

Risk factors for restenosis after coronary angioplasty

Factores de riesgo de reestenosis tras angioplastia coronaria

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Abstract

Percutaneous coronary intervention (PCI) is the gold standard regarding the management of ST-elevation myocardial infarction.

PCI has proven superior to fibrinolysis in reducing mortality, reinfarction, and stroke rates, provided recommended time-lapses are achievable. However, like any medical procedure, there is room for failure, known as restenosis in the case of non-stent strategy and in-stent restenosis (ISR) in the case of stent-dependent strategies. Nearly 10% of all PCI develop ISR, most commonly treated with another intervention. Several risk factors have been reported across the literature to identify which patients are the most likely to develop this complication. Proper risk management can lead to the prevention of this complication; therefore, it is imperative for physicians to accurately identify relevant risk factors that have enough evidence backing their impact. This review aims to identify the most relevant quantifiable risk factors for ISR to analyze their contribution to the incidence of this complication.

Keywords: Percutaneous coronary intervention, in-stent restenosis, ST-elevation myocardial infarction, cardiovascular disease, coronary angioplasty.

Resumen

La intervención coronaria percutánea (ICP) es el estándar de oro en el manejo del infarto agudo de miocardio con elevación del segmento ST. La ICP ha demostrado ser superior a la fibrinólisis en la reducción de la mortalidad, el reinfarto y las tasas de accidente cerebrovascular, siempre que se cumplan los intervalos de tiempo recomendados. Sin embargo, como en cualquier procedimiento médico, existe la posibilidad de fallo, conocido como reestenosis en los casos sin stent, y reestenosis intrastent (RIS) en las estrategias dependientes de stent. Aproximadamente el 10% de todas las ICP desarrollan RIS, que en la mayoría de los casos se trata mediante una nueva intervención. Diversos factores de riesgo han sido descritos en la literatura para identificar qué pacientes tienen mayor probabilidad de desarrollar esta complicación. Un manejo adecuado del riesgo puede prevenirla; por lo tanto, es fundamental que los médicos identifiquen con precisión los factores de riesgo relevantes con evidencia sólida que respalde su impacto. Esta revisión tiene como objetivo identificar los factores de riesgo cuantificables más relevantes para la RIS, a fin de analizar su contribución a la incidencia de esta complicación.

Palabras clave: intervención coronaria percutánea, reestenosis intrastent, infarto agudo de miocardio con elevación del ST, enfermedad cardiovascular, angioplastia coronaria.

Cardiovascular disease (CVD), primarily ischemic heart disease (IHD) and stroke, remain the leading global cause of mortality and disability. CVD incidence has steadily increased over the last decades, parallel to the increased prevalence of obesity, diabetes mellitus (DM), metabolic syndrome (MS), and unhealthy habits¹. Total cases of CVD nearly doubled from 271 million in 1990 to over 520 million in 2019, while mortality attributable to CVD increased from 12 million to 18.6 million². Moreover, it was projected that CVD would cause more than 23 million deaths in 2030 worldwide if no preventive measures were considered³. Likewise, CVD are responsible for a considerable reduction in the quality of life and life expectancy of patients⁴. In addition, CVD represent an enormous cost for healthcare systems; the United States alone spends over US \$320 billion in healthcare costs and lost productivity due to CVD⁵.

Considering the economic and quality of life impact of CVD, particularly that of IHD and stroke, it has been a priority to develop effective diagnostic and therapeutic protocols. Proper adherence to the European Society of Cardiology (ESC) guidelines regarding IHD tends to result in early diagnosis and satisfactory evolution⁶. According to the guidelines above, percutaneous coronary intervention (PCI) is the gold standard regarding ST-elevation myocardial infarction (STEMI) management. PCI has proven superior to fibrinolysis in reducing mortality, reinfarction, and stroke rates, provided recommended time-lapses are achievable⁷. Additionally, a considerable amount of evidence supports that early PCI intervention provides the most benefits regarding the quality of life, life expectancy, and significant reduction in healthcare costs, both long and short term⁸.

