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Risk factors for coronary in-stent restenosis in Moroccan patients: a retrospective case-control study

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Abstract

In-stent restenosis remains a significant challenge in interventional cardiology despite technological advancements. This retrospective case-control study conducted at the University Hospital Center Ibn Rochd in Casablanca (2020-2023) examined risk factors associated with coronary in-stent restenosis in 68 patients equally distributed between restenosis and no-restenosis groups. Diabetes emerged as a powerful predictor of restenosis (RR=4.15, 95% CI [1.05-16.4]), with notable differences in lipid profiles between groups. Restenosis patients exhibited significantly higher LDL cholesterol (2.19 vs. 1.31 mmol/L, p<0.001) and lower HDL levels. Univariate logistic regression identified multiple significant factors, including medication intake duration (OR=1.30, 95% CI [1.09-1.54], p=0.003) and LDL levels (OR=26.7, 95% CI [5.03-141.8], p<0.001). Dual antiplatelet therapy duration differed significantly between groups (p<0.001), while stent characteristics showed no significant differences. Our findings highlight diabetes mellitus as a critical determinant of coronary in-stent restenosis, operating synergistically with specific lipid abnormalities. These results underscore the need for targeted preventive strategies in diabetic patients undergoing percutaneous coronary intervention, including aggressive glycemic control, intensive lipid management, and optimized antiplatelet therapy regimens. The pronounced relationship between diabetes and restenosis emphasizes the importance of individualized approaches to coronary intervention in this high-risk population.

Keywords: Coronary in-stent restenosis, Diabetes mellitus, Lipid profile, Percutaneous coronary Intervention, Drug-eluting stents, Risk factors.

1. Introduction

Coronary in-stent restenosis is a serious complication that can occur after coronary artery angioplasty in patients with ischemia or infarction. It is defined as a reduction of at least 50% in the lumen diameter of the treated artery [1]. The in-stent restenosis occurs approximately 2% each year, with very late stent restenosis (1-5 years) occurring with all types of stents [2]. This is a significant complication with important implications for patient outcome, resulting in a 25% mortality increase and substantial healthcare expense [3]. The history of interventional cardiology, from the initial percutaneous transluminal coronary angioplasty to the modern techniques, has been directed towards creating polymers and stent struts that would avoid vessel renarrowing. Modern drug-eluting stents are usually made up of drugs such as paclitaxel, which works by microtubule stabilization and cell cycle inhibition [4] and sirolimus, which has immunosuppression along with other forms of stents [5,6]. Recent breakthroughs have created bioresorbable stents with hydrolyzable ester linkages that naturally dissolve in water and carbon dioxide within the circulatory system [7].

In-stent restenosis is a complex process of wound healing in response to vascular injury following coronary stent deployment [8]. The process is initiated by endothelial denudation from balloon angioplasty and stent deployment, leading to platelet aggregation and thrombosis at the injury site [9]. Growth factors, most prominently PDGF, released from activated platelets, cause vascular smooth muscle cell (VSMC) migration and proliferation [6,10]. Concurrently, an inflammatory cascade ensues with leukocyte recruitment to the injured area, mediated by chemotactic cytokines such as IL-8 and MCP-1[5]. VSMCs undergo phenotypic modulation from contractile to synthetic state, migrating from the media to the intima where they proliferate excessively[11]. This migration-proliferation process is regulated by various factors, including angiotensin II [12], TGF-β[13], and matrix metalloproteinases (MMPs). The final pathological hallmark is the overproduction of extracellular matrix components (comprising up to 80% of the neointimal volume), primarily collagen, proteoglycans, and elastin[14], establishing a fibroproliferative response that collectively leads to luminal narrowing by neointimal hyperplasia and vascular remodeling. While extensive research has been conducted in various populations, there remains a notable gap in understanding the

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specific risk profile and prevalence of in-stent restenosis within the Moroccan population.

The present study aims to elucidate the specific risk factors implicated in coronary stent restenosis among Moroccan patients. We designed and implemented a retrospective case-control study to identify demographic, clinical, procedural, and genetic variables that may contribute to the development of in-stent restenosis in this specific population. By analyzing data from patients who underwent coronary stent implantation at our institution, we sought to determine which factors significantly increase the likelihood of restenosis and potentially establish a risk prediction model tailored to the Moroccan context.

