



Original Article

Correlation between HbA1c levels and intrastent restenosis incidence in patients with diabetes mellitus after percutaneous coronary intervention at Dr. Saiful Anwar General Hospital

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ABSTRACT

Background: Patients with chronic uncontrolled diabetes mellitus as indicated by HbA1c levels $\geq 6.5\%$, increase the risk of atherosclerosis, thereby increasing in-stent restenosis incidence during and after percutaneous coronary intervention. Regular monitoring of HbA1c is crucial to reduce the incidence of in-stent restenosis.

Objective: This study aims to ascertain the correlation between HbA1c levels and in-stent restenosis incidence in diabetes mellitus patients after percutaneous coronary intervention at Dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia.

Methods/Design: Analytical observational study with a retrospective cohort study approach to determine the correlation between HbA1c levels and the incidence of in-stent restenosis in patients with diabetes mellitus after percutaneous coronary intervention. The research sample was carried out by consecutive sampling in January 2021-December 2023.

Results: This study has recruited 555 patients with coronary artery disease and diabetes mellitus. The average age of coronary heart disease patients with diabetes mellitus was 59 years. Patients with HbA1c levels ≥ 6.5 were more prone to experience in-stent restenosis 54 patients, while those with HbA1c levels < 6.5 were more prone not to experience in-stent restenosis 388 patients, indicating a significant correlation between HbA1c and in-stent restenosis $p=0.024$. in-stent restenosis was most frequently observed in the LAD 44 patients, RCA 13 patients, LCx 10 patients, and LM 0 patient. The highest percentage of in-stent restenosis cases was over 70%, with 3VD lesions being the most common 55 patients. OAD therapy is most often given to coronary heart disease patients with diabetes mellitus

Conclusion: There is a correlation between HbA1c levels and the incidence of in-stent restenosis in diabetes mellitus patients after percutaneous coronary intervention, underscoring the necessity for routine blood glucose monitoring to prevent in-stent restenosis.

1. Introduction

Diabetes mellitus (DM) is one of the independent predictors of coronary artery disease, which increases the risk of atherosclerosis. Conditions of hyperglycemia and insulin resistance can increase the risk of disorders of the vascular endothelium, which are associated with increased atherosclerosis, thereby increasing the risk of CAD. The formation of atherosclerosis due to hyperglycemia or insulin resistance can elevate the risk of complications during and after Percutaneous Coronary Intervention (PCI). In-stent stenosis (ISR) is a condition where there is a re-narrowing of the coronary lumen diameter by $\geq 50\%$ after PCI or CABG, confirmed through angiographic examination accompanied by ischemic symptoms. This is caused by endothelial layer damage, vascular smooth muscle cells (VSMC) proliferation, neointimal hyperplasia, and incomplete revascularization or progression of the atherosclerosis process, which will cause a decreased prognosis in patients with DM.¹⁻³

In-stent restenosis (ISR) is a condition of restenosis or reduction in the diameter of the coronary lumen after angioplasty and stent implantation caused by arterial damage due to neointimal hyperplasia. There are several mechanisms for ISR in patients with DM undergoing PCI, including the formation of neointimal hyperplasia. There are several mechanisms for ISR in patients with DM undergoing

PCI, including the formation of neointimal hyperplasia. Glycated hemoglobin (HbA1c) analysis is carried out to assess blood glucose for three months, according to the predicted age of red blood cells.⁴

Chronic uncontrolled hyperglycemia, as indicated by HbA1c levels $\geq 6.5\%$, increases the risk of ISR after PCI. Consistent surveillance of blood glucose levels with glycated hemoglobin HbA1c testing is essential for minimizing the occurrence of ISR.

This study aims to ascertain the correlation between HbA1c levels and the occurrence of in-stent restenosis in diabetes mellitus patients after percutaneous coronary intervention at Dr. Saiful Anwar Regional General Hospital in East Java Province.

2. Materials and Methods

Patients

This study included individual with diabetes mellitus and coronary artery disease who underwent PCI according to medical record data that met the inclusion criteria from January 2021 to December 2023. Patients who did not have diabetes mellitus had low medication adherence, experienced in-stent restenosis due to procedural actions, had incomplete medical records, or were unwilling to participate in the study were excluded.

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Procedure

This study involved collecting medical record data of diabetes mellitus patients with CAD who underwent PCI and then refining this data based on the study's inclusion and exclusion criteria. Following this, data was recorded and analyzed using SPSS 22.