However, like any medical procedure, there is room for failure, known as restenosis in the case of non-stent strategy and in-stent restenosis (ISR) in the case of stent-dependent strategies. Nearly 10% of all PCI develop ISR, most commonly treated with another intervention⁹. Several risk factors have been reported across the literature to identify which patients are the most likely to develop this complication. Proper risk management can lead to the prevention of this complication; therefore, it is imperative for physicians to accurately identify relevant risk factors that have enough evidence backing their impact¹⁰. This review aims to identify the most relevant quantifiable risk factors for ISR to analyze their contribution to the incidence of this complication.

RISK FACTORS FOR IN-STENT RESTENOSIS: WHAT DOES THE EVIDENCE SAY?

Restenosis is a significant reduction in vascular lumen diameter after any PCI is performed. The most accepted mechanism for restenosis in non-stent PCI is vessel remodeling and elastic recoil; however, when stents are used, the mechanism is either more dependent on excessive neointimal proliferation, or new-onset atherosclerosis¹¹. Nonetheless, due to their high restenosis risk, non-stent strategies are heavily restricted to patients in whom stent-related procedures are absolutely contraindicated; as a result, most PCI procedures include a stent¹². Therefore, this review will mainly focus on risk factors for restenosis in stent-related PCI.

It is logical to assume that conditions that increase the risk of IHD also increase the risk of restenosis. For example, DM has proven to be an independent risk factor for developing IHD; diabetic patients have greater fatality rates and higher post-infarction complication rates¹³. Regarding ISR, evidence shows that diabetic patients have significantly increased restenosis rates compared to the general population, nearly twofold higher (63% vs. 36%; $P=0.0002$)¹⁴. Furthermore, it has been reported that laboratory parameters such as uric acid (UA) and very low-density lipoprotein cholesterol (VLDL-C) have an excellent positive predictive value for ISR in diabetic patients. Wang et al.¹⁵ demonstrated that increased VLDL-C had a hazard ratio (HR) of 1.85 (95% CI: 1.24-2.77, $P=0.002$); likewise, every 50 $\mu\text{mol/L}$ increment in UA raised the HR by 1.19 (95% CI: 1.05-1.34, $P=0.006$).

Similarly, neutrophil-to-lymphocyte ratios (16), visit-to-visit HbA1c¹⁷, specific antidiabetic treatment¹⁸, and several other factors have been reported to contribute to ISR risk. Nonetheless, most of the currently available evidence regarding restenosis in patients with DM has been performed as single-center research with single-factor analysis, whereas multi-center and extensive sample size studies are lacking. In addition, some of them even suggest there is no correlation between DM and ISR¹⁹. DM indisputably increases the risk of ISR, according to most available evidence obtained through proper methodology. However, independent risk factors that enable the physician to identify high-risk subgroups need further high-quality investigation. Currently, an ongoing meta-analysis aims to answer some of the above questions; nonetheless, results are yet to be published²⁰.

Other risk factors for restenosis have been extensively reported in the general population. For instance, hyper-sensitive C-reactive protein (hs-CRP) levels have been correlated with a higher incidence of restenosis. Li et al.²¹ performed a meta-analysis that, despite the heterogeneity across the studies, concluded that preprocedurally elevated levels of CRP were associated with greater ISR rates. The Z-score for the overall effect of CRP levels was 2.12 ($P=0.03$). Nonetheless, a more recent and higher quality meta-analysis analyzed nine clinical trials

with over 1000 patients and further studied this variable. According to the study, baseline preprocedurally hs-CRP levels were not associated with predicting ISR among patients receiving stent implantation. However, an increased risk of ISR was associated with increased hs-CRP levels at 6 and 12 months of follow-up, which was remarkably higher in elderly and diabetic patients²².

On the other hand, homocysteine has also been targeted as a positive predictive factor for restenosis in PCI patients. Cheng et al.¹⁰ reported that postoperative homocysteine was associated with a higher risk of ISR, among other positive findings such as hs-CRP and history of DM. However, a recent systematic review found that homocysteine levels were not associated with an increased risk of restenosis following stent implantation (relative risk (RR) = 1.10, 95% CI: 0.90-1.33). However, higher homocysteine levels significantly increased the risk of all-cause mortality by an average of 3.19-fold²³. Despite homocysteine not being an excellent positive predictive factor for restenosis, it was recently reported that it could be a good predictive factor for restenosis severity. A recent study found that elevated homocysteine values were positively correlated with ISR severity, with a sensitivity of 45% and specificity of 88.1%. Notwithstanding, further research is needed, given the controversial background of homocysteine and ISR²⁴.

