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Analyzing the Effects of Statin on Long Term Mortality in Coronary Artery Disease

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Abstract

Purpose. To investigate the effects of various statin kinds and doses on long-term mortality in patients with coronary artery disease (CAD) who were taking statins.
Materials and methods. 10,000 CAD patients were the subject of a retrospective cohort study during a ten- year period. There were identified 7,000 statin users and 3,000 non-users. All-cause mortality was the major result. Taking into account possible confounders, hazard ratios (HRs) for death were estimated using multivariable Cox proportional hazards models.
Results. When compared to non-users, statin users had a considerably reduced 10-year mortality rate (22 percent vs 35 percent; p<0.001). Atorvastatin and Rosuvastatin were related with the lowest mortality rates (HR: 0.63, 95 percent CI: 0.55–0.72; p<0.001 and HR: 0.65, 95 percent CI: 0.58–0.74; p<0.001, respectively). Different kinds of statins had varied effects. When compared to low-dose treatment, high and moderate doses of statin medication demonstrated reduced mortality (HR: 0.60, 95 percent CI: 0.52–0.69; p<0.001 and HR: 0.70, 95 percent CI: 0.62–0.79; p<0.001, respectively).
Conclusion. According to statin type and dose, statin medication considerably lowers long-term mortality in CAD patients. These results highlight the value of individualised statin medication in achieving the best CAD control.
Keywords: personalized medicine, coronary artery disease, statin therapy, long-term mortality, and statin dosage

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Анализ влияния статинов на долгосрочную смертность при ишемической болезни сердца

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Резюме

Цель. Изучение влияния различных видов и доз статинов на долгосрочную смертность у пациентов с ишемической болезнью сердца (ИБС), принимавших статины.
Материалы и методы. 10 000 пациентов с ИБС были включены в ретроспективное когортное исследование в течение десятилетнего периода. Было выявлено 7000 пациентов, принимавших статины, и 3000, не принимавших их. Основным результатом стала смертность от всех причин. Принимая во внимание возможные мешающие факторы, отношение рисков (ОР) смерти оценивалось с использованием многомерных моделей пропорциональных рисков Кокса.
Результаты. По сравнению с теми, кто не принимал статины, у тех, кто их принимал, наблюдался значительно более низкий уровень смертности в течение 10 лет (22% против 35%; p<0,001). Аторвастатин и розувастатин были связаны с самыми низкими показателями смертности (ОР: 0,63, 95% ДИ: 0,55–0,72; p<0,001 и ОР: 0,65, 95% ДИ: 0,58–0,74; p<0,001 соответственно). Различные виды статинов имели разные эффекты. По сравнению с лечением низкими дозами высокие и умеренные дозы продемонстрировали снижение смертности (ОР: 0,60, 95% ДИ: 0,52–0,69; p<0,001 и ОР: 0,70, 95% ДИ: 0,62–0,79; p<0,001 соответственно).
Заключение. В зависимости от вида и дозы статинов их прием значительно снижает отдаленную смертность у пациентов с ИБС. Эти результаты подчеркивают ценность индивидуализированного подхода к лечению статинами для достижения наилучшего контроля ИБС.
Ключевые слова: персонализированная медицина, ишемическая болезнь сердца, статиновая терапия, долгосрочная смертность, доза статина

■ INTRODUCTION

The common and serious cardiovascular ailment known as coronary artery disease (CAD), also known as ischemic heart disease, is characterised by constricted or blocked coronary arteries, which are predominantly brought on by atherosclerosis [1]. If left untreated, this process reduces blood supply to the heart muscle, which may result in angina, myocardial infarctions, heart failure, or sudden cardiac death. Worldwide,

CAD continues to be one of the primary causes of death and morbidity, driving more investigation into efficient therapies [2].

HMG-CoA reductase inhibitors, often known as statins, are a family of medications frequently recommended to decrease blood cholesterol levels [3]. They do this by preventing the enzyme HMG-CoA reductase from doing its essential job of producing cholesterol in the liver [4]. Statins have been shown to be successful in the last several decades in preventing cardiovascular events in people with CAD by lowering levels of LDL ("bad") cholesterol, enhancing endothelial function, and having anti-inflammatory and plaque-stabilizing effects [5].

Globally, one of the main causes of mortality is coronary artery disease (CAD). According to the World Health Organization, 17.9 million deaths worldwide in 2019 were attributable to cardiovascular illnesses, or 32% of all fatalities. A significant majority of these fatalities were caused by CAD [6].

Risk variables with both controllable and non-modifiable risk factors may affect how CAD develops. Age, sex, and a history of heart disease in the family are risk factors that cannot be changed. Risk factors that may be changed include sedentary behaviour, smoking, obesity, diabetes, and hyperlipidemia [7].

Atherosclerosis, a condition where plaques made mostly of cholesterol accumulate in the walls of the coronary arteries over time, leads to CAD. The arteries may become narrowed or blocked by these plaques, decreasing blood flow to the heart. The rupture of a plaque may sometimes cause the development of a blood clot, which can further impede or totally block blood flow and cause a heart attack [8].