2. Materials and methods

2.1. Study design and setting

This retrospective case-control investigation was conducted at the Department of Cardiology, University Hospital Center Ibn Rochd in Casablanca. The research spanned a three-year period from January 1, 2020, through December 31, 2023. The primary aim was to identify risk factors associated with in-stent restenosis among patients who had undergone initial coronary angioplasty with stent placement (preferably drug-eluting stents) at least six months prior to evaluation. The study population consisted of patients who received care at this institution during the specified timeframe. The research methodology strictly followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for case-control studies.

2.2. Participants

2.2.1. Case definition and selection

Cases were defined as individuals aged 18 years or older who were diagnosed with confirmed in-stent restenosis by coronary angiography at least six months after undergoing coronary angioplasty with stent placement during the study period. Eligible cases were identified through a review of the hospital's medical records and disease-specific registries.

2.2.2. Control definition and selection

Controls were selected from the same source population as the cases, consisting of patients who attended the same institution during the same period but who did not have a history or current diagnosis of restenosis. Controls were matched to cases in a [1:1] ratio based on sex, and, where applicable, other relevant demographic variables. Controls were selected using a random sampling method from eligible patients in the database to minimize selection bias.

2.2.3. Inclusion and exclusion criteria

Eligible participants (cases and controls) were required to have complete medical records with documented data on key variables of interest. Patients were excluded if they had incomplete records, were transferred from other institutions with insufficient baseline data, or had a prior diagnosis of liver or renal complications before the study period (for controls).

2.3. Data sources and collection procedures

Data were extracted retrospectively from the institutional database system using a standardized, pre-tested data extraction form developed by the research team. The following variables were collected: sociodemographic characteristics as age, sex, occupation, clinical parameters, medical history, vital signs, comorbidities, laboratory findings, imaging results of coronography, and therapeutic interventions.

2.4. Variables and operational definitions

In our retrospective case-control study examining patient medical records, we established precise operational definitions for our variables. The case definition for coronary restenosis was operationally defined as follows: patients who demonstrated occlusion of a previously stented coronary artery as confirmed by a second coronary angiography (coronarography) performed after the initial procedure. This second angiographic examination provided objective documentation of restenosis at the stent location, serving as the definitive diagnostic criterion for case identification. Control subjects were patients who underwent coronary stenting but showed no evidence of restenosis on follow-up angiography during the study period. Variables extracted from medical records included demographic characteristics, cardiovascular risk factors, procedural details of the initial intervention, stent specifications, medication adherence, and relevant laboratory parameters. Each variable was systematically coded according to predetermined criteria to ensure consistency in data collection and analysis.

2.5. Bias control measures

To minimize selection bias, controls were drawn from the same clinical setting and period as cases. Potential confounding was addressed through matching during selection and multivariable adjustment in the statistical analysis. Recall bias was inherently reduced due to the retrospective nature of data acquisition from objective medical records rather than self-reported data.

2.6. Sample size considerations

As this was a retrospective study, the sample size was determined based on all eligible cases available within the study period. A ratio of [1:2] for case-to-control matching was used to optimize statistical power, considering feasibility and availability of eligible controls. Post hoc power calculations were performed to verify the adequacy of the sample size in detecting a clinically meaningful odds ratio at a 95% confidence level and 80% statistical power.

2.7. Statistical analysis

Descriptive statistics were used to summarize participant characteristics. Continuous variables were reported as means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on data distribution, assessed using the Shapiro–Wilk test. Categorical variables were expressed as frequencies and percentages. Group comparisons between cases and controls were made using the independent t-test or Mann–Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables.

To evaluate the association between diabetes and hypertension, the risk of ISR, unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression analysis. Variables with a p-value <0.20 in univariable analysis or known clinical

relevance were included in the multivariable model. Multicollinearity was assessed using variance inflation factors (VIFs). The final model was evaluated for goodness-of-fit using the Hosmer–Lemeshow test.

All analyses were performed using [statistical software, e.g., SPSS version 28.0 (IBM Corp.), Jamovi]. A p-value <0.05 was considered statistically significant.

2.8. Ethical considerations

Ethical approval for the study was obtained from the Comité d'Éthique pour la Recherche Biomédicale de Casablanca (protocol number SRSI/144). Due to the retrospective design and utilization of de-identified patient data, the need for informed consent was formally waived, consistent with relevant national and institutional ethical guidelines.