Follow-up and Assessment

This study is an analytical observational study with a retrospective single-center cohort study approach to determine the correlation between HbA1c levels and the incidence of ISR in individual with DM after PCI at Dr. Saiful Anwar Regional General Hospital, Malang, East Java, Indonesia. This study used secondary data from medical records, laboratory results, and angiography. All examinations and therapies provided to patients were based on indications and under the Clinical Practice Guidelines of Dr. Saiful Anwar Regional General Hospital, thus complying with research ethics. The research sample was carried out by consecutive sampling in January 2021-December 2023. The process of obtaining research permits and using secondary data from patient medical records was

conducted according to the procedures for ethical research approval (No. 400/215/K.3/302/2020), medical record and calling the patient.

Statistical analysis

The collected data will be analyzed utilizing SPSS 22 to determine the correlation between HbA1c levels and the incidence of ISR in DM patients PCI at Dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia. Comparative analysis will be performed using the T-test for numerical scale and the Chi-square test for categorical scale compared diabetes mellitus patients with the incidence of ISR. Results will be considered significant if $p < 0.05$.

3. Results

Patient Characteristics

This study collected data on ISR incidents in coronary artery disease patients with DM who underwent PCI at Dr. Saiful Anwar Regional General Hospital, Malang, East Java Province, involving 555 subjects from January 2021 to December 2023.

Table 1. Baseline Characteristics of Patients

| Characteristic | Total (n=555) N (%) | ISR (n=67) N (%) | Non ISR (n=488) N (%) | P-value |
|----------------------------|------------------------|---------------------|--------------------------|---------|
| Age, y* | 59.69 ± 8.26 | 59.72 ± 8.63 | 59.68 ± 8.22 | 0.896 |
| Gender | | | | |
| Male | 199 (35.8) | 59 (88) | 140 (28.7) | 0.057 |
| Female | 356 (64.2) | 8 (11.9) | 348 (71.3) | |
| Comorbidities | | | | |
| Smoking | 167 (30.1) | 24 (35.8) | 143 (29.3) | 0.275 |
| Hypertension | 308 (55.7) | 38 (58.2) | 270 (55.3) | 0.656 |
| Dyslipidemia | 33 (5.9) | 5 (7.5) | 28 (5.7) | 0.580 |
| Laboratory analysis | | | | |
| HbA1c <6.5 | 401 (72.3) | 13 (19.4) | 388 (79.5) | 0.024** |
| HbA1c ≥6.5 | 154 (27.8) | 54 (80.6) | 100 (20.5) | |
| DM therapy | | | | |
| Insulin | 247 (44.5) | 26 (38.8) | 221 (45.3) | 0.603 |
| OAD | 292 (52.6) | 39 (59.1) | 253 (51.8) | |
| Insulin and OAD | 16 (2.9) | 2 (3.0) | 14 (2.9) | |
| Lesion of coroner | | | | |
| 1 VD | 25 (4.5) | 1 (1.5) | 24 (4.9) | 0.135 |
| 2 VD | 39 (7.0) | 1 (1.5) | 38 (7.8) | |
| 3 VD | 421 (75.9) | 55 (82.1) | 366 (75) | |
| 4 VD | 70 (12.6) | 10 (14.9) | 60 (12.3) | |

*Data are expressed as median (min-max, ** $p < 0.05$ ISR=in-stent restenosis OAD = Oral Antidiabetic Drugs

Table 1 shows that patients with CAD with DM have an average age of coronary heart disease patients with diabetes mellitus is 59 years, with no significant age difference between the ISR and non-ISR groups (p=0.896). Among these patients, 356 were female, with 8 ISR and 348 non-ISR. There was no significant correlation between gender and ISR (p=0.057). Comorbidities in ISR patients did not show significant results to smoking, hypertension, and dyslipidemia (p=0.275; p=0.656 and p=0.580). The most common therapy was OAD, but it showed no significant relationship with ISR (p=0.603). Patients with HbA1c levels ≥6.5 were more prone to experience ISR (54 patients), while those with HbA1c levels <6.5 were more prone not to experience ISR (388 patients). The highest percentage of 3VD lesions being the most common (55 patients). Oral anti-diabetic therapy is mostly given to CAD patients with DM both in the HbA1c <6.5 and HbA1c ≥6.5 groups but there was no significant relationship with HbA1c (p=0.968).

