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RESEARCH ARTICLE

CORONARY IN-STENT RESTENOSIS: A LITERATURE REVIEW

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Abstract

Intrastent restenosis is a narrowing of the lumen of a coronary vessel previously treated with angioplasty It is the result of two histopathological processes: vascular remodeling and neointimal hyperplasia due to smooth muscle migration and proliferation, with the latter mechanism predominating. It manifests clinically with symptoms of ischemia and angiographic findings showing at least a 50% reduction in the lumen of a vessel previously treated with balloon angioplasty or a stent. Second generation drug eluting stents or drug eluting balloons are recommended for treatment, depending on the type of restenosis being treated.
We present a review of the literature about of the various aspects of this topic which remains a clinical challenge for interventional cardiologists, starting from its origin its historical background.to various treatment options.

Introduction:-

Since the beginning of coronary angioplasty, restenosis has been the most common late complication that interventional cardiologists have encountered. A significant advance was made with the stent implant, preventing the vessel's retraction that we observed in the months following balloon expansion alone. For the first time, using stents, it was possible to significantly reduce restenosis. However, we learned that stent implantation was accompanied by a strong cellular proliferative reaction followed by intra-stent deposition of the extracellular matrix that constitutes neointimal hyperplasia. This tissue can cause the vessel's restenosis, even occlusion.

The incidence of restenosis is difficult to establish accurately. In the pre-stent era, it ranged from 32% to 55% of all balloon angioplasties, and declined to 17-41% in the BMS-Bare Stent era (1-2).

Drug eluting stents (DES) have been the technological response to antagonize the biological process of neointimal hyperplasia and reduce restenosis. Highly effective in their functioning, DES reduced the rates of restenosis by up to 75% compared to Bare metal stents (BMS) (3), and significantly reduced restenosis in clinical practice, but unfortunately, it has not disappeared.

The widespread use for small arteries, long lesions, complex coronary lesions (left main disease, complex bifurcations and complex calcified lesions) and diabetic patients explains the persistence of this ISR in contemporary clinical practice

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History of coronary angioplasty:
In May 1977 at St Mary Hospital in San Francisco, Gruentzig and Myler performed the first coronary angioplasty on a human subject; by balloon dilatation during coronary artery bypass grafting (CABG). (4). The angiographic results were good.

On September 16, 1977 in Zurich, Dr. Gruentzig performed the first coronary balloon angioplasty on a conscious patient (5). The patient was 43 years old and had a tight stenosis of the proximal left descending artery (LAD). Ten years later this patient remained asymptomatic and coronary angiography showed no restenosis at the initial angioplasty site (6).

However, this technique has brought its share of complications, the two main risks of which were per-procedure acute occlusion, which sometimes required conversion of the procedure to coronary bypass surgery (7) and whose mechanism is multifactorial (coronary spasm (23), dissection (8) (9) or thrombosis (11), and arterial restenosis by constrictive remodeling at the level of the dilated lesion (elastic recoil) (12).

Nine years later, in 1986, Jacques Puel in Toulouse performed the first coronary stent implantation in the anterior descendind artery (LAD) at the site of restenosis after a balloon angioplasty performed 6 months earlier (13). A tool developed in an attempt to overcome the shortcomings of balloon angioplasty, this spring-like metal device was deployed in the arterial lumen to provide a scaffolding function preventing the risk of restenosis.

The multicenter study by Schatz et al. in 1991 (14) demonstrated the safety and efficacy of the Palmaz-Schatz coronary stent implantation technique, the first stent created in 1985 by Palmaz in association with Dr. Schatz (Figure 1).