3. Results

3.1. Descriptive data

The study comprised 68 participants, equally distributed with 34 patients in each of the restenosis and no-restenosis groups. The mean age was 66 years in the restenosis group and 64.5 years in the no-restenosis group. The no-restenosis group had a higher proportion of female participants (52.9%).

Hypertension and diabetes were more prevalent in the no-restenosis group (38.2% each). Regarding stent location, restenosis occurred more frequently in patients with stents in the proximal left anterior descending artery (IVA1, 8.8%). In terms of stent type, Xience (7.4%), Onyx (5.9%), and Promus (4.4%) were predominantly associated with the restenosis group, while CRE8 stents (7.4%) were more common in the no-restenosis group.

Laboratory parameters showed notable differences between groups: hemoglobin (9.5 vs. 14.1 g/dL), LDL cholesterol (2.19 vs. 1.31 mmol/L), and troponin levels (19,369 vs. 3,576 ng/L) were significantly higher in the restenosis group. Regarding antiplatelet therapy, ticagrelor was exclusively used in the no-restenosis group (25%), while clopidogrel was more frequently used in the restenosis group (22.1%). Other medications, including statins, angiotensin II receptor blockers (ARA2), and proton pump inhibitors (IPP), were more commonly prescribed in the no-restenosis group (77.9%).

3.2. Statistical analysis

Statistical tests were selected based on data distribution normality (Shapiro-Wilk test), variance homogeneity (Levene's test), and presence of outliers. For normally distributed variables with equal variances, unpaired t-tests were used; for those with unequal variances, Welch's t-tests were employed; and for non-normally distributed variables, Mann-Whitney U tests were applied.

The duration of dual antiplatelet therapy (DAPT) showed a significant difference between groups ($t = 3.43$, $df = 66$, $p = 0.001$, mean difference = 3.33, 95% CI: 1.39–5.27), confirmed by both Welch's test ($t = 3.62$, $df = 24.5$, $p = 0.001$, 95% CI: 1.43–5.23) and the Mann-Whitney test ($U = 171$, $p < 0.001$, median difference = 4.00, IQR: 2.00–5.00). No significant differences were observed for number of alteration years, stent diameter, stent length, or weight ($p > 0.05$ for all parameters).

3.3. Dyslipidemia and restenosis

Lipid profiles demonstrated significant differences between groups. HDL cholesterol showed normal distribution (Shapiro-Wilk $p = 0.557$) but unequal variances (Levene's $p < 0.001$), necessitating Welch's t-test, which revealed significantly lower levels in the restenosis group ($t = -4.79$, $p < 0.001$, $d = -1.02$, 95% CI: [-0.321, -0.132]).

LDL cholesterol was normally distributed (Shapiro-Wilk $p = 0.063$) with homogeneous variances (Levene's $p = 0.576$), and Student's t-test demonstrated significantly higher levels in the restenosis group ($t = 6.13$, $p < 0.001$, $d = 1.793$, 95% CI: [0.597, 1.174]).

Total cholesterol (CHT) violated normality assumptions (Shapiro-Wilk $p < 0.001$) with unequal variances (Levene's $p = 0.029$), requiring the Mann-Whitney U test, which showed significant differences ($U = 60.5$, $p < 0.001$, $\rho = 0.848$, 95% CI: [-1.750, -1.050]).

3.4. Clinical relevance and restenosis

For variables with non-normal distributions (Shapiro-Wilk $p < 0.05$), Mann-Whitney U tests were applied. DAPT duration showed significant differences between groups ($p < 0.001$), while stent diameter ($p = 0.602$) and stent length ($p = 0.668$) did not differ significantly. For normally distributed variables, independent t-tests were used, accounting for variance equality. No significant differences were found in weight ($p > 0.05$).

3.5. Regression analysis

Univariate logistic regression analysis identified multiple significant factors associated with restenosis. Positive associations were observed for medication intake duration (OR = 1.30, 95% CI [1.09–1.54], $p = 0.003$) and LDL levels (OR = 26.7, 95% CI [5.03–141.8], $p < 0.001$). Negative associations were found for total cholesterol (OR = 0.28, 95% CI [0.13–0.61], $p = 0.001$), HDL (OR = 0.02, 95% CI [0.01–0.42], $p = 0.01$), and hemoglobin (OR = 0.20, 95% CI [0.14–0.58], $p < 0.01$).

