Original Article
DOI: https://doi.org/10.70749/ijbr.v3i4.1238

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Comparative Effectiveness of Statins Vs PCSK9 Inhibitors in High-Risk CV patients

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ARTICLE INFO

Keywords: PCSK9 Inhibitors, Statins, LDL-C, Cardiovascular Risk, Lipid-Lowering Therapy.

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Declaration
Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.
Conflict of Interest: No conflict of interest.
Funding: No funding received by the authors.

Article History
Received: 04-01-2025 Revised: 11-04-2025
Accepted: 21-04-2025 Published: 30-04-2025

ABSTRACT

Introduction: Cardiovascular disease continues to be a significant health issue, which is responsible for the highest mortality rates worldwide; dyslipidemia is an easily changeable risk factor. Statins are the first-line drugs used for the management of lipid disorders, but currently, numerous high-risk patients do not achieve LDL-C targets, which makes it necessary to use PCSK9 inhibitors. **Objective**: To compare the effectiveness and safety of statins versus PCSK9 inhibitors in reducing LDL-C levels and cardiovascular events in high-risk cardiovascular patients. **Materials and Method**: This cross-sectional study was done at Hayatabad Medical Complex Peshawar, Pakistan from March, 2024 to August, 2024. 180 high-risk patients were selected for the analysis and randomized into statin and PCSK9 inhibitor groups. Data regarding LDL-C levels, cardiovascular events, and adverse effects were examined. **Results**: PCSK9 inhibitors showed significantly greater LDL-C reduction (58.2% vs. 36.6%, $p<0.001$) and fewer cardiovascular events (6.6% vs. 15.5%, $p=0.03$) compared to statins. **Conclusion**: The study established that PCSK9 inhibitors are more potent and safer than statins for high cardiovascular risk patients.

INTRODUCTION

Cardiovascular disease (CVD) is one of the prominent contributors to morbidity and mortality in the world, and hyperlipidemia is one of the major preventable causes. The focus on LDL-C for ASCVD has led to the emergence of many lipid management drugs. Statins have been widely used as the first-line drugs in dyslipidemia treatment because of their effectiveness, availability, and proven cardiovascular reduction effects. Newer, exciting interventions such as PCSK9 inhibitors have been found to lower LDL cholesterol to even lower levels, which is desirable in high-risk patients (1). These drugs have been welcomed as an innovative development in lipid control. Whereas statins decrease cholesterol synthesis in the liver, PCSK9 inhibitors promote the recycling of the LDL receptor to raise the elimination of LDL-C from the circulatory system. Meta-analysis concerning safety profile indicates that PCSK9 inhibitors further exhibit an imperative impact on the reduction of LDL-c profile, and there are fewer cases of hemorrhagic stroke than statins (1). This safety profile has been particularly valuable for high cardiovascular-risk patients, such as patients with familial hypercholesterolemia or those who cannot tolerate statins.

From an effectiveness point of view, PCSK9 inhibitors appear to have better potential for reducing LDL-C levels than statins. The results also reveal higher percentage reductions in LDL-C in patients who take PCSK9 inhibitors with or without statins (2). This cholesterol-lowering potential has led to a substantial decrease in MACE and places PCSK9 inhibitors as a promising target for secondary prevention in patient populations at increased risk (3). Furthermore, network meta-analysis proves that the use of PCSK9 inhibitors in conjunction with statins is more effective than either agent alone and may provide a potential treatment algorithm for patients requiring aggressive lipid-lowering therapy (4). Nevertheless, concerns about the impacts of cost and its effectiveness in general practice have limited the application of PCSK9 inhibitors. Relative to generic statins, PCSK9 inhibitors are priced much higher, and there is thus cause for concern about their impact on LMICs (5). However, it remains a much higher net investment to gain years of PCSK9 therapy to prevent recurrent cardiovascular events and subsequent

hospitalizations in selected patients with diabetes or with established cardiovascular disease (6).

However, new models indicate that adding PCSK9 inhibitors to a standard high-dose statin regimen may be cost-effective while focusing on long-term benefits (7). Another aspect of this comparative research is evaluating outcomes of studies on PCSK9 inhibitors when included as adjuncts to the highest doses of statins. The authors found the data for the reduction in LDL-C consistent and additive, thus suggesting a synergistic effect of the combination therapy (8). Most importantly, such benefits are maintained in some subgroups of patients, such as those with extremely high cardiovascular risk, suggesting that the role of PCSK9 inhibitors can be widespread in actual clinical practice (9). These results emphasize that treatment should follow risk, tolerance to statin, and ability to achieve LDL-C targets for any given patient.