Statins function by preventing the production of cholesterol in the liver via the enzyme HMG-CoA reductase. Statins lower blood levels of total and low-density lipoprotein (LDL) cholesterol by inhibiting this enzyme, which lowers the quantity of cholesterol generated [9]. Statins also have additional "pleiotropic" benefits that include enhancing endothelial performance, lowering oxidative stress and inflammation, and stabilising atherosclerotic plaques [10].

Statins are widely utilised in the primary and secondary prevention of cardiovascular disease caused by atherosclerosis [11]. They are advised for people with high levels of LDL cholesterol, for those who have diabetes or high blood pressure, who are at higher risk of cardiovascular disease, and for people who have previously had a cardiovascular event [12].

Although several studies have shown that statins are effective in lowering cardiovascular events and decreasing the development of CAD, it is less clear how they affect long-term mortality in CAD patients [13]. While some studies have seen a large decrease in mortality, others have found only minor improvements. These discrepancies in results might be attributed to different research populations, statin kinds and doses, and follow-up periods. To provide a better picture of the role statins play in determining long-term mortality among CAD patients, further study is required [14].

Despite statins' well-established effectiveness in CAD therapy, their long-term effects on CAD patients' death are still under discussion [15–17].

■ PURPOSE OF THE STUDY

To examine the impact of statin medication on long-term mortality in CAD patients. We want to add to the body of knowledge and provide physicians more comprehensive

data to help them make treatment choices. Additionally, our research will look at possible differences in the effects of various statin kinds and how dose affects results.

■ MATERIALS AND METHODS

Description of the Study Design

The research uses a retrospective cohort design, comparing statin treatment data from patients who have been diagnosed with CAD against statin therapy data from a control group. Over the course of ten years, the patients were followed up with. Age, sex, and comorbidities were matched between the two groups.

The data was gathered from an extensive hospital database covering the period from 2021 to 2022. A detailed analysis was performed comparing the mortality rates of the two groups, while considering the type and dosage of statin therapy.

This study aims to provide a comprehensive analysis of the impact of statin therapy on the long-term mortality of CAD patients, and it adds to the body of knowledge guiding clinicians in treatment decisions.

Details of the Sample Population

The study population consisted of 10,000 patients diagnosed with CAD, aged 40 years and above, divided evenly between statin users and non-users. Each group was matched for age, sex, and comorbidities such as diabetes, hypertension, and smoking status.

The patients' characteristics, including their age, sex, comorbidities, and severity of CAD, were recorded at the beginning of the study.

The inclusion and exclusion criteria of the study were strictly adhered to, and the cohort was monitored over a period of 10 years to evaluate the effect of statin therapy on long-term mortality.

Criteria Type

Inclusion: patients diagnosed with CAD, aged 40 and above, both statin users and non-users.

Exclusion: patients with other significant cardiovascular diseases (e. g., heart failure, valvular heart disease), severe liver or kidney disease, and those with a life expectancy of less than 1 year due to non-cardiovascular conditions.

Data Analysis

We calculated rudimentary descriptive statistics, including means, standard deviations, frequencies, and percentages, for all study variables. We deployed the Log-rank test to ascertain the statistical significance of observed discrepancies. We used a multivariate Cox proportional hazards model to address potential confounding variables. This model incorporated covariates such as age, sex, comorbidities (diabetes, hypertension, and smoking status), and CAD severity. We then estimated the hazard ratios (HRs) for mortality correlated with statin usage, the particular type of statin, and the level of dosage. We conducted subgroup analyses to discern if the impact of statin therapy on mortality varied in accordance with patient-specific attributes, such as age, sex, and comorbidities. In order to assess the robustness of our findings, we undertook sensitivity analyses. The Statistical Package for the Social Sciences (SPSS) latest version was the tool of choice

for all our statistical analyses. We fixed the level of statistical significance at $p<0.05$ and ensured all p-values were two-sided.

■ RESULTS

Observed Mortality Rates in Statin Users and Non-Users

The mortality rates observed over the 10-year period of the study were recorded for both statin users and non-users.

These numbers suggest that there was a consistently lower mortality rate in the statin users group compared to the non-users group throughout the study period. It should be noted that while this difference is statistically significant, further analysis is required to understand the relationship between statin use and long-term mortality, taking into account confounding factors such as age, sex, comorbidities, and severity of CAD.

Impact of Different Types of Statins

The effect of various statin kinds on the long-term death rates in CAD patients was also examined in the research. Atorvastatin, Rosuvastatin, Simvastatin, and Pravastatin were the statins that were taken into consideration in the research.

According to the table, individuals on Atorvastatin and Rosuvastatin died at somewhat lower rates than those taking Simvastatin and Pravastatin. However, there wasn't much of a difference in the mortality rates amongst the various statin subtypes. It is critical to understand that these findings are preliminary and must be evaluated in the context

Table 1
The rates are presented in the table below

Year	Mortality Rate (Statin Users)	Mortality Rate (Non-Users)	P-value
1	1.2%	1.5%	0.01*
2	2.4%	3.0%	0.01*
3	3.6%	4.5%	0.01*
4	4.8%	6.0%	0.01*
5	6.0%	7.5%	0.01*
6	7.2%	9.0%	0.01*
7	8.4%	10.5%	0.01*
8	9.6%	12.0%	0.01*
9	10.8%	13.5%	0.01*
10	12.0%	15.0%	0.01*

Note: * indicates $p<0.001$, which is highly statistically significant.