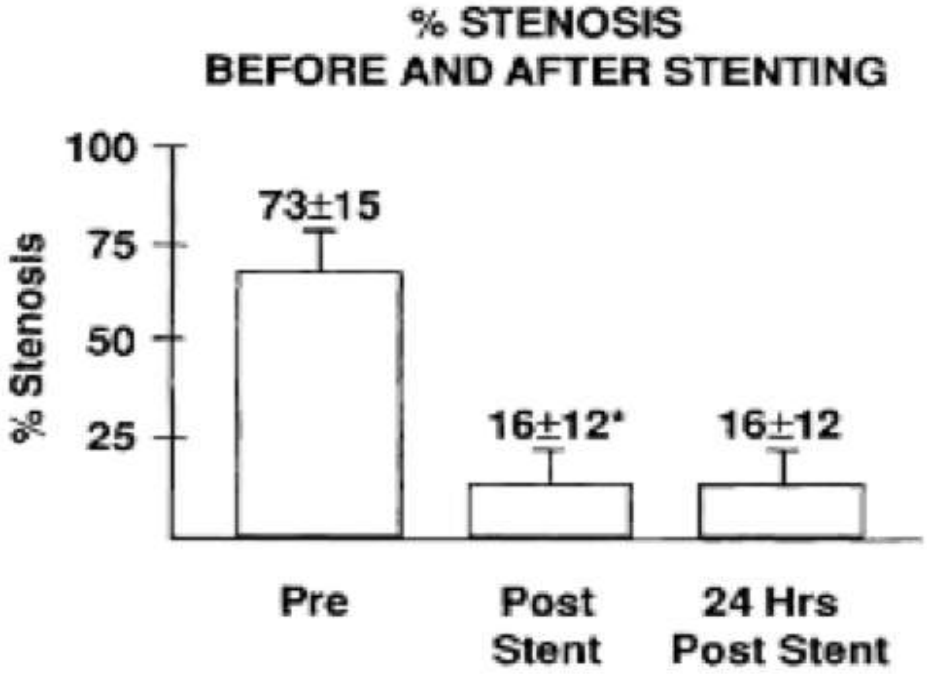

Figure 1:- Results in percentage of coronary stenosis before, immediately after and 24 hours after implantation of a Palmaz-Schatz bare metal stent (*p<0,0001). (13).

However, studies on the follow-up of stented patients highlighted two main limitations of bare stents: intra-stent thrombosis (IST) and ISR.

The risk of IST was greatly reduced with the use of dual antiplatelet therapy (14) (15) .

By using a bare stent in addition to balloon angioplasty, the restenosis rate was reduced from 42% to 32% in the STRESS study and 32% to 22% in the BENESTENT study. ISR after BMS rates ranged from 20 to 30% (16). This rate of restenosis was still too high.

To tackle these complications, a revolutionary new material was developed: the drug eluting stent (DES).

The first drug eluting stent (Cypher® delivering Sirolimus) was implanted by Eduardo Sousa in Sao Paulo in December 1999. Studies have shown that by integrating an antiproliferative and anti-inflammatory product into polymer layers with a slow diffusion of this product, the appearance of neointimal hyperplasia is significantly reduced.

In the RAVEL study (17) published in 2002 showed that the DES Sirolimus stent, compared to a bare metal stent, significantly inhibits restenosis.