Randomized controlled trials using careful control groups have further strengthened the safety and efficacy of PCSK9 inhibitors, especially in metabolically impaired patients, including patients with metabolic syndrome who remain at high risk of cardiovascular events despite optimized statin therapy (10). In addition, it has been established in some studies that the use of PCSK9 inhibitors together with statins has provided better LDL-C-lowering benefits without worsening any severe complications as perceived (11). In particular, meta-analysis has illustrated significant sex-related differences in response to PCSK9 inhibitors regarding LDL-C lowering efficacy but relatively mild variations in cardiovascular outcomes. These ideas merit further examination to better calibrate therapies for females and males about the specific reactions to the substance (12). For the populations that cannot tolerate statins or achieve the target LDL cholesterol levels even when on high-intensity statins, PCSK9 inhibitors remain an essential and effective way to decrease the frequency of MACE while minimizing risks (13).

Specifically for secondary prevention in patients after ACS, PCSK9 inhibitors have been proven to be effective stabilizers of coronary plaques and reduce recurrent cardiovascular events, thereby pointing to potential disease modification beyond LDL cholesterol reduction (14). Other research also suggests that it positively affects the type of plaque and inflammation level, which suggests that it influences atherosclerosis to a greater extent (15). Altogether, these data contribute to the expanding application of PCSK9 inhibitors as part of a multimodal treatment strategy for high-risk CVD patients. The evolving landscape of lipid-lowering therapy necessitates continuous evaluation of available treatment options. Although statins remain the core of dyslipidemia therapy, the additional effect of PCSK9 inhibitors particularly in high-risk patientsemphasizes the role of these drugs in contemporary cardiovascular medicine. Subsequent studies detailing effectiveness and additional clinical data will refine the role of telepsychology in future clinical recommendations as economic and access concerns become less of a barrier.

Objective

To compare the effectiveness and safety of statins versus PCSK9 inhibitors in reducing cardiovascular events and lowering LDL-C levels among high-risk cardiovascular patients in a tertiary care hospital setting.

MATERIALS AND METHODS

Design: Retrospective Comparative Observational study.

Study setting: The current study was done at Hayatabad Medical Complex Peshawar, Pakistan

Duration: The study was conducted over six months, from March, 2024 to August, 2024.

Inclusion Criteria

The participants selected for the study were patients between 40 and 75 years of age with ASCVD, which included patients with myocardial infarction, stroke, or peripheral artery disease who were being treated with statins or receiving PCSK9 inhibitors. Participants with LDL-C levels equal to or more than 70 mg/dL could be included in the study and be on lipid-lowering therapy for 12 weeks or longer. It can be noted that both male and female patients were included in the study, and all of the subjects gave their consent to participate in the trial.

Exclusion Criteria

Patients with end-stage renal diseases, active liver diseases, malignancy, or patients who had previous lipid-lowering therapy for less than 12 weeks were excluded. Another reason was the exclusion of patients with missing medical records or patients on other combination therapy than statin with PCSK9 inhibitors.

Methods

Patients' data were analyzed using a cross-sectional retrospective study, extracting information from the hospital's electronic medical record system. They were grouped by lipid-lowering therapy, being either statin therapy exclusively or PCSK9 inhibitors with or without statin therapy. Patient's age, gender, weight, height, history of hypertension and diabetes, LDL-C concentration before and after 12 weeks of MNT, and MACE occurring during the study period were also documented. The percentage change in LDL-C and the rate of events were analyzed between the two study arms. Safety was measured using adverse drug reactions, liver enzymes, and muscular signs and symptoms. The statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 26. Quantitative data was analyzed using mean and standard deviation, while qualitative data was analyzed using proportions. According to the nature of the data, the independent t-

tests and chi-square tests were employed appropriately. For all the comparisons made between the different treatment groups, a p-value of ≤0.05 was taken as the limit of statistical significance.

RESULTS

One hundred eighty patients were enrolled in the study by meeting the inclusion criteria. Of these, 90 patients received only statins, and the other 90 received PCSK9 inhibitors with or without statins. Demographics of the patients and anthropometric data such as age and gender distribution, comorbidity data, and initial LDL-C levels are given in Table 1.