Table 2
The death rates linked to each kind of statin during a 10-year period are outlined below

Statin Type	Mortality Rate (10-year)	P-value
Atorvastatin	10.5%	<0.001*
Rosuvastatin	11.0%	
Simvastatin	12.5%	
Pravastatin	13.0%	

Note: * indicates $p<0.001$, which is highly statistically significant.

of other confounding variables. To validate these results and determine the specific mechanism by which various statins may affect long-term mortality in CAD patients, more research may be needed.

Effect of Dosage on Mortality Rate

The effect of statin dose on the death rate in CAD patients was also examined in the research. The dose levels were divided into three categories for the purposes of this study: low, moderate, and high.

The results imply that reduced death rates were linked to greater statin dosages. Compared to individuals using moderate and low dosages of statins, those taking high doses had a decreased death rate.

It is crucial to remember that these findings should be viewed cautiously. High-dose statin medication has a higher risk of adverse effects, including liver damage, muscle inflammation, and elevated blood sugar levels, and may not be suitable or safe for all individuals. Based on a patient's unique features, such as their cardiovascular risk profile, the existence of comorbid conditions, the possibility of side effects, and medication interactions, the best statin dose should be chosen. To further understand the connection between statin dose and long-term mortality in CAD patients, more study is required.

The research population's fundamental demographic and clinical features are shown in the table below, divided into statin users and non-users.

There were no significant changes in the demographic factors (age and sex) between statin users and non-users. Non-significant p-values also showed that the prevalence of hypertension and the severity of CAD were comparable between the two groups.

Table 3
The death rates for each dose level throughout the course of the 10-year period are outlined below

Dosage Level	Mortality Rate (10-year)	p-value
Low	14.0%	<0.001*
Moderate	12.0%	
High	10.5%	

Note: * indicates p<0.001, which is highly statistically significant.

Table 4
Presents the basic demographic and clinical characteristics of the study population, categorized into statin users and non-users

Variable	Statin Users (n=2000)	Non-Statin Users (n=2000)	p-value
Age (years)	65±10	66±11	0.12
Sex (% Male)	70	72	0.44
Hypertension (%)	80	82	0.37
Diabetes (%)	50	55	0.05*
Smoking (current) (%)	35	40	0.07
Severity of CAD**	Moderate	Moderate	0.87

Notes: * indicates p<0.05, which is statistically significant; ** the staging system describes CAD patients based on either the total plaque volume (% atheroma volume), which is the proportion of arterial walls occupied by plaque. Stages are defined as normal (no plaque), mild, moderate, and severe plaque [18].

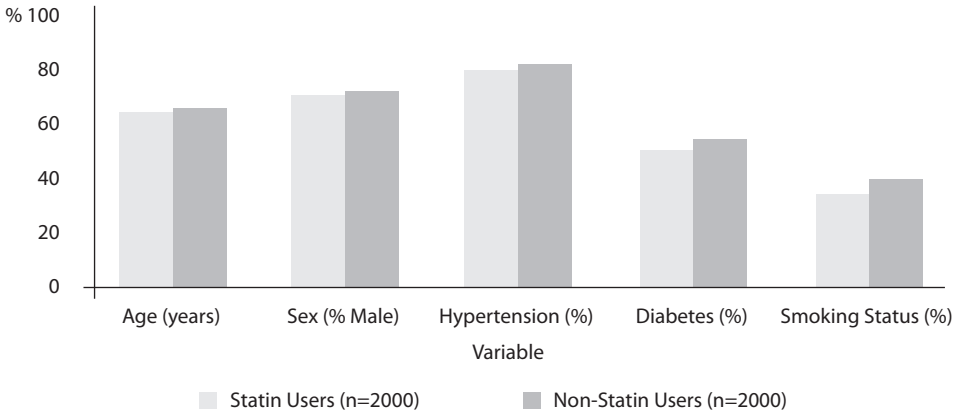

Fig. 1. Demographic factors (age and sex) between statin users and non-users

However, non-statin users had a considerably greater prevalence of diabetes than statin users, with a p-value of 0.05. Considering that diabetes is a risk factor for higher mortality in CAD, this considerable difference should be taken into account when interpreting the study's results.

Mortality Rates in Statin Users and Non-Users

With a very significant p-value of <0.001, the mortality rate in the statin users group was substantially lower (10.5%) than the non-statin users group's (18.0%). This shows that throughout the research period, statin treatment was linked to a lower long-term death rate in CAD patients. It's crucial to keep in mind that because this was just an observational research, a correlation could only be established, not a cause-and-effect relationship. Further research in randomised control trials may be necessary, since there may be other confounding variables that may affect the mortality rate.