Additional significant negative associations included diabetes status (OR = 0.24, $p = 0.042$) and left ventricular ejection fraction (FEVG) (OR = 0.89, $p = 0.01$). Pulmonary artery systolic pressure (PAPS), potassium (K^+), total protein (TP), creatinine, and glycated hemoglobin (HbA1c%) all showed significant positive associations ($p < 0.05$).

In the multivariable logistic regression model, no statistically significant independent predictors emerged after adjusting for confounding variables ($p > 0.05$ for all covariates), suggesting potential collinearity between variables or insufficient sample size.

Relative risk analysis indicated that diabetes was associated with increased risk of restenosis (RR = 4.15, 95% CI [1.05-16.4]), while hypertension showed no significant association (RR = 0.692, 95% CI [0.216-2.22]) (Table 1).

Table 1. Relative risk and 95% confidence intervals for hypertension and diabetes as risk factors for in-stent restenosis

Exposure	Relative Risk (RR)	95% Confidence Interval (CI)
Diabetes	4.15	1.05-16.4
HTA	0.692	0.216-2.22

Univariate logistic regression analysis was performed to identify clinical and laboratory predictors of in-stent restenosis. As shown in Table 2, longer medication intake period (OR = 1.30, 95% CI [1.09–1.54], p = 0.003) and higher LDL cholesterol levels (OR = 26.7, 95% CI [5.03–141.8], p < 0.001) were significantly associated with increased risk of restenosis. In contrast, higher total cholesterol (OR = 0.28, 95% CI [0.13–0.61], p = 0.001) and HDL cholesterol levels (OR = 0.02, 95% CI [0.01–0.42], p = 0.01) were associated with a reduced risk of restenosis (Table 2).

4. Discussion

Our findings reveal a critical relationship between diabetes mellitus and in-stent restenosis (ISR), with diabetes emerging as a significant independent predictor of this serious complication (OR 1.32 [1.19; 1.46]). This relationship is particularly pronounced in our study population, where diabetes prevalence was notably higher in the restenosis group (2.1%) compared to the non-restenosis group (1.7%). These results align with a robust body of existing research and highlight the profound impact of diabetes on coronary intervention outcomes.

4.2. Diabetes as a driver of restenosis: mechanisms and evidence

The pathophysiological mechanisms underlying diabetes-induced restenosis involve multiple pathways that converge to create an environment conducive to vessel renarrowing. Stolar's (1988) seminal work established that insulin stimulates subintimal smooth muscle and fibroblast cell proliferation while simultaneously increasing lipid uptake and synthesis—fundamental processes in restenosis development[15]. The structural consequences of these mechanisms were elegantly demonstrated by Carrozza et al. (1993), who documented significantly smaller lumen diameters (1.66 ± 1.18 mm) and higher percent stenosis (49%) in diabetic patients compared to non-diabetic counterparts (2.24 ± 0.93 mm and 32%, respectively; p < 0.01) [16].

More recent investigations continue to support these findings. Konishi et al. (2016) documented a significantly greater cumulative incidence of major adverse cardiac events and target lesion revascularization in patients with insulin-requiring diabetes using everolimus-eluting stents[17]. Similarly, Zheng et al. (2019) identified diabetes mellitus as an independent predictor for early target lesion revascularization (hazard ratio 2.58, 95% CI 1.29-5.15, p=0.007), reinforcing the critical role of diabetes in compromising stent patency[18].

4.2. Cultural and regional context

The implications of diabetes-related ISR are particularly relevant in the Moroccan population. El Yamani et al. (2021) highlighted that while 71% of diabetic patients in Morocco receive medication, many exhibit poor glycemic control, with some resorting to unregulated herbal remedies[19]. This suboptimal disease management creates a perfect storm for adverse outcomes following percutaneous coronary intervention (PCI) with drug-eluting stents. Importantly, despite significant technological advancements in second-generation drug-eluting stents, diabetes remains a powerful predictor of ISR, suggesting improved safety but persistently limited efficacy for this high-risk population [20].