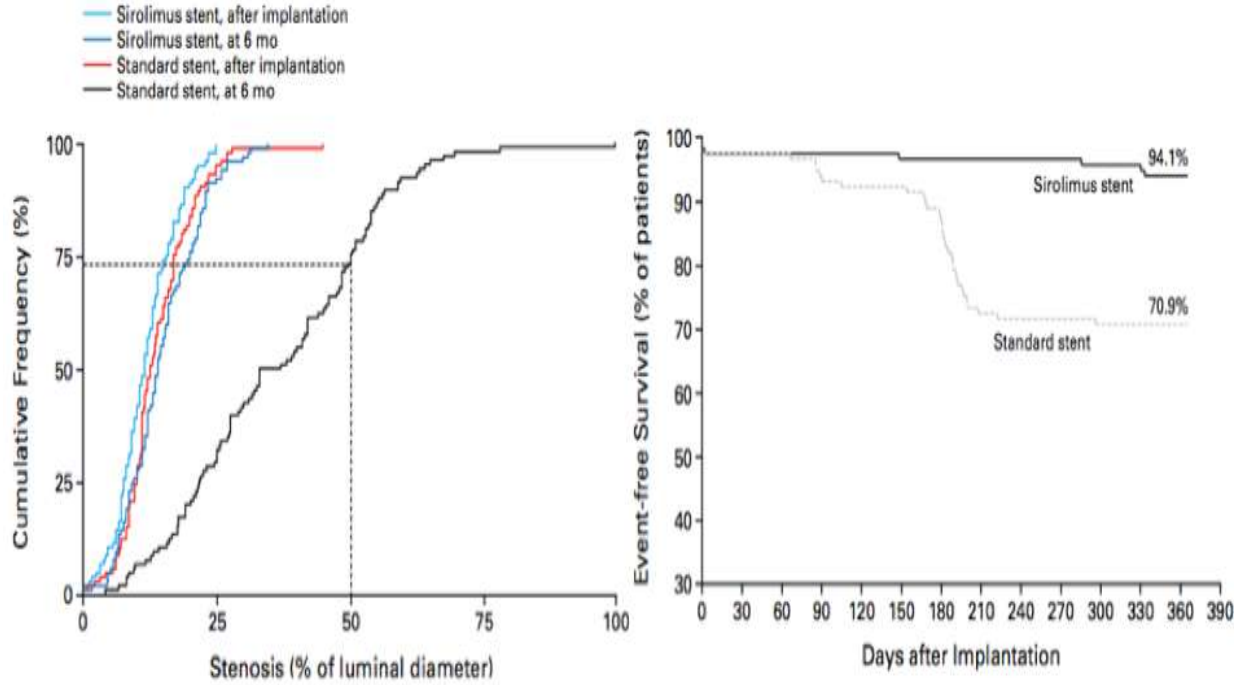

Figure 2:- RAVEL study comparing DES with Sirolimus and BMS. Left: the percentage of stenosis immediately after angioplasty and at 6 months. Right: Event free (myocardial infarction and/or target lesion revascularization) survival curve (significant difference between the 2 groups p<0.001). (17).

Nevertheless, some studies warned of a higher frequency of early and late ISTs, which are responsible for an increase in mortality, compared to bare metal stents (18) (19). These complications were partly explained by poor endothelialization of the active stent. The identification of these defects led to improvements with the production of second-generation, more sophisticated stents to replace the previous stents.

These more modern stents are composed of finer meshes with a thinner polymer layer, are more flexible and easier to handle, allow better delivery of the active product and better re-endothelialization.

Their efficacy and safety were demonstrated in the FUTURE I study (20) with a lower rate of RIS, TIS and mortality.

The 3rd generation is radically innovative by using a biodegradable polymer. We will thus have the advantages of the DES in the short term (restenosis rate <5%), then the advantages of the bare metal stent in the medium and long term (no late thrombosis).

The development of these techniques has been marked by pitfalls, the main ones being thrombosis and intrastent restenosis. Thrombosis could finally be controlled with the use of anti-aggregants. On the other hand, the problem of restenosis has not yet been solved after more than twenty years of existence of coronary stents with the systematic use of active stents which have certainly reduced the incidence of restenosis but have encouraged to widen the indications to high-risk patients and complex lesions which represents a new clinical challenge which is the subject of an intense clinical research activity.

ISR Definition:

The clinical definition of ISR combines the presence of an Intra-stent stenosis >50% of the Intra-stent lumen diameter or within 5 mm of the stent edges and one of the following conditions: recurrent angina, objective signs of ischemia on electrocardiogram, positive coronary hemodynamic assessment with FFR <0.80, IVUS area <4 mm^2 (6 mm^2 for the left main coronary artery). In the absence of any symptoms, angiographically significant restenosis must reduce >70% of the intrastent lumen diameter (21).

ISR Classification:

Roxana Mehran (38) established a classification designed for restenosis lesions on BMS: focal, diffuse, proliferative or occlusive. This classification has a prognostic value, with respective recurrence rates after balloon alone of 19%, 35%, 50% and 98%. This classification also has a prognostic value in ISR (22).

- Focal restenosis (type I): length of restenosis less than 10 mm
  - type IA = The articulation or gap between stents
  - Type IB = The proximal or distal margin of the stent (but not both)
  - type IC = The body of the stent
  - type ID = Multifocal
- Diffuse restenosis (types II to IV): length of restenosis greater than 10 mm
  - Type II = diffuse restenosis, not exceeding the edges of the stent
  - Type III = proliferative restenosis exceeding the edges of the stent
  - Type IV = Total occlusionwith TIMI 0 flow.