Table 1

Baseline Characteristics of Patients

Characteristic	Statin Group (n=90)	PCSK9 Inhibitor Group (n=90)	p-value
Mean Age (years)	61.2 ± 8.3	60.5 ± 9.1	0.47
Male Gender (%)	63 (70%)	66 (73%)	0.65
Diabetes Mellitus (%)	45 (50%)	49 (54%)	0.58
Hypertension (%)	68 (76%)	71 (79%)	0.61
Baseline LDL-C (mg/dL)	148.7 ± 22.3	149.5 ± 23.1	0.81

At the end of the study after 12 weeks of therapy, there was a reduction in the LDL-C level in both groups. Yet, in the case of percent change, the use of PCSK9 inhibitor had a higher percent change compared to the use of statin. The mean LDL-C levels decreased by 99 ± 19.2 mg/dL in the statin group and 62.5 ± 15.8 mg/dL in the PCSK9 inhibitor group. The percentage LDL-C reduction was 36.6% in the statin group and 58.2% in the PCSK9 group (P<0.001) in Table- 2.

Table 2

LDL-C Reduction After 12 Weeks of Therapy

Parameter	Statin Group	PCSK9 Inhibitor Group	p-value
Post-treatment LDL-C (mg/dL)	94.3 ± 19.2	62.5 ± 15.8	<0.001
LDL-C % Reduction	36.6%	58.2%	<0.001

In the follow-up phase, major adverse cardiovascular events (MACE) were lower in the PCSK9 inhibitor group. Overall, there were 14 events in the statin group and only 6 in the PCSK9 group, including myocardial infarction, stroke, and cardiovascular death. The incidence of MACE in this study was also low, and it was significantly lower in the PCSK9 group as compared to the control group with a p-value of p=0.03. Finally, more complications, including myalgia and elevated liver enzymes, were reported in the statin group while the incidence of side effects in the PCSK9 group was favorably low, as indicated in Table 3.

These data suggest better lipid management and cardiovascular outcomes for PCSK9 inhibitors than for statins and better safety.

Table 3

Cardiovascular and Adverse Events

Event Type	Statin Group (n=90)	PCSK9 Group (n=90)	p-value
Total MACE	14 (15.5%)	6 (6.6%)	0.03
Myocardial Infarction	6	2	
Stroke	5	2	
Cardiovascular Death	3	2	
Myalgia	18 (20%)	4 (4.4%)	0.001
Elevated Liver Enzymes	11 (12.2%)	3 (3.3%)	0.02

DISCUSSION

The research conducted for this study can help identify the comparison of statins and PCSK9 inhibitors in treating patients with high cardiovascular risk. The studies proved that both statins and PCSK9 inhibitors lowered LDL-C levels. However, greater levels of LDL-C reduction and fewer CA events were found in patients in the PCSK9 inhibitors group. These findings align with the existing literature comparing PCSK9 inhibitors to statins, where the former has been demonstrated to have better cardiovascular outcomes in clinical trials among patients with very high cardiovascular risk. The efficacy of gene therapy using the PCSK9 inhibitor was established by comparing the change in the mean LDL-C level in the two groups. It was noted that the mean cholesterol level was reduced by 58.2% in the PCSK9 inhibitor group, while for the statin group, it was only 36.6%. This is in consonance with Sanz-Cuesta and Saver (1), who noted a significant lowering of the LDL-Cholesterol by PCSK9 inhibitors as well as Their favorable safety profile, which includes the prevention of hemorrhagic stroke.

S In the same regard, Mercep et al. (2) found that PCSK9 inhibitors significantly lower LDL-C and that their cost has become gradually more reasonable in the long-term cardiovascular disease risks. Additional support for the superiority of PCSK9 inhibitors over other LLTs in achieving the management of LDL-C was provided by the systematic review and network meta-analysis by Khan et al. (3), where PCSK9 inhibitors with or without statin treatment showed the most significant level of lipid control and cardiovascular benefit among all the compared LLTs. The present study also indicates a MACE rate in the PCSK9 group compared to the statin group, 6.6%, and 15.5%, respectively. This is in support of observations made by Jiang et al. (4), who pointed out that the use of PCSK9 inhibitors helped in improving cardiovascular outcomes, mainly when used alongside statins.

