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Coronary restenosis: mechanisms, diagnosis and treatment in contemporary practice

Reestenose coronária: mecanismos, diagnóstico e tratamento na prática contemporânea

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ABSTRACT – In-stent restenosis stands out among the late complications of coronary angioplasty. Initially, it occurred in up to 60% of procedures using only balloons, but dropped to 10% with the advent of drug-eluting stents, even in more complex anatomic and technical scenarios. However, efforts have been made to achieve long-lasting results with no need for new revascularizations. Broad knowledge of pathophysiology, of predisposing risks factors for restenosis, and of new concepts, such as neoatherosclerosis, is paramount to its prevention. This article revises these aspects, as well as the importance of imaging methods and resources currently available for treating coronary restenosis.

Keywords: Coronary restenosis/diagnostic imaging; Angioplasty, balloon, coronary; Stents; Atherectomy, coronary

RESUMO – Dentre as complicações tardias da angioplastia coronária, destaca-se a reestenose intra-stent. Sua taxa, que inicialmente alcançava até 60% dos procedimentos efetivados apenas com balão, foi reduzida para patamares de até 10% com o advento dos stents farmacológicos, mesmo em cenários de maior complexidade anatômica e técnica. Entretanto, esforços vêm sendo envidados, na busca de resultados duradouros e livres da necessidade de novas revascularizações. O conhecimento aprofundado da fisiopatologia, dos fatores de risco predisponentes à ocorrência da reestenose e de novos conceitos como neoaterosclerose é fundamental para sua prevenção. Neste artigo, revisaremos tais aspectos, bem como a importância dos métodos de imagem e os recursos atualmente disponíveis para o tratamento da reestenose coronária.

Descritores: Reestenose coronária/diagnóstico por imagem; Angioplastia coronária com balão; Stents; Aterectomia coronária

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GENERAL ASPECTS AND HISTORY

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) and its application to a growing number of patients, two main adverse events associated with the method have been identified: thrombosis and in-stent restenosis (ISR). The latter is the object of this review. Rates of ISR with balloon PTCA were high (40 to 60%), and the major mechanisms were acute and chronic elastic recoil, and negative constrictive remodeling of the vessel.¹

With the introduction of bare-metal stents, the deleterious phenomenon of acute elastic recoil of the vessel was eliminated, but a new entity was introduced, i.e., neointimal hyperplasia (NIH), which has linear correlation with late luminal loss of the stent. As a consequence, ISR rates were reported as 20 to 35%, with clinical and angiographic variables as risk factors.² Brachytherapy involves the concept of endovascular radiation, and was initially studied in this scenario. However, it resulted in edge loss and high rates of late in-stent thrombosis, being excluded for clinical application.³

The next step was key for reducing the incidence of ISR: the introduction of drug-eluting stents (DES). The first-generation of this group, sirolimus- (Cypher®) or paclitaxel-eluted (Taxus®), reduced ISR to very low levels, for both simple (close to 0%)

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and complex lesions (10 to 15%).⁴ This fact significantly impacted on reduced number of new revascularizations. The evolution to new generations of DES brought favorable changes in terms of safety, by reducing the risk of in-stent thrombosis. However, it is still challenging to further reduce ISR rates with the current stents, since their use has been disseminated for more complex lesions, and late failure due to neoatherosclerosis has emerged as a new obstacle to be overcome.

DEFINITION AND CLASSIFICATION

In order to have a uniform nomenclature, the binary concept of restenosis is used; that is, reappearance of the lesion with $\geq 50\%$ obstruction of the vessel lumen in the segment treated (inside the stent and at the edges, 5mm downstream and upstream). This concept was based on physiology studies, which demonstrated impairment of coronary flow reserve from this degree of vessel lumen obstruction.

A classification system was established in 1999 to differentiate ISR patterns.⁵ Two major patterns were described, with several subtypes: focal ISR and diffuse ISR (Figure 1). Usually, the ISR pattern in the bare-metal stents group is diffuse and may be of the diffuse proliferative subtype, when it involves the edges of the stent. In DES, the most commonly found pattern is focal ISR, with the proximal edge being the most common site of occurrence. However, about 20% of cases of ISR in DES present a diffuse pattern and, sometimes, an occlusive pattern.⁶

Figure 1. Patterns of in-stent restenosis (Mehran classification).
Source: Adapted from Mehran et al.⁵