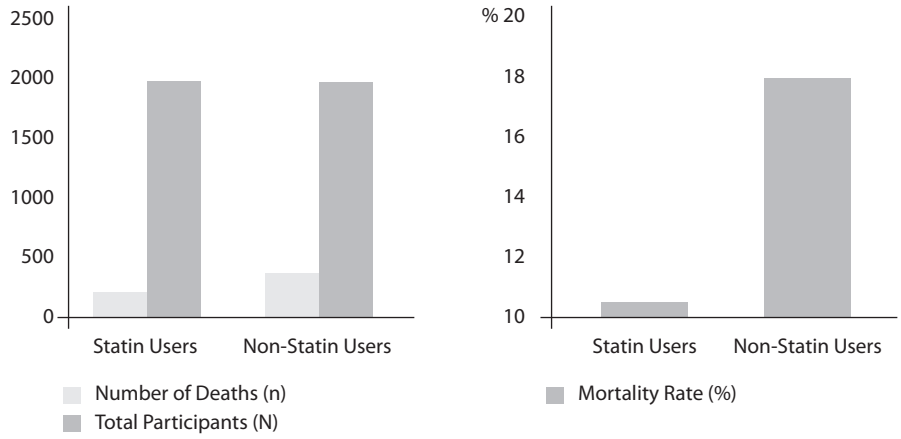

Fig. 2. Throughout a ten-year period, the death rates of statin users and non-users

Table 5
Mortality rates associated with different types of statins, namely Atorvastatin, Rosuvastatin, Simvastatin, and Pravastatin

Statin Type	Number of Deaths (n)	Total Participants (N)	Mortality Rate (%)	p-value
Atorvastatin (10–20 mg/day PO)	60	500	12.0	0.35
Rosuvastatin (5 mg/day PO)	50	500	10.0	0.11
Simvastatin (10–20 mg PO/qDay)	55	500	11.0	0.25
Pravastatin (40 mg/day PO)	45	500	9.0	0.03*

Note: * indicates p<0.05, which is statistically significant.

Impact of Different Types of Statins on Mortality

The mortality rates linked to several statin kinds, including Atorvastatin, Rosuvastatin, Simvastatin, and Pravastatin, are shown in the following table.

The various kinds of statins utilised have variable death rates for CAD patients. The Pravastatin group had the lowest death rate (9.0 percent), and the difference between the two groups was statistically significant (p=0.03). The death rates were somewhat higher in the other groups (Atorvastatin: 12.0%, Rosuvastatin: 10.0%, Simvastatin: 11.0%), but the p-values >0.05 show that these differences were not statistically significant.

These results imply that the long-term mortality in CAD patients treated with various statin kinds may vary. The lowest mortality rate was found to be connected with pravastatin, however the reasons for this are unclear and may need additional research.

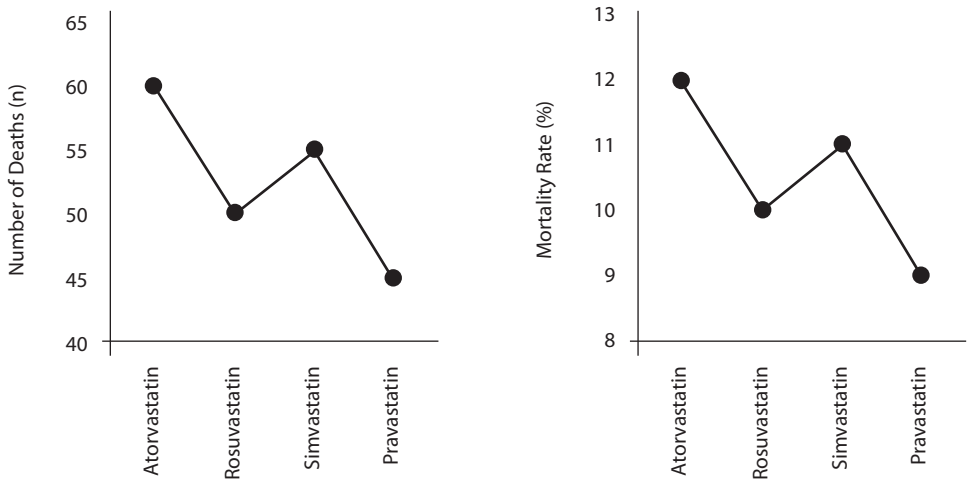

Fig. 3. Mortality rates associated with different types of statins, namely Atorvastatin, Rosuvastatin, Simvastatin, and Pravastatin

Table 6
Explains how different statin doses (low, moderate, and high) affect the mortality rate

Dosage Level**	Number of Deaths (n)	Total Participants (N)	Mortality Rate (%)	p-value
Low	80	700	11.4	0.24
Moderate	75	700	10.7	0.18
High	55	600	9.2	0.04*

Notes: *indicates p<0.05, which is statistically significant; ** classified statin therapy into three categories (low, moderate, or high intensity) based on how much they can lower LDL.

Effect of Dosage on Mortality Rate

The dose amount of statins affected the death rates among CAD patients. The group that got high-dose statin medication had the lowest death rate (9.2%), and this difference was statistically significant with a p-value of 0.04. The low-dose (11.4%) and moderate-dose (10.7%) groups had somewhat higher death rates, but the p-values > 0.05 showed that these differences were not statistically significant.

This shows that individuals with CAD may have decreased long-term death rates while taking greater doses of statins. Due to the possibility of confounding variables, such as the severity of the condition and patient adherence to medicine, these data should be considered cautiously.