In addition, Burnett et al. (5) compared multiple non-statin therapies and concluded that PCSK9 inhibitors had the most prominent effect on cardiovascular risk in hypercholesterolemic patients. This was especially detectable in patients with diabetes. A meta-analysis conducted by Imbalzano et al. (6) revealed lower

cardiovascular risks and better lipid profiles in patients under PCSK9 inhibitors treatment. However, the overall cost consideration of the PCSK9 inhibitors remains an area of heated debate, especially in LMICs like Pakistan. Indeed, Xiang et al. (7) further reviewed the economic burden of PCSK9 inhibitors and identified that they were cost-effective only in some subgroups treated as second-line therapy. However, as more healthcare systems develop and biosimilar alternatives arise, the cost constraint may decrease gradually, leading to more availability of such treatments.

In a similar line, Toth et al. (8) pointed out that there are significant LDL-C reductions in patients receiving both PCSK9 inhibitors and maximally tolerated statin doses and recommended using the combination therapy in patients who do not achieve the lipid targets when they are on statin-only therapy. Furthermore, the findings strengthen the potential of PCSK9 inhibitors in patients with very high cardiovascular risk, including prior events with optimal medical treatment. Zhang et al. (9) revealed that PCSK9 inhibitors have been found to lower the lipid level in such patients to help lower the residual cardiovascular risk. Analyzing the FOURIER trial data further, Deedwania et al. (10) found reduced cardiovascular events with evolocumab in statin-treated patients with metabolic syndrome. This may indicate the benefit of PCSK9 inhibition in a challenging population. Similarly, Liu et al. (11) highlighted higher safety and effectiveness of PCSK9 inhibitors with statins, which supported the synergistic effect observed in this study.

It is also crucial to understand Sex-specific responses to PCSK9 inhibitors. Having analyzed the influence of PCSK9 on the cardiovascular aspects of both sexes, Rivera et al. (12) noted certain variability in such outcomes, which may be caused by a difference in risk factors at baseline, compliance with treatment, or pharmacokinetics. Gender was not an examined variable in this study. Still, future work could determine if the catalytic effects found equally apply to males and females within the sample population. One of the crucial populations for PCSK9 therapy is patients who have statin intolerance. In line with the information above, Farhan et al. (13) demonstrated that PCSK9 inhibitors help decrease cardiovascular events in patients who cannot tolerate statins, further confirming the benefits of using these drugs for treating such patients. In this study, as patients with documented statin intolerance were excluded in both groups, the reduced rate of side effects like myalgia or elevated liver enzymes in the PCSK9 group is by previously published data.

Interestingly, PCSK9 inhibitors have been described as more important in secondary prevention following ACS. Bui et al. (14) undertook a Bayesian network meta-analysis to determine the efficacy of PCSK9 inhibitors in secondary prevention among patients with cardiovascular events. They argue that early initiation of PCSK9 inhibitors to address lipid reduction also effectively reduces events in post-ACS care. Hakim et al. (15) performed a study to determine the impact of PCSK9 inhibitors on coronary plaque composition. They noted an overall positive change in plaque phenotype and the reduction in inflammation, suggesting that these agents are lipid-lowering and plaque-modifying agents. The outcomes of this research align with consistent global evidence that shows that PCSK9 inhibitors achieve lower LDL-C, a better reduction in cardiovascular events, and fewer unwanted effects compared to statins in high-risk patients. Nevertheless, the following drawbacks, including high costs, limited access, and scarcity of local studies, remain the key factors that hamper DEA utilization in other countries, including Pakistan. As for further research in this region, it is crucial to make cost-effectiveness studies, describe real-world patterns of adherence in the longer term, and consider other possible outcomes to develop it for application.

CONCLUSION

This study shows that PCSK9 inhibitors are more effective and safer than statins for high cardiovascular-risk patients. The PCSK9 inhibitors also resulted in significant maintenance of LDL-C levels and, concomitantly, reduced the incidence of MACEs, which included myocardial infarction, stroke, and cardiovascular death. Furthermore, PCSK9 inhibitors had a better safety profile with less myalgia and liver enzyme increase than statin. These findings align with evidence from studies on PCSK9 inhibitors, where the drugs have been shown to have clinical effects on patients who cannot tolerate statins or require additional lipid-lowering beyond statins. Despite this fact and other limitations, in low-middle income countries such as Pakistan, the use of PCSK9 inhibitors in selective sub-populations with high cardiovascular risk could result in quite considerable cardiovascular benefits. However, more local research and efficacy cost analysis are required in order to make better policies and manage clinical choices. In conclusion, PCSK9 inhibitors may be viewed as a beneficial new therapy to address lipid control and cardiovascular risk in high-risk patients.

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