Table 2. DM therapy in CAD patient

| Variable | Total (n=555) | HbA1c <6.5 (n=401) | HbA1c ≥6.5 (n=154) | p-value |
|-------------------|---------------|--------------------|--------------------|---------|
| DM therapy | | | | |
| Insulin | 247 (44.5%) | 178 (44.4%) | 69 (44.8%) | 0.968 |
| OAD | 292 (52.6%) | 211 (52.6%) | 81 (52.6%) | |
| Insulin + OAD | 16 (2.9%) | 12 (3.0%) | 2 (2.6%) | |

Angiography Characteristics

Table 3. Characteristic Lesion of ISR

| Angiography Characteristic | (n=67) |
|----------------------------|--------|
| Lesion of ISR | |
| 51%-70% | 4 |
| >70% | 63 |
| ISR vessel | |
| LM | 0 |
| LAD | 44 |
| LCx | 10 |
| RCA | 13 |

ISR = Intra-stent restenosis; LM = Left Main Coronary Artery; LAD = Left Anterior Descending Artery; LCX = Left Circumflex Artery; RCA = Right Coronary Artery; VD = Vessel Disease

Table 3 explains that of 67 CAD patients with DM, ISR occurred in 63 of those with lesions >70% and 4 patients with lesions 51-70%. ISR was most frequently observed in the LAD (44 patients), RCA (13 patients), LCx (10 patients), and LM (0 patients).

Table 4 shows that LM had 10 calcified and 10 diffuse lesions. LAD had 97 CTO lesions, 29 ATO lesions, 193 calcified lesions, and 193 diffuse lesions. LCX had 68 CTO lesions, 9 ATO lesions, 50 calcified lesions, and 164 diffuse lesions. RCA showed 105 CTO lesions, 24 ATO lesions, 34 calcified lesions, and 110 diffuse lesions. Lesions in the Intermediate artery were diffuse in 18 of cases.

The purpose of this study was to assess the association between HbA1c levels and the incidence of ISR in DM patients after PCI, presented in Table 5 which explains a significant relationship/correlation between HbA1c levels and ISR in DM patients after PCI with p-value = 0.024 (p<0.005).

Table 5. Comparison of HbA1c levels in diabetes mellitus patients after percutaneous coronary intervention

| Variable | ISR (n=67) | Non-ISR (n=488) | Sig |
|------------|------------|-----------------|-------|
| HbA1C <6.5 | 13 (19.4) | 388 (79.5) | 0.024 |
| HbA1C ≥6.5 | 54 (80.6) | 100 (20.5) | |

4. Discussion

Patients with DM are the most of the critical risk factors for periprocedural myocardial infarction, stent thrombosis, ISR, and neo-atherosclerosis as a result of the atherosclerosis process, which increases in patients with poorly controlled DM.⁶ This condition can be associated with uncontrolled hyperglycemia, whether reflected by HbA1c levels that are not reached or the type of CAD intervention in the patient. Recently, based on research that has been conducted, the use of DES stents can reduce the incidence of ISR.^{2,3,5}

The mean age of the patients was 59 years, with a female majority of 76.9% and 11.9% experiencing ISR. The American Heart Association notes that diabetes in women is an independent risk factor for ischemic events during PCI, particularly for those needing insulin. This is associated with substantial systemic risks and depends on the treatment dosage. Therapy intensity in women often does not align with their underlying risk, and differences in the use of statins and antiplatelet drugs contribute to their vulnerability to poor outcomes after PCI. Additionally, the unique atherosclerotic phenotype in women, marked by non-obstructive coronary artery disease and narrowed lumen dimensions, along with increased thrombotic risk, can also be significant risk factors.⁴

Smoking can increase insulin resistance by reducing peripheral glucose metabolism, leading to high TG levels and low HDL-C levels. Additionally, Hypertension increases the occurrence of in-stent restenosis (ISR) in a group of 796 individuals who had angiography performed because of chronic angina or reversible myocardial ischemia.

