103-09.
[29] 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults | Circulation [Internet]. [cited 2024 Aug 27]. Available from: https://www.ahajournals.org/doi/10.1161/01.cir.0000437738.63853.7a.
[30] 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines | Circulation [Internet]. [cited 2024 Aug 27]. Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625.
[31] Borghi C, Fogacci F, Agnoletti D, Cicero AFG. Hypertension and dyslipidemia combined therapeutic approaches. High Blood Press Cardiovasc Prev. 2022;29(3):221-30.

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