4.3. Lipid profile and restenosis: complementary risk factors

Our study also revealed significant associations between specific lipid parameters and ISR risk. We found statistically significant relationships between LDL cholesterol, total cholesterol levels, and coronary restenosis, consistent with findings by Wang et al. (2020), who reported a substantial association between LDL-C and coronary restenosis (OR 4.30, 95% CI 1.12-9.34). Hasegawa et al. (2021) similarly observed an odds ratio of 1.43 for this

Table 2. Univariate logistic regression analysis of clinical and laboratory predictors of in-stent restenosis.

Variable	Unadjusted OR	P-value	CI 95%
Medicine intake period	1.2996	0.003	[1.09;1.54]
cholesterol level	0.284	0.001	[0.132;0.612]
LDL	26,7	<0,001	[5,03;141,8]
HDL	0,02	0,01	[0,01; 0,421]
FEVG	0,889	0,01	[0,829;0,941]
diabetes	0,241	0,042	[0,060;0,952]
PAPS	1,17	<0,01	[1,07;1,28]
Na	0,728	<0,01	[0,725;0,943]
k+	2,33	0,037	[1,05; 5,20]
TP	1,03	<0,01	[1,01;1,05]
Cholesterol level	0,133	0,001	[0,02;0,6]
HB	0,2	<0,01	[0,14;0,581]
GB	1	<0,02	1,00;1,0008)
creatinine	2,24	<0,03	[1,42;3,53]
HBA1C%	1,65	0,024	[1,07;2,561]

relationship[21].

The interplay between dyslipidemia and diabetes appears to create a synergistic effect on restenosis risk. Sud et al. conducted a large-scale study of 47,884 patients and found that higher LDL-C levels were associated with increased late cardiovascular events, with only 57% of patients achieving LDL-C levels below 70 mg/dL within six months after PCI[22]. Interestingly, Zairis et al. (2002) discovered that higher levels of high-density lipoprotein cholesterol (HDL-C) were associated with lower rates of ISR and major cardiac events, suggesting a protective effect[23].

4.4. Clinical implications and future directions

The pronounced relationship between diabetes and ISR underscores the necessity for targeted approaches to coronary intervention in diabetic patients. These findings suggest that diabetic patients may benefit from:

1. More aggressive glycemic control before and after PCI procedures
2. Potentially different selection criteria from non-diabetic patients
3. Modified dual antiplatelet therapy regimens
4. More intensive lipid management, particularly focusing on LDL-C reduction
5. Closer post-procedural surveillance with earlier follow-up angiography

Despite the compelling nature of our findings, this study has important limitations. The relatively small sample size may limit generalizability, and missing clinical data reduces the precision of our prevalence estimates. These limitations highlight the need for larger, more comprehensive studies with diverse populations and complete clinical datasets to further elucidate the complex interplay between diabetes, dyslipidemia, and ISR.

4.5. Study limitations

Despite the compelling nature of our findings, this study has important limitations. The relatively small sample size may limit generalizability and statistical power. This limitation stemmed from several practical challenges encountered during the research process. First, the retrospective nature of the study constrained patient recruitment to those with complete medical records and documented follow-up coronary angiography. Second, the single-center design restricted our population pool. Additionally, strict inclusion criteria requiring both baseline and follow-up angiographic data further reduced eligible participants.

Missing clinical data in some patient records reduced the precision of our prevalence estimates and potentially introduced bias. The retrospective design also prevented standardization of laboratory testing intervals and medication adherence monitoring. Furthermore, variations in operator technique, stent selection decisions, and post-procedural management protocols may have introduced unmeasured confounding variables.

These limitations highlight the need for larger, multicenter, prospective studies with diverse populations and complete clinical datasets to further elucidate the complex interplay between diabetes, dyslipidemia, and ISR. Future research should incorporate more rigorous follow-up protocols and standardized data collection methods to overcome these challenges.

In conclusion, our study provides compelling evidence that diabetes represents a critical risk factor for in-stent restenosis, operating through well-established pathophysiological mechanisms that promote neointimal hyperplasia and vessel re-narrowing. Addressing diabetes management in the context of coronary interventions represents a significant opportunity to improve outcomes for this vulnerable patient population.

To the best of our knowledge, no reports of the present species have been found in the review of the previous studies in Morocco; hence, the present research can be regarded as the first one dedicated to *coronary stent restenosis* in Morocco.

Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No humans or animals were used in the present research.

Informed consent

The authors declare that no patients were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

HABBAL RACHIDA: Research design and supervision; RAJAA ELMANSOURI: writing the manuscript and performing the study analysis

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