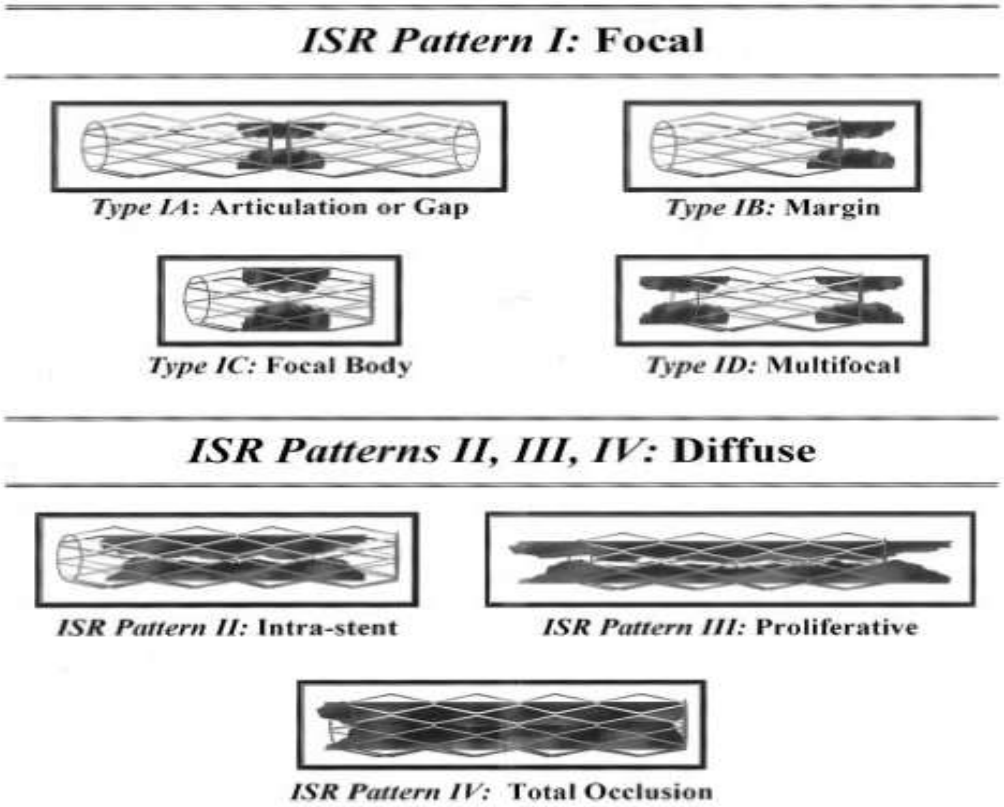

Figure 3:- Mehran's classification of in-stent restenosis into 4 types (focal, diffuse, proliferative and occlusive). (23).

Pathophysiology of ISR:
The three main mechanisms leading to the development of restenosis are:
1) Early elastic return (recoil);
2) Vascular remodeling
3) Neointimal hyperplasia.

The first and second mechanisms are typical of old-style angioplasty before the stent era. On the other hand, the presence of a foreign body represented by the different components of the stent, leads to inflammation which favors a new mechanism called neointimal hyperplasia. Ultimately, the optimal healing is a complete covering of the struts, a large arterial lumen, the absence of residual inflammation and a preserved vasoreactivity upstream and downstream of the stent.

The persistence of chronic inflammation, on the other hand, is responsible for two late consequences: the first is neoatherosclerosis which is the development of a new plaque in the lumen of the stent. The other is a hypersensitivity reaction with necrotizing vasculitis of the vascular wall, positive remodeling and risk of secondary thrombosis.

Elastic recoil and vascular remodeling:
Arterial recoil and immediate reduction in arterial lumen size after dilation is due to treated segment contraction. The internal and external elastic lamina (IEL/EEL) contain elastin fibers that can lead to ER after excessive balloon stretch resulting in a 40% loss of luminal diameter and occurs within seconds to minutes after balloon deflation.

The extent of the recoil depends on the composition of the plaque and generally follows a two-phase process. Immediate acute recoil is primarily seen in fibrous plaques.

Negative vascular remodeling then occurs within 6 months after balloon angioplasty. This is a complex phenomenon that also includes a medial and/or adventitial reaction that causes contracting scarring of the treated segment. (24)

On the other hand, after balloon angioplasty, the contribution of neointimal hyperplasia to restenosis is relatively limited, and luminal narrowing is primarily determined by vessel remodeling (25).

Neointimal Hyperplasia:
Proliferation or migration and activation of vascular smooth muscle cells (SMCs) in the intima is the result of disruption of the internal elastic lamina IEL. Endothelial denudation and exposure to circulating mitogens (angiotensin II and plasmin) may also play a role; in addition, platelets, endothelial cells, vascular smooth muscle, and inflammatory cells may release mitogens and cytokines such as cytosine.

Stent implantation deposits a significant amount of foreign components in the artery. These different components (metallic, plastic and pharmacological) lead to an acute inflammation.

It is therefore the understanding of Intra stent restenosis and in particular of its essential mechanism, neointimal hyperplasia, which led to the development of the concept of drug eluting stent combining mechanical effect and pharmacological action on cell multiplication and inflammation.