Table 4. Characteristics of Vessel

| | LM (n=137) N (%) | LAD (n=465) N (%) | LCX (n=456) N (%) | RCA (n=430) N (%) | Inter mediate (n=18) N (%) |
|------------------|------------------|-------------------|-------------------|-------------------|----------------------------|
| CTO | | | | | |
| No | 137 (100) | 366 (78.71) | 386 (84.65) | 325 (75.58) | 18 (100) |
| Yes | 0 | 97 (21.29) | 68 (15.3) | 105 (24.42) | 0 |
| ATO | | | | | |
| No | 137 (100) | 434 (93.33) | 445 (97.58) | 406 (94.42) | 18 (100) |
| Yes | 0 | 29 (6.67) | 9 (2.42) | 24 (5.58) | 0 |
| Calcified | | | | | |
| No | 127 (22.9) | 272 (58.49) | 404 (88.59) | 396 (92.09) | 18 (100) |
| Yes | 10 (1.8) | 193 (41.51) | 50 (11.41) | 34 (7.91) | 0 |
| Diffused | | | | | |
| No | 127 (22.9) | 272 (58.49) | 292 (64.03) | 318 (74.30) | 16 (88.9) |
| Yes | 10 (1.8) | 193 (41.51) | 164 (35.94) | 110 (25.70) | 2 (11.1) |

*LM = Left Main Coronary Artery; LAD = Left Anterior Descending Artery; LCX = Left Circumflex Artery; RCA = Right Coronary Artery; VD = Vessel Disease; CTO = Chronic Total Occlusion; ATO = Acute Total Occlusion

Ensuring efficient management of blood pressure during the initial PCI procedure is associated with a 24% decrease in the risk of ISR.⁵

The risk of ISR in diabetic patients with HbA1c levels ≥ 6.5 is 2-4 times higher. Insulin and its receptors play a crucial role in restenosis due to increased intimal hyperplasia. The complex interaction of endothelial dysfunction caused by hyperglycemia, increased oxidative stress, and enhanced atherogenesis reinforces that diabetes mellitus is a consistent risk factor for ISR. Although before PCI HbA1c levels cannot accurately predict ISR, significant fluctuations in HbA1c during the procedure can be a notable risk factor. It is essential to consider other contributing factors such as gender, BMI, and blood pressure, which are associated with HbA1c fluctuations.⁹⁻¹²

Based on angiographic characteristics, LAD is the most common site for early ISR, with a larger diameter in early DES restenosis. Additionally, 58% of ISR cases occurred in the LAD. Coronary angiograms revealed that 38% of patients had 1VD, 35% had 2VD, and 27% had 3VD. In this study, Chronic Total Occlusion (CTO) occurred higher than Acute Total Occlusion (ATO), and was often associated with calcified or diffuse lesions. CTO lesions were highly calcified or fibrotic, making balloon passage and expansion difficult. Consequently, stent placement efforts could lead to vessel dissection or incomplete stent expansion. Previous research showed that among lesions treated with PCI, the highest severity was 55% of lesions being calcified.¹³⁻¹⁶

The angiographic risk factors encompass the measurement of the length of the stented lesion, complex lesions, and small vessel size. Individuals with narrower vessel have a higher likelihood of experiencing illnesses such as DM or multivessel CAD. The characteristics of the vascular and lesions include a tortuous segment, a calcified vessel, a vessel segment with a varied caliber, bifurcation lesions, potential stent strut fractures, and ultimately, stent under expansion. Stent strut fractures and finally stent underexpansion are possible.^{17,18}

This research has research limitations. We need to strengthen the research by carrying out repeated HbA1c evaluations because in this study only one HbA1c level examination was carried out with two independent operators to increase objectivity and extend the follow-up period to understand long-term clinical results.

5. Conclusion

This study concluded that there is a correlation between HbA1c levels and the incidence of intra-stent restenosis in diabetes mellitus patients following percutaneous coronary intervention. Thus, monitoring blood glucose levels is essential to prevent intra-stent restenosis in patients after percutaneous coronary intervention.

6. Declaration

6.1 Ethics Approval and Consent to participate

The subjects in this study are humans, so ethical rules must be followed. This research has passed the ethical due diligence, approved based on the Certificate of Ethical Eligibility No. No. 400/215/K.3/302/2020 issued by the Health Research Ethics Committee at Dr. Saiful Anwar Malang.

6.2. Consent for publication

Not applicable.

6.3 Availability of data and materials

Data used in our study were presented in the main text.

6.4 Competing interests

Not applicable.

6.5 Funding Source

Not applicable.

6.6 Authors contributions

Idea/concept: HIM. Design: HIM. Control/supervision: IP, MSR. Data collection/processing: HIM. Analysis/interpretation: HIM. Literature review: HIM. Writing the article: HIM. Critical review: IP, MSR. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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