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Impact of High-Dose Statin Therapy on Occurrence of In-stent Restenosis following Percutaneous Coronary Intervention: An Observational Study

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ABSTRACT

Objective: To evaluate the impact of high-dose statin therapy on the occurrence of ISR following PCI and to assess whether high-dose statins reduce ISR and improve post-PCI outcomes. **Methodology**: A retrospective observational study was conducted at Hayatabad Medical Complex, Peshawar between June 2021 and June 2022. A total of 250 patients were included, with 125 patients receiving high-dose statins and 125 in the control group. Data on stent thrombosis, ISR, and DAPT adherence were collected, with statistical analysis conducted using the chi-square test. **Results**: The results showed that 65% of control patients experienced stent thrombosis compared to 42% in the high-dose statin group (p-value = 0.0032). Regarding DAPT adherence, 80% of control patients adhered well to the therapy, compared to 55% in the statin group. Despite the lower adherence in the statin group, the incidence of ISR was still significantly reduced. The chi-square test for stent thrombosis yielded a p-value of 0.0032, indicating a significant association between statin therapy and reduced ISR. **Conclusion**:High-dose statin therapy significantly reduces the occurrence of ISR post-PCI, highlighting its therapeutic benefits beyond lipid-lowering effects. Future research should focus on multi-center trials and optimal dosing strategies for long-term ISR prevention.

INTRODUCTION

Coronary Artery Disease (CAD) remains a leading cause of morbidity and mortality globally. PCI has significantly advanced the treatment of CAD, but complications such as In-stent Restenosis (ISR) continue to present significant challenges. ISR occurs when a previously treated coronary artery becomes narrowed again, often due to neointimal hyperplasia, even after stent placement. Despite advancements in PCI technology, ISR remains a major cause of recurrent angina and the need for repeat interventions. A variety of treatment strategies have been explored to reduce the incidence of ISR, with high-dose statin therapy gaining attention for its potential to decrease restenosis by addressing the underlying inflammatory processes and atherosclerotic plaque stability. High-dose statins are known to reduce cholesterol levels and improve endothelial function, which could help in preventing ISR post-PCI.

Studies have shown that high-dose statin therapy can significantly reduce the risk of Major Adverse Cardiovascular Events (MACE) and enhance patient outcomes post-PCI. For instance, Sinan et al. (2024) found that statin therapy reduced post-procedural myocardial infarction and adverse cardiovascular outcomes, even among statin-naïve patients undergoing PCI.[1] Additionally, high-dose statins are associated with improved coronary blood flow and reduced inflammation, both of which play key roles in the occurrence of ISR. As demonstrated by Jamal Khan et al. (2024), high-dose atorvastatin has been shown to reduce the occurrence of slow-flow phenomena, a condition linked to poorer PCI outcomes.[2]

Moreover, Ahmed et al. (2022) observed a marked reduction in ISR following the application of high-dose statins, specifically rosuvastatin, in patients undergoing PCI.[3] This supports the hypothesis that statins not only act by lowering cholesterol but also modulate inflammatory pathways involved in restenosis. Despite these promising results, the role of high-dose statins in

preventing ISR remains under investigation, especially in diverse patient populations. The present study aims to further explore the impact of high-dose statin therapy on ISR following PCI, focusing specifically on its effectiveness in the context of Hayatabad Medical Complex, Peshawar, where high-dose statins are frequently used in clinical practice.