Predictive factors for intrastent restenosis:
Numerous studies have identified various patient-, lesion-, and procedure-related predictors of ISR (26)(27).

a. Patient-related
- higher age
- female gender.
- diabetes mellitus.
- chronic kidney disease.
- previous restenosis at another site.
- multivessel disease.

b. Lesion-related
- ISR lesion.
- lesion on saphenous bypass.
- chronic total occlusion. (CTO)
- small diameter vessel.
- minimal luminal diameter (MLD) before and after stenting.
- calcified lesion.
- ostial lesion.
- lesion involving the LAD artery.

c. Procedure-related
- Emergency angioplasty (acute coronary syndrome (ACS), MI…).
- treatment of multiple lesions.
- long stent.
- small diameter stent.
- under-expansion and malapposition of the stent.
- type of DES used: for 1st generation stents, Paclitaxel stents are more likely to cause ISR than Sirolimus stents. 2nd generation stents are more effective.
- MLD at the end of the procedure.

Neoatherosclerosis:
In-stent atherosclerosis called 'neoatherosclerosis' has been reported as untoward complication of coronary stent implants, which leads to late drug-eluting stents (DES)/baremetal stent (BMS) failure, typically, beyond 1 year, from restenosis or stent thrombosis due to plaque rupture. (28)(29)

Neoatherosclerosis is histologically identified by lipid-laden foamy macrophages with or without complications of a necrotic core and/or calcification within the nascent intima.60

It tends to appear earlier and more frequently with DES (30–50% at 1–2 years) than BMS (16% at 5 years).(30)

Polymer Hypersensitivity Reactions:
In addition to delayed healing, polymer hypersensitivity reactions have been reported with the use of DES. This reaction is characterized by a local inflammatory reaction, with infiltration of eosinophils, lymphocytes and multinucleated giant cells, which leads to positive vessel remodeling, poor apposition and ultimately stent thrombosis (31). This reaction is described one year after stent implantation. It is therefore attributed to the drug-releasing polymer, with the drug itself being completely released. These cases of localized hypersensitivity to the polymer are described with the Cypher stent. Symptoms vary from a mild reaction to an excessive inflammatory reaction with eosinophilic and giant cell infiltrates, associated with media destruction, poor stent apposition, and aneurysm formation, ultimately responsible for stent occlusion (32). In addition, an electron microscopy study of DES deployed at 37°C in saline solution showed several types of defects in the polymer layer on the surface of the stents, associated with potential risks of thrombosis, coronary microemboli or inflammatory reaction (33).

1. Treatment of ISR :
The medical devices used for the treatment of intra-stent restenosis are:
- The Plain old balloon angioplasty (POBA), its use is simple, but its effectiveness is limited especially to focal restenosis. (34) This technique still has some rare indications, particularly in patients at very high risk of bleeding.
It must be used systematically before any use of an active balloon.
- Cutting balloon:a technique that avoids the occurrence of balloon slippagecalled "Watermelon seeding" phenomenon that occurs with the classic balloon. The randomized RESCUT trial (35) did not show the superiority of this technique over the classic balloon.
- Brachytherapy, equivalent to an instantaneous local curitherapy, is more effective but its use is complex.
- The drug eluting stent DES was first used in restenosis on bare metal stents with a much higher efficacy than the balloon alone (ISAR DESIRE and RIBS II) (36,37) and with good long-term results, it is rapidly becoming the treatment of choice for DES ISR, whatever the anti-proliferative molecule chosen is (ISAR-DESIRE 2, RIBS III). (38,39)

- The drug coated balloon DCB has been shown to be effective in intra-stent restenosis (BMS and DES) with superiority over the balloon alone and comparable efficacy to first-generation DES. It is a procedure using semi-compliant balloons layered with a cytotoxic chemotherapeutic drug which is paclitaxel (40), applied locally to the restenosis. Paclitaxel is an antiproliferative substance, that at very low doses has regulatory effects but does not completely eliminate cell accumulation, which is why its properties are applied to reduce intimal proliferation in restenosis.

2. What treatment strategy?

The ESC guidelines advocate revascularization using either DES or DCB in caseof intra-stent restenosis, with the same level of evidence (IA) (41); DES being preferable in cases of BMS restenosis.

In situations of recurrent and/or diffuse restenosis, coronary artery bypass grafting should be considered (IIC), especially in the diabetic patient (42).

IVUS and OCT can be used to detect the mechanism of ISR (IIa).

Conclusion:-

Although ISR is less frequent with the routine use of DES, the expansion of indications to high-risk patients and complex lesions has also introduced a new interventional therapeutic dilemma: DES in-stent restenosis

ISR remains difficult to treat, and optimization of stent implantation during stent deployment with image-guided techniques may be the best strategy to minimize it.

The treatment of intrastent restenosis ultimately relies on different methods that must be mastered by every interventional cardiologist.

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