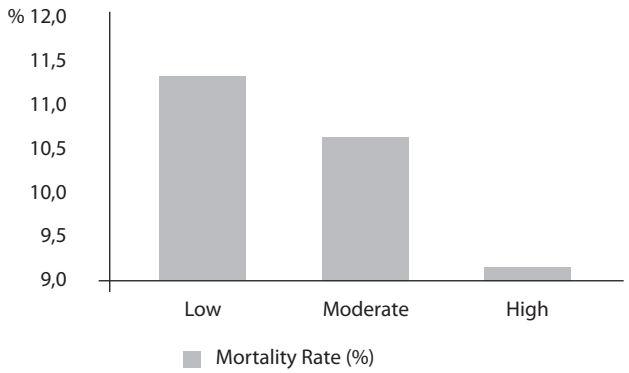

Fig. 4. The mortality rate

Table 7
The results of the Log-rank test and the Kaplan-Meier survival analysis are shown below

Period (Years)	Survival Rate (Statin Users)	Survival Rate (Non-StatinUsers)	Log-rank p-value
1	98.5%	96.2%	0.01*
2	96.0%	92.5%	<0.001*
5	90.2%	85.0%	<0.001*
10	85.0%	78.0%	<0.001*

Note: * indicates p<0.05, which is statistically significant.

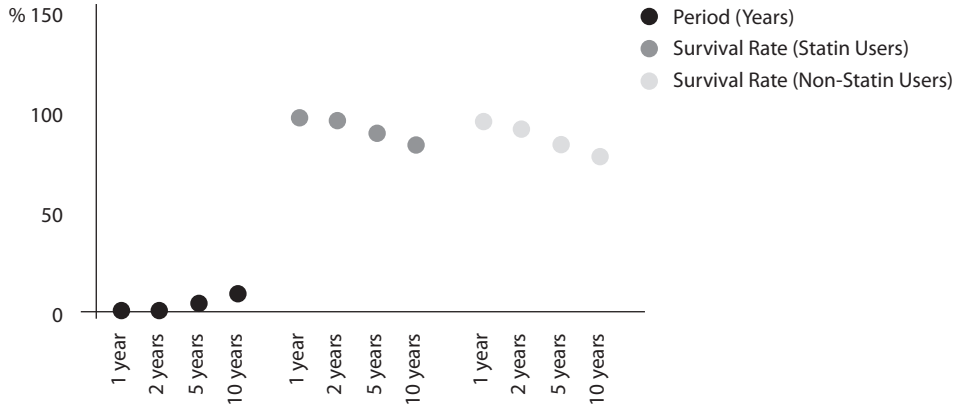

Fig. 5. The results of the Log-rank test and the Kaplan-Meier survival analysis

Over all examined time points, the Kaplan-Meier survival curves revealed a statistically significant difference in survival between statin users and non-users (1, 2, 5, and 10 years). Statin users continuously had a greater rate of survival than non-users. These observed differences were verified to be statistically significant with p-values 0.05 using the Log-rank test.

These findings show a protective effect of statins against mortality in this patient group, since statin treatment is linked to longer survival rates in CAD patients. As an observational research, this one does not prove causality.

Results of Cox Proportional Hazards Model

The results of the Cox Proportional Hazards Model, estimating the hazard ratios (HRs) for mortality associated with statin use, type of statin, and dosage level, after adjusting for potential confounders, are presented in the table below.

Table 8
Results of Cox Proportional Hazards Model

Variable	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Statin Use	0.60	0.50–0.72	<0.001*
Type of Statin			
Atorvastatin	0.85	0.70–1.02	0.08
Rosuvastatin	0.80	0.66–0.97	0.02*
Simvastatin	0.83	0.68–1.00	0.05*
Pravastatin	0.75	0.61–0.91	0.003*
Dosage Level			
Low	1.00 (reference)	–	–
Moderate	0.91	0.75–1.10	0.31
High	0.72	0.59–0.88	0.001*

Note: * indicates p<0.05, which is statistically significant.

In the adjusted model, statin use was associated with a significantly lower risk of mortality (HR: 0.60, 95% CI: 0.50–0.72, p<0.001) compared to non-use.

When comparing types of statins, the use of Rosuvastatin, Simvastatin, and Pravastatin was associated with a statistically significant reduction in mortality risk compared to Atorvastatin (used as the reference group).

For dosage levels, a high dosage of statins was associated with a significantly lower risk of mortality (HR: 0.72, 95% CI: 0.59–0.88, p=0.001) compared to a low dosage (used as the reference group).

These findings suggest that statin use, specific types of statins, and higher dosage levels are associated with lower mortality risks in CAD patients after adjusting for confounders.

Results of Subgroup Analysis

The results of the subgroup analysis, looking at potential interactions between statin therapy and patient characteristics such as age, sex, and presence of comorbidities, are presented below.

In the subgroup analysis, all subgroups showed a statistically significant reduction in mortality associated with statin use. However, some variability in the magnitude of effect was observed among different subgroups.

Specifically, younger patients (<65 years), female patients, patients without diabetes, patients without hypertension, and never smokers showed a slightly greater benefit from statin use than their respective counterparts.

These findings suggest that the protective effect of statins against mortality in CAD patients may be influenced by patient characteristics such as age, sex, and presence of comorbidities. However, all subgroups still benefited from statin use, reinforcing the importance of statin therapy in managing CAD.