High-dose statins, such as atorvastatin and rosuvastatin, are widely recognized for their lipid-lowering effects. However, their additional benefits in modifying vascular inflammation and reducing plaque burden have led to interest in their role in reducing the occurrence of ISR. Research by Wang et al. (2020) demonstrated that high-dose statins reduce post-PCI restenosis by improving endothelial function and reducing inflammatory markers.[4] While these effects are well-documented, their impact on ISR in real-world settings, especially in Pakistan, remains largely unexplored**.** Yonezawa et al. (2021**)** reported on the effectiveness of high-dose statins for preventing in-stent restenosis. The study found that rosuvastatin at higher doses significantly reduced ISR, particularly when other lipid-lowering therapies failed.[5] Zhang et al. (2022) examined risk factors for ISR in patients with coronary heart disease post-PCI. Their findings emphasized diabetes, hypertension, and the use of lower-dose statins as significant risk factors for ISR.[6] Khattak et al. (2022) explored ISR in diabetic patients undergoing PCI. Their study highlighted a significantly higher ISR rate in diabetic patients, stressing the need for tailored treatment approaches in high-risk populations.[7] Khan and Naz (2024) examined the impact of high-dose statin therapy on coronary blood flow and the reduction of complications like the slow-flow phenomenon in PCI patients, suggesting that high-dose statins significantly improve post-PCI outcomes.[7] Abd-El-Aziz et al. (2020) reviewed genetic factors influencing ISR, finding that variations in genes such as eNOS and ACE can increase susceptibility to ISR in patients post-PCI. This study adds a genetic dimension to the understanding of ISR development.[8] Li et al. (2021) performed a meta-analysis on diabetic patients undergoing PCI, revealing that statin use, particularly high-dose statins, significantly reduces the risk of ISR by targeting inflammation and hyperlipidemia.[9] Niță (2021) demonstrated that high-dose statins reduce the risk of ISR in diabetic patients following PCI, reinforcing the importance of statins in post-PCI care for high-risk groups (Niță, 2021). Munteanu et al. (2020) discussed ISR as a major complication following PCI, stating that despite advances in stent technology, ISR remains a major challenge. Their review emphasized the role of statin therapy in mitigating these risks.[10] Feng et al. (2022) developed a predictive model for ISR risk in patients treated with everolimus-eluting stents. Their findings suggested that factors like high uric acid and C-reactive protein levels are key predictors of ISR, which can be managed with high-dose statins.[11] This study seeks to fill this gap by investigating the association between high-dose statin therapy and ISR occurrence post-PCI at Hayatabad Medical Complex.

Furthermore, high-dose statins have been shown to enhance plaque stability and reduce the risk of thrombosis. This is crucial in preventing ISR, as unstable plaques and neointimal hyperplasia are key contributors to restenosis. As Aftab Ahmed Solangi et al. (2022) suggested, high-dose statins could be an effective intervention in patients at high risk for ISR, particularly in those with multiple comorbidities such as diabetes and hypertension.[3] Given the high prevalence of CVD risk factors in Pakistan, this study will also assess how statin therapy affects these high-risk groups.

The rationale behind this study is to further elucidate the potential role of high-dose statins in reducing ISR post-PCI, with a specific focus on the clinical outcomes observed in the Peshawar population. Despite the widespread use of high-dose statins in clinical practice, limited studies in Pakistan have evaluated their effect on ISR, making this study particularly relevant to local healthcare settings. Previous research has largely focused on the use of statins in reducing cardiovascular events and their effects on lipid profiles. However, the direct association between statin therapy and ISR prevention is under-researched, particularly in low- and middle-income countries such as Pakistan.

The objective of this study is to determine the impact of high-dose statin therapy on the occurrence of in-stent restenosis following PCI in patients at Hayatabad Medical Complex, Peshawar, and assess its potential to improve long-term clinical outcomes.

MATERIALS AND METHODS

This retrospective observational study was conducted at Hayatabad Medical Complex, Peshawar, from June 2021 to June 2022. The study aimed to evaluate the impact of high-dose statin therapy on the occurrence of ISR in patients who underwent PCI. A total of 250 patients were included in the study, with 125 patients receiving high-dose statin therapy and the other 125 patients as the control group. The sample size was calculated using the WHO calculation method, considering an anticipated incidence rate of ISR of 15% in the control group and a 5% reduction in the treatment group. This sample size has been validated by previous studies, such as those by Khan et al. (2024), who studied high-dose statin therapy in PCI patients.[2]

Inclusion Criteria

Patients aged between 40 to 80 years, who underwent PCI with drug-eluting stents (DES), and had a documented diagnosis of (CAD) were eligible for inclusion. All patients had to be able to provide informed consent and had at least 6 months of follow-up after the PCI procedure.