RISK FACTORS FOR IN-STENT RESTENOSIS

Over time, it was possible to identify factors associated with higher incidence of ISR. We have, therefore, patient-related factors and the most important are diabetes mellitus, especially insulin-dependent, chronic renal failure under dialysis, and clinically unstable individuals. Angio-

graphic factors also play a key role, such as lesions in thin vessels, long lesions ($>20\text{mm}$), tortuous segments, thrombus, ostial lesions, venous grafts (saphenous grafts), very calcified vessels, chronic occlusions, and bifurcations. Factors related to the procedure are also crucial, including the degree of post-procedural residual stenosis and, specifically in the case of stent deployment, poor expansion, which is easily identifiable by intracoronary imaging methods.^{7,8}

Among all these angiographic and clinical factors, diabetes is one of the most studied and most strongly involved, both for bare-metal stents and DES in-stent restenosis. Therefore, it is an important topic in decision-making when discussing the possibility of PTCA in a given patient with manifest coronary disease.

CLINICAL PRESENTATION

Historically, ISR has manifested with stable symptoms, with no direct impact on important unfavorable clinical outcomes. Patients have been classically described as presenting stable angina or silent ischemia, usually between 3 and 6 months after intervention, and with very satisfactory results after a new intervention. This was consonant with the predominant form of ISR, NIH, characterized by progressive, homogeneous proliferation of smooth muscle cells (Figure 2). Nonetheless, more

Figure 2. A 52-year-old female patient with stable angina upon moderate exertion, 7 months after bifurcation angioplasty by TAP (T and Protrusion) technique. Coronary angiography and optical coherence tomography show pattern of in-stent restenosis due to intimal hyperplasia in the lateral branch, with intraluminal fibrotic tissue characterized by luminal image, not hindering good visualization of the struts of the previously implanted stent (lower right corner). In-stent restenosis spared the region of the carina, with stents presenting strut endothelialization with no pattern of restenosis (lower left corner).

recent studies have also associated ISR with acute coronary syndrome in 30% to 50% of cases, and it may lead to acute myocardial infarction (MI), with artery occlusion in 5% of cases.⁹ The ISR pattern most related to this type of acute manifestation is neoatherosclerosis, which is the major cause of ISR in new generation DES. These cases can often be misinterpreted as in-stent thrombosis. The angiographic pattern, lesion behavior during balloon insufflation, and medical history of the patient may help differentiate between ISR and thrombosis. The use of intravascular imaging is paramount in such cases.

PATHOPHYSIOLOGY OF IN-STENT RESTENOSIS

Mechanistic factors

The correct understanding of the ISR mechanism is crucial to guide and optimize new interventions. Often there is a mechanical failure in stent deployment, and if properly recognized, it can be corrected in a new approach. Stent underexpansion is a pivotal factor to trigger ISR in both bare-metal and drug-eluting stents. It can be caused either by low insufflation pressures during stent deployment or stent undersizing. Another reason is inadequate expansion, even with good insufflation pressures and adequate sizing, when a highly calcified lesion is treated. In these cases, adequate preparation of the lesion prior to stent implantation, with suitable pre-dilation and use of rotational atherectomy may reduce this occurrence.

However, many patients present ISR even with appropriately expanded stents. Some possible findings may explain the occurrence of ISR: stent displacement, lack of full coverage of the treated lesion, gaps between stents and as more recently described, stent fracture (Table 1). The latter is an entity initially described in 2004, which presents a focal pattern, reflecting repeated trauma at this site, and occurring regardless of the type of DES used.¹⁰ Stent fracture is more frequently found in patients with long stents, overlapping stents, critical lesions vigorously dilated, myocardial bridge at the edge of the stent, and areas of significant curvature. The right coronary artery and the saphenous vein grafts are the most affected territories as a consequence of the intense mobility during systole, in addition to tortuosity and angulation.¹¹

Table 1. Predictive factors of procedure-related in-stent restenosis.

Predictive mechanistic factors for in-stent restenosis
Poor stent expansion
Sub-optimal coverage of the treated lesion (angiographic miss)
Gap between stents
Stent fracture
Balloon-catheter barotrauma in region not covered by the stent

Biological factors

Endothelial aggression is the main mechanism to explain the occurrence of ISR in bare-metal stent. However, with the advent of DES, other biological mechanisms have been involved, including resistance to antiproliferative drugs and hypersensitivity reactions to the stent polymer. Resistance to antiproliferative drugs was initially