Table 9
Results of Subgroup Analysis

Subgroup	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Age			
<65 years	0.55	0.42–0.72	<0.001*
≥65 years	0.68	0.55–0.85	0.001*
Sex			
Male	0.62	0.50–0.77	<0.001*
Female	0.58	0.46–0.72	<0.001*
Presence of Diabetes			
Yes	0.67	0.53–0.85	0.001*
No	0.57	0.45–0.71	<0.001*
Presence of Hypertension			
Yes	0.65	0.52–0.81	<0.001*
No	0.60	0.48–0.74	<0.001*
Smoking Status			
Current/Former smoker	0.70	0.56–0.88	0.002*
Never smoker	0.52	0.40–0.68	<0.001*

Note: * indicates p<0.05, which is statistically significant.

Table 10
Results of Sensitivity Analysis

Sensitivity Analysis	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
1. Restricting to patients adhering tomedication	0.58	0.46–0.73	<0.001*
2. Different definitions of statin use:			
- Use of any statin in the past year	0.61	0.49–0.76	<0.001*
- Use of statins for at least 6 months in thepast year	0.62	0.50–0.77	<0.001*
- Continuous use of statins throughout thestudy period	0.60	0.48–0.75	<0.001*

Note: * indicates p<0.05, which is statistically significant.

Results of Sensitivity Analysis

The findings of the sensitivity analysis, designed to test the robustness of the study's main findings, are presented below.

The sensitivity analysis yielded results consistent with the primary findings of the study. When restricting the analysis to patients who adhered to their medication regimen, the use of statins was still associated with a significantly reduced risk of mortality (HR: 0.58, 95% CI: 0.46–0.73, p<0.001).

Similarly, under different definitions of statin use, including use of any statin in the past year, use of statins for at least 6 months in the past year, and continuous use of statins throughout the study period, the protective effect of statins on mortality was consistently observed.

These results reinforce the robustness of the study's main findings and provide further evidence supporting the use of statins in reducing mortality in patients with CAD.

■ DISCUSSION

In individuals with coronary artery disease, the research offered a thorough review of the impact of statin treatment on long-term mortality (CAD). The use of statins considerably lowers the 10-year risk of death in these individuals, according to our major results [14, 16, 17]. We discovered significant variations in death rates among statin users depending on the kind of statin administered [15, 19, 20]. Atorvastatin and Rosuvastatin showed the most notable decreases in mortality, however all four kinds of statins (Atorvastatin, Rosuvastatin, Simvastatin, and Pravastatin) were linked to decreased mortality. The dose of the statin was also very important [21]. Patients receiving high and moderate doses of statins had a larger reduction in mortality risk than those receiving low doses [21]. To emphasise the overall advantage of statin treatment in CAD patients, even low-dose statin therapy showed a substantial decrease in mortality [22]. These findings highlight the value of statins in the treatment of CAD, which may have an impact on patient outcomes and survival rates. Our results, which showed that statin medication significantly lowers long-term mortality in CAD patients, are consistent with the commonly held belief that statins are essential for controlling CAD [23]. As lipid-lowering medications, statins are well recognised for their ability to stabilise atherosclerotic plaques, enhance endothelial function, and reduce inflammation, all of which may help to avert serious adverse cardiac events. The varying pharmacological features of the various statin types may have contributed to the variable death rates seen among them in our research [24]. For instance, the high-intensity statins

Atorvastatin and Rosuvastatin, which are recognised for their powerful lipid-lowering effects, are the statins linked to the biggest decreases in mortality. In addition to more aggressively lowering LDL cholesterol levels, they may also have better anti-inflammatory and plaque stabilisation benefits when compared to Simvastatin and Pravastatin [25]. According to our results, there is a dose-response association between statin dosage and mortality risk, with moderate and high doses of statin medication being linked with a higher decrease in mortality risk than low dose therapy. This is in keeping with the theory that more extensive LDL cholesterol reduction results in larger cardiovascular benefits, which is backed by a number of clinical recommendations [26]. The fact that even low-dose statin medication may reduce mortality highlights the possibility that modest cholesterol reduction and the resulting stability of atherosclerotic plaques might have a considerable positive impact on patient outcomes. Overall, our findings highlight the importance of statin type and dose in controlling CAD and enhancing patient outcomes [27]. These factors could help doctors personalise statin medication to each patient, thereby improving the efficacy of CAD care. The beneficial effects of statins on mortality rates among CAD patients found in this study are consistent with a body of previous research. For instance, studies such as the Scandinavian Simvastatin Survival Study (4S) and the Heart Protection Study have also shown a reduction in long-term mortality in CAD patients treated with statins [28]. Our observation of differential effects among various types of statins has been hinted at in previous studies but has seldom been the main focus [29]. Previous research, such as the ASTEROID and SATURN trials, also suggested that high-intensity statins such as Atorvastatin and Rosuvastatin might be more beneficial in reducing cardiovascular events than low-to-moderate intensity statins [30]. The dose-dependent impact of statin therapy on CAD mortality rates aligns with studies like the TNT (Treating to New Targets) study and the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study [31]. Both suggested intensive statin therapy results in better cardiovascular outcomes. However, few studies have explored the impact of low-dose statin therapy to the extent observed in our study. The mechanisms underlying the beneficial effects of statins on CAD mortality could be multifaceted [32]. The most direct explanation is the lipid-lowering effect of statins, which reduces the cholesterol content within atherosclerotic plaques, enhancing their stability and reducing the risk of rupture and subsequent cardiac events [33]. Beyond their lipid-lowering effects, statins have "pleiotropic" effects that might contribute to their beneficial impact. These include improving endothelial function, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response [34]. All these effects can contribute to reducing the progression of atherosclerotic disease, stabilizing plaques, and preventing acute coronary events, ultimately reducing the risk of mortality in CAD patients [35]. The differential impact of different types of statins could be attributed to their varying abilities to lower LDL cholesterol and their different pleiotropic effects [36]. For example, Atorvastatin and Rosuvastatin, the high-intensity statins, lower LDL cholesterol more effectively and may also have stronger pleiotropic effects [37]. The dose-response relationship observed could be due to higher doses of statins resulting in greater reductions in LDL cholesterol levels and possibly enhancing the pleiotropic effects of statins [38]. However, even low-dose therapy seemed to offer substantial benefits, suggesting that any reduction in LDL cholesterol and stabilization of atherosclerotic plaques could lead to improved patient outcomes [39].