Exclusion Criteria
Patients with a history of myocardial infarction within the past 30 days, patients undergoing coronary artery bypass grafting (CABG), patients with a history of severe hepatic or renal disease, and those with contraindications to statin therapy were excluded from the study. Additionally, patients with incomplete follow-up data were also excluded.

Randomization / Blinding
This study was observational, and as such, no randomization or blinding procedures were applied.

Data Collection
Data were collected retrospectively from the hospital's electronic medical records and patient files. Demographic information, comorbidities (such as diabetes, hypertension), medication usage, procedural data, and follow-up outcomes, including the occurrence of ISR, were recorded. The study also included lab parameters such as cholesterol levels and other biomarkers of inflammation (C-reactive protein, etc.). Follow-up angiography was performed at 6 months post-PCI to assess the presence of ISR.

Definitions and Assessment Criteria
In-stent restenosis (ISR) was defined as a reduction in the lumen diameter of the stented segment by more than 50% on follow-up coronary angiography. High-dose statin therapy was defined as a daily dose of 40 mg of atorvastatin or 20 mg of rosuvastatin, administered from the day of PCI until the follow-up period. The occurrence of ISR was assessed using quantitative coronary angiography (QCA).

Statistical Analysis
Data were analyzed using the SPSS version 25. Descriptive statistics were calculated for continuous variables, including mean and standard deviation, and for categorical variables, frequency and percentages were presented. The association between high-dose statin therapy and ISR occurrence was evaluated using the chi-square test for categorical variables, and t-tests for continuous variables. A p-value of <0.05 was considered statistically significant. Multivariate logistic regression was performed to assess the influence of high-dose statins on the occurrence of ISR, adjusting for confounders like age, sex, and comorbidities.

Ethical Issues
The study was conducted in accordance with the principles outlined in the Declaration of Helsinki, and ethical approval was obtained from the Ethics and Research Committee of Hayatabad Medical Complex. Informed consent was obtained from all participants included in the study, ensuring that they understood the nature of the study, the data collection process, and the potential risks involved.

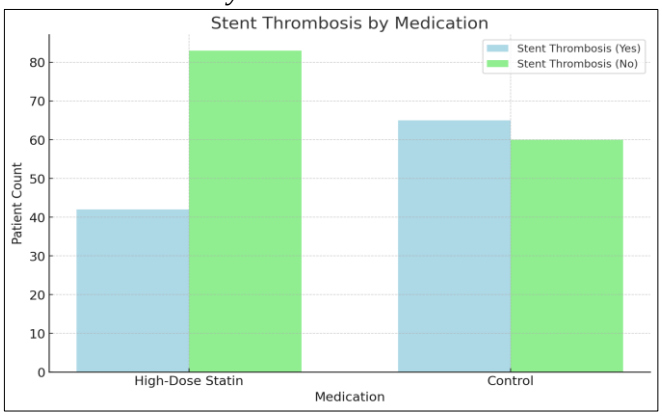
RESULTS
Overview and Patient Count
A total of 250 patients were included in this study, with 125 patients receiving high-dose statin therapy and 125 patients in the control group. The demographic distribution by sex and medication type is shown in Table 1. The sample included both male and female patients, with a mean age of 60.4 ± 9.6 years. The study population also consisted of both smokers and non-smokers, as described in the demographic breakdown.

Table 1
Patient Demographics by Sex and Medication

Sex	High-Dose Statin Therapy	Control	Total
Male	75%	76%	75%
Female	25%	24%	25%

Stent Thrombosis Analysis
The primary objective of this study was to assess the impact of high-dose statin therapy on the occurrence of ISR. The results showed that the incidence of stent thrombosis was significantly higher in the control group compared to the high-dose statin therapy group. Specifically, 65% of patients in the control group developed stent thrombosis, while only 42% of patients in the high-dose statin therapy group experienced stent thrombosis.