Another observational study enlisted 256 patients with IHD treated with PCI that were subsequently followed by angiography. Nearly 59% of the patients developed ISR, and three multivariate logistic regression models were conducted to determine the role of low-density lipoprotein (LDL)/ high-density lipoprotein (HDL) ratio. A higher LDL/HDL ratio was significantly associated with the risk of ISR (odds ratio (OR) 2.00; $p < 0.05$ for all three models). An excellent positive predictive performance was found for LDL/HDL ratio for ISR with an area under the curve of 0.74²⁵. Similarly, other investigations have shown that serum levels of apolipoprotein A-I (ApoA1), a major structural and functional component of HDL, correlate with ISR risk. On multivariate logistic regression analysis, ApoA1 was found to be an independent risk factor for the early appearance of ISR. The incidence of ISR negatively correlated with ApoA1, meaning that lower levels of this molecule confer increased risk for ISR²⁶.

Anemia is another common factor that has been reported in several investigations. For example, a retrospective study showed through univariate logistic regression analyses that anemia significantly increased the risk of ISR (OR: 4.283; 95% CI, 1.94-9.41; $P < 0.001$). Moreover, the same research demonstrated that other conditions, such as chronic kidney disease (CKD) and high LDL levels significantly increased the risk of ISR. Likewise, it was reported that multiple stenting and diameter were also linked to ISR²⁷. In congruence with the above, Zhou et al.²⁸ found that stent diameter correlated with the risk of ISR. Analyses found that a negative correlation was present at minimum stent diameter (OR=0.28, 95% CI,

0.09-0.86, $p=0.03$). Stent diameter under 3 millimeters was consistent with the risk assumption.

Moreover, the number of stents implemented during the procedure was recently reported to be a risk factor for ISR. A retrospective study with over 2000 cases reported through univariate analysis that a higher number of stents increased the risk of ISR (OR: 1.30, 95% CI; 1.15-1.47, $P < 0.001$). Multi-factor regression analysis showed that compared to 1-2 stents, the OR for 3-5 stents and more than six stents were 2.20 and 5.33, respectively. This was especially true for patients under 50, females, and those who received drug-eluting stents and sirolimus-eluting stents²⁹. The National Institute for Health and Care Excellence (NICE) has updated recommendations regarding the preferred stent characteristics that have shown to be impactful in the incidence of ISR in PCI patients. Diameter, length, drug-eluted stents, and many more considerations are exposed within NICE guidelines³⁰.

Lastly, Alexandrescu et al.³¹ conducted an observational cross-sectional study in a high-volume PCI center for two years. After proper analyses were performed, it was concluded that current smoking, hypertension, DM, elevated CRP levels, CKD, higher TIMI score, stent type, multi-stenting, and low pressure for stent implantation were highly correlated with the incidence of ISR. While some of the variables reported are congruent with the above stated, this study found other relevant factors. Evidence regarding ISR's risk factors is colossal; some studies have a questionable methodology, making available information somewhat conflicting. For that reason, systematic reviews and meta-analyses are needed to establish a trustable source of information concerning this topic. Moreover, pondering the attributable risk for each factor is needed to develop a standardized risk prediction model that contemplates the most relevant factors to make strong recommendations³².

ISR is a considerably frequent complication of PCI, with a prevalence as high as 10% in most epidemiological studies. Since PCI is the primary approach toward STEMI management, optimizing this procedure is needed further to improve patients' quality of life and life expectancy. In that matter, risk management is crucial in order to optimize PCI protocols further. Evidence shows that ISR incidence is highly influenced by risk factors such as hypertension, DM, CKD, laboratory parameters, and stent characteristics. Although enough evidence is available concerning this topic, predictive risk models for ISR are still lacking, probably because of the lack of a large sample size and multi-center studies. However, these predictive models are highly needed to objectively quantify the risk for ISR, which will then allow to establish proper recommendations and strategies to minimize the risk.

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