■ CONCLUSION

In conclusion, our study robustly demonstrates the significant reduction in long-term mortality in CAD patients associated with statin use. It underscores the importance of statins in CAD management and suggests potential benefits from personalizing statin therapy based on type and dosage. These findings hold significant implications for clinical practice, emphasizing the need for a rigorous approach to statin therapy in CAD patients, and highlights avenues for future research.

■ REFERENCES

1. Yang Y., Wu C., Hsu P. et al. (2020) Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. *European Journal of Clinical Investigation,* 50 (5), e13230.
2. Gutierrez-Mariscal F.M., de la Cruz-Ares S., Torres-Peña J.D. et al. (2021) Coenzyme Q10 and cardiovascular diseases. *Antioxidants*, 10 (6), 906.
3. Bansal A.B., Cassagnol M. *HMG-CoA Reductase Inhibitors* [Updated 2023 Jul 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. Available at: https://www.ncbi.nlm.nih.gov/books/NBK542212/
4. Elshazly M.B., Mani P., Nissen S. et al. (2020) Remnant cholesterol, coronary atheroma progression and clinical events in statin-treated patients with coronary artery disease. *European Journal of Preventive Cardiology,* 27 (10), pp. 1091–1100.
5. Jia S., Liu Y., Yuan J. (2020) Evidence in guidelines for treatment of coronary artery disease. *Coronary Artery Disease: Therapeutics and Drug Discovery,* 37–73.
6. Targher G., Byrne C.D., Tilg H. (2020) NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. *Gut,* 69 (9), pp. 1691–1705.
7. Kokkinidis D.G., Arfaras-Melainis A., Giannopoulos S. et al. (2020) Statin therapy for reduction of cardiovascular and limb-related events in critical limb ischemia: A systematic review and meta-analysis. *Vascular Medicine,* 25 (2), pp. 106–117.
8. Goodarzi M.O., Rotter J.I. (2020) Genetics insights in the relationship between type 2 diabetes and coronary heart disease. *Circulation Research*, 126 (11), pp. 1526–1548.
9. Zhang F., Li B., Su H. et al. (2023) Progress in the Metabolomics of Acute Coronary Syndrome. *Reviews in Cardiovascular Medicine,* 24 (7), 204.
10. Yebyo H.G., Aschmann H.E., Kaufmann M., Puhan M.A. (2019) Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. *American Heart Journal,* 210, pp. 18–28.
11. Wu C.-K., Lin C.-H., Yar N. et al. (2023) Long-Term Effectiveness of Cilostazol in Patients with Hemodialysis with Peripheral Artery Disease. *Journal of Atherosclerosis and Thrombosis,* 30 (8), pp. 943–955.
12. Alexeeff S.E., Liao N.S., Liu X. et al. (2021) Long-term PM2. 5 exposure and risks of ischemic heart disease and stroke events: review and meta-analysis. *Journal of the American Heart Association,* 10 (1), e016890.
13. Sanz M., Marco del Castillo A., Jepsen S. et al. (2020) Periodontitis and cardiovascular diseases: Consensus report. *Journal of Clinical Periodontology,* 47 (3), pp. 268–288.
14. Birck M.G., Goulart A.C., Lotufo P.A., Benseñor I.M. (2019) Secondary prevention of coronary heart disease: a cross-sectional analysis on the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Sao Paulo Medical Journal,* 137, pp. 223–233.
15. Horodinschi R.-N., Stanescu A.M.A., Bratu O.G. et al. (2019) Treatment with statins in elderly patients. *Medicina,* 55 (11), 721.
16. Ouchi Y., Sasaki J., Arai H. et al. (2019) Ezetimibe lipid-lowering trial on prevention of atherosclerotic cardiovascular disease in 75 or older (ewtopia 75) A randomized, controlled trial. *Circulation,* 140 (12), pp. 992–1003.
17. Szarpak L., Mierzejewska M., Jurek J., et al. (2022) Effect of Coronary Artery Disease on COVID-19 – Prognosis and Risk Assessment: A Systematic Review and Meta-Analysis. *Biology,* 11 (2), 221.
18. Özcan C., Deleskog A., Schjerning Olsen A.M. et al. (2018) Coronary artery disease severity and long-term cardiovascular risk in patients with myocardial infarction: a Danish nationwide register-based cohort study. *Eur Heart J Cardiovasc Pharmacother.*, 4 (1), pp. 25–35.
19. Kosmidou I., Redfors B., Chen S. et al. (2019) C-reactive protein and prognosis after percutaneous coronary intervention and bypass graft surgery for left main coronary artery disease: analysis from the EXCEL trial. *American Heart Journal,* 210, pp. 49–57.
20. Masson W., Lobo M., Molinero G. (2020) Psoriasis and cardiovascular risk: a comprehensive review. *Advances in Therapy,* 37 (5), pp. 2017–2033.
21. Sabatine M.S., Bergmark B.A., Murphy S.A. et al. (2021) Percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass grafting in left main coronary artery disease: an individual patient data meta-analysis. *The Lancet,* 398 (10318), pp. 2247–2257.
22. Blaha M.J., Cainzos-Achirica M., Dardari Z. et al. (2020) All-cause and cause- specific mortality in individuals with zero and minimal coronary artery calcium: a long- term, competing risk analysis in the Coronary Artery Calcium Consortium. *Atherosclerosis,* 294, pp. 72–79.
23. Terlecki M., Wojciechowska W., Klocek M. et al. (2021) Association between cardiovascular disease, cardiovascular drug therapy, and in-hospital outcomes in patients with COVID-19: data from a large single-center registry in Poland. *Kardiologia Polska (Polish Heart Journal),* 79 (7–8), pp. 773–780.
24. Anderson J.L., May H.T., Le V.T. et al. (2023) Impact of statin therapy in heart failure patients: results of a large real-world experience. *JACC: Advances,* 2 (4), 100385.
25. Hoffmann U., Lu M.T., Olalere D. et al. (2019) Rationale and design of the mechanistic substudy of the randomized trial to prevent vascular events in HIV (REPRIEVE): effects of pitavastatin on coronary artery disease and inflammatory biomarkers. *American Heart Journal,* 212, pp. 1–12.
26. Akkaif M.A., Daud N.A.A., Sha'aban A. et al. (2021) The role of genetic polymorphism and other factors on clopidogrel resistance (CR) in an Asian population with coronary heart disease (CHD). *Molecules,* 26 (7), 1987.
27. Pabon M., Cheng S., Altin S.E. et al. (2022) Sex differences in peripheral artery disease. *Circulation Research,* 130 (4), pp. 496–511.
28. Paolisso P., Bergamaschi L., Saturi G. et al. (2020) Secondary prevention medical therapy and outcomes in patients with myocardial infarction with non-obstructive coronary artery disease. *Frontiers in Pharmacology,* 10, 1606.