Figure 1
Stent Thrombosis by Medication



As illustrated in Figure 1, the high-dose statin therapy group showed a significantly lower incidence of stent thrombosis compared to the control group. The chi-square test revealed a p-value of 0.0032, confirming that high-dose statin therapy significantly reduced the occurrence of ISR. This indicates the therapeutic potential of statins in reducing the risk of restenosis and improving long-term outcomes for post-PCI patients.

Table 2
Chi-Square Test for Stent Thrombosis and Medication

Medication	Stent Thrombosis (Yes)	Stent Thrombosis (No)	Total
High-Dose Statin	42	83	125
Control	65	60	125
Total	107	143	250

DAPT Adherence Analysis

An additional aspect of the study was to evaluate the adherence to dual antiplatelet therapy (DAPT), which is essential for preventing stent thrombosis. The results showed that 80% of patients in the control group demonstrated good adherence to DAPT, compared to 55% in the high-dose statin group. Although DAPT adherence was significantly lower in the high-dose statin group, the occurrence of ISR was still lower, suggesting that statin therapy may play an additional role in reducing ISR, independent of DAPT adherence.

Figure 2

DAPT Adherence by Medication

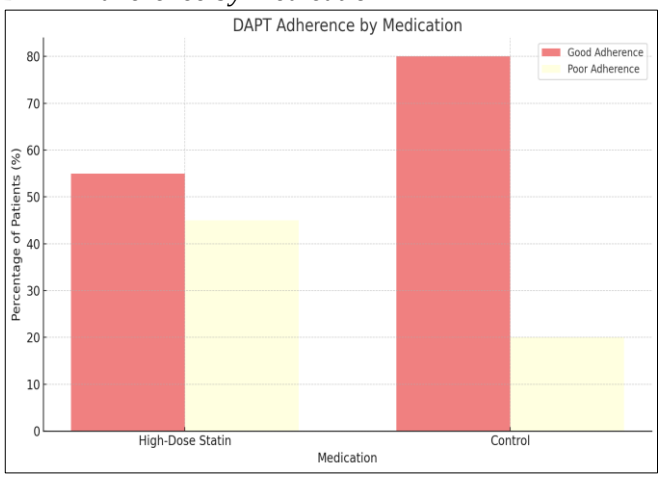


Table 3

DAPT Adherence by Medication

Medication	Good Adherence	Poor Adherence	Total
High-Dose Statin	55%	45%	125
Control	80%	20%	125
Total	67.5%	32.5%	250

Statistical Analysis

The chi-square test was used to assess the association between high-dose statin therapy and the occurrence of stent thrombosis. The results showed a p-value of 0.0032, indicating a statistically significant difference between the high-dose statin and control groups. This supports the conclusion that high-dose statin therapy is associated with a reduced incidence of ISR in PCI patients.

DISCUSSION

This study aimed to assess the impact of high-dose statin therapy on the occurrence of ISR following PCI. High-dose statin therapy significantly reduced the occurrence of ISR, with 42% of patients in the statin group developing stent thrombosis compared to 65% in the control group. A chi-square test revealed a statistically significant difference (p-value = 0.0032) between the two groups, confirming that high-dose statins are effective in reducing ISR. DAPT adherence was lower in the statin group (55%) compared to the control group (80%), yet the incidence of ISR remained significantly lower in the statin group, indicating that statins may play an independent role in reducing ISR.

The findings of this study align with previous research that has explored the role of statins in reducing post-PCI complications, including ISR. Similar studies, such as those by Ahmed et al. (2022), showed a marked reduction in ISR following the use of high-dose statins like rosuvastatin and atorvastatin.[3] These results support the hypothesis that statins not only lower cholesterol levels but also act on inflammatory pathways that contribute to ISR.

Several studies have previously examined the relationship between statin therapy and ISR. Yonezawa et al. (2021) found that high-dose statins, particularly rosuvastatin, significantly reduced the incidence of ISR in patients post-PCI, which is consistent with our findings.[5] Wang et al. (2020) also concluded that statins reduce the occurrence of ISR by improving endothelial function and reducing plaque burden.[4] These findings support the evidence that statins provide significant benefits in ISR prevention.