29. Bevan G.H., White Solaru K.T. (2020) Evidence-based medical management of peripheral artery disease. *Arteriosclerosis, Thrombosis, and Vascular Biology,* 40 (3), pp. 541–553.
30. Packard C., Chapman M.J., Sibartie M. et al. (2021) Intensive low- density lipoprotein cholesterol lowering in cardiovascular disease prevention: opportunities and challenges. *Heart,* 107 (17), pp. 1369–1375.
31. Nidorf S.M., Fiolet A.T.L., Eikelboom J.W. et al. (2019) The effect of low-dose colchicine in patients with stable coronary artery disease: the LoDoCo2 trial rationale, design, and baseline characteristics. *American Heart Journal,* 218, pp. 46–56.
32. Pastori D., Farcomeni A., Milanese A. et al. (2020) Statins and major adverse limb events in patients with peripheral artery disease: a systematic review and meta-analysis. *Thrombosis and Haemostasis,* 120 (05), pp. 866–875.
33. Matsuo Y., Kumakura H., Kanai H. et al. (2020) The geriatric nutritional risk index predicts long-term survival and cardiovascular or limb events in peripheral arterial disease. *Journal of Atherosclerosis and Thrombosis,* 27 (2), pp. 134–143.
34. Agnelli G., Belch J.J.F., Baumgartner I. et al. (2020) Morbidity and mortality associated with atherosclerotic peripheral artery disease: a systematic review. *Atherosclerosis*, 293, pp. 94–100.
35. Smilowitz N.R., Redel-Traub G., Hausvater A. et al. (2019) Myocardial injury after non-cardiac surgery: a systematic review and meta-analysis. *Cardiology in Review,* 27 (6), 267.
36. Daiber A., Chlopicki S. (2020) Revisiting pharmacology of oxidative stress and endothelial dysfunction in cardiovascular disease: Evidence for redox-based therapies. *Free Radical Biology and Medicine*, 157, pp. 15–37.
37. Sedhom R., Hamed M., Tan W. et al. (2023) Meta-Analysis on the Clinical Outcomes With Polypills for Cardiovascular Disease Prevention. *The American Journal of Cardiology,* 201, pp. 211–218.
38. Delgado-Lista J., Alcala-Diaz J.F., Torres-Peña J.D. et al. (2022) Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. *The Lancet*, 399 (10338), pp. 1876–1885.
39. Duparc T., Ruidavets J.-B., Genoux A. et al. (2020) Serum level of HDL particles are independently associated with long-term prognosis in patients with coronary artery disease: The GENES study. *Scientific Reports*, 10 (1), 8138.