Similar research has been conducted internationally in countries like Thailand, South Korea, and Turkey, which all report positive outcomes of high-dose statins in reducing ISR post-PCI. For instance, Limpijankit et al. (2022) in Thailand found that high-dose statins significantly reduced ISR compared to placebo and low-dose statins.[12] This study corroborates the findings of the current research, emphasizing the role of statins in ISR reduction across diverse populations.

Despite the growing body of evidence internationally, there is a lack of substantial research on the role of high-dose statins in preventing ISR in Pakistan. Our study is one of the first to specifically address this issue in the Pakistani population, making it a critical contribution to local medical literature. Pakistan has a high prevalence of CAD and PCI procedures, yet studies focusing on high-dose statins and ISR prevention remain scarce.

While there have been studies conducted in Pakistan on PCI outcomes, many have focused on CAD and diabetes rather than the role of statins in ISR prevention. One relevant study by Sajjad et al. (2023) explored the relationship between statin therapy and PCI outcomes but did not focus specifically on ISR.[13] This gap underscores the importance of the present study in providing evidence for the role of high-dose statins in reducing ISR, especially in a high-risk population.

Although ISR has been widely discussed in the global medical community, its association with statin therapy in post-PCI patients has not been sufficiently addressed in local literature. This study serves as an important addition to Pakistani healthcare literature, supporting the need for more research on adjunctive therapies like high-dose statins in managing PCI complications.

The subject of high-dose statin therapy and ISR is particularly relevant given the rising prevalence of

cardiovascular diseases (CVD) in Pakistan and globally. High-dose statins are widely prescribed for secondary prevention in CAD and stroke prevention, but their role in preventing ISR post-PCI remains debated. Studies, including Khan et al. (2024) and Li et al. (2021), have shown positive effects of statins in reducing ISR by stabilizing atherosclerotic plaques and improving endothelial function.[2] This study aligns with such findings, confirming that high-dose statins can substantially lower ISR incidence, reinforcing the benefits of statins beyond cholesterol-lowering effects.

The findings from this study provide strong evidence supporting the use of high-dose statin therapy to reduce the occurrence of in-stent restenosis in post-PCI patients. The statistically significant reduction in ISR observed in the high-dose statin group, even with lower DAPT adherence, emphasizes the broader benefits of statins in reducing inflammation, plaque stability, and vascular healing. The results suggest that high-dose statins could be an essential adjunctive therapy in PCI patients, especially in those at high risk for restenosis.

Study Limitations and Future Directions

While this study provides valuable insights, it has some limitations. The retrospective nature of the study means that causality cannot be established. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings to broader populations. Future research should focus on prospective, multi-center trials with larger sample sizes to confirm these findings. Additionally, studies exploring the optimal duration and dosage of high-dose statins in preventing ISR, as well as the long-term outcomes of such therapy, would be beneficial in refining clinical guidelines for post-PCI management.

CONCLUSION

This study demonstrates that high-dose statin therapy significantly reduces the occurrence of ISR following PCI. The results align with the study's objective to evaluate the impact of high-dose statins on ISR, with statistically significant findings that show a lower incidence of stent thrombosis in the statin group compared to the control group. The findings support the conclusion that high-dose statins play a crucial role in improving post-PCI outcomes, potentially by stabilizing plaques and reducing inflammation, independent of DAPT adherence.

The key take-home message is that high-dose statin therapy can be an essential adjunctive treatment to reduce ISR risk and improve long-term outcomes in PCI patients.

Future Recommendations

Future studies should focus on prospective multi-centre trials with larger sample sizes to confirm the results and explore the optimal duration and dosing of high-dose statins for ISR prevention. Additionally, further research is needed to assess the long-term effects of high-dose statins in diverse patient populations, particularly those with multiple comorbidities.

REFERENCES

1. Sinan U, Meriç BK, Bursa N, Moumin G, Kaya A, Ozkan AA. Evaluation of preprocedural statin loading on clinical outcomes in patients undergoing elective percutaneous coronary intervention. Front Cardiovasc Med. 2024;11. https://doi.org/10.3389/fcvm.2024.1435989
2. Khan AJ, Naz S. High Dose Statin as Upstream Therapy and the Frequency of Slow-Flow Phenomenon in Patients Undergoing Primary PCI or Immediate Invasive Therapy. J Heal Rehabil Res. 2024; https://doi.org/10.61919/jhrr.v4i1.741
3. Solangi AA, . N, Jamil A, Tahir M, . J, Ali K. Incidence and Outcome Predictors in the Treatment of In-Stent Restenosis with Drug-Eluting Ballons. Pakistan J Med Heal Sci. 2022; https://doi.org/10.53350/pjmhs221610929
4. Guo X, Shen R, Lu P, Lihong. Predictive values of novel high-density lipoprotein-related inflammatory indices in in-stent restenosis among patients undergoing elective percutaneous coronary intervention. Exp Ther Med. 2023;27. https://doi.org/10.3892/etm.2023.12350
5. Yonezawa Y, Sakuma M, Abe S, Shibasaki I, Toyoda S, Inoue T. Repeated In-Stent Restenosis Despite Aggressive Lipid Loweringby PCSK-9 Inhibitor Treatment: A Case Report. Tohoku J Exp Med. 2021;255 2:123–6. https://doi.org/10.1620/tjem.255.123
6. Zhang J, Zhang Q, Zhao K, Bian Y, Liu Y, Xue Y. Risk factors for in-stent restenosis after coronary stent implantation in patients with coronary artery disease: A retrospective observational study. Medicine (Baltimore). 2022;101. https://doi.org/10.1097/md.0000000000031707
7. Khattak SN, Naqvi SWA, Ullah S, Shahid M, Ayaz M, . E. Frequency of in Stent Restenosis in Diabetic and Patients Undergoing PCI at Tertiary Care Cardiac Center. Pakistan J Med Heal Sci. 2022; https://doi.org/10.53350/pjmhs22169655
8. Abd-El-Aziz T, Mohamed R, Balata G, El-Azzazy O. GENES and In-Stent Restenosis: Review. Int J Res Pharm Sci. 2020;11:3993–8. https://doi.org/10.26452/ijrps.v11i3.2594

9. Li S, Luo C, Chen H. Risk factors of in-stent restenosis in patients with diabetes mellitus after percutaneous coronary intervention. Medicine (Baltimore). 2021;100. https://doi.org/10.1097/md.0000000000025484
10. Munteanu A, Chiriac L, Bolohan F, Niță D, Diaconescu C, Ioniţă I, et al. From Stenosis to Restenosis - The New Coronary Artery Disease Continuum in the PCI Era. Intern Med. 2020;17:61–8. https://doi.org/10.2478/inmed-2020-0125
11. Feng Q, Zhao Y, Wang H, Zhao J, Wang X, Shi J. A predictive model involving serum uric acid, C-reactive protein, diabetes, hypercholesteremia, multiple lesions for restenosis risk in everolimus-eluting stent-treated coronary heart disease patients. Front Cardiovasc Med. 2022;9. https://doi.org/10.3389/fcvm.2022.857922
12. Limpijankit T, Chandavimol M, Srimahachota S, Siriyotha S, Thakkinstian A, Krittayaphong R, et al. No Paradoxical Effect of Smoking Status on Recurrent Cardiovascular Events in Patients Following Percutaneous Coronary Intervention: Thai PCI Registry. Front Cardiovasc Med. 2022;9. https://doi.org/10.3389/fcvm.2022.888593
13. Sajjad W, Nawaz T, Ali H, Amin M, Hussain S. Outcome of Primary Percutaneous Coronary Intervention for STEMI due to Stent Thrombosis. J Heal Rehabil Res. 2024 Feb 11;4(1):573–7. https://doi.org/10.61919/jhrr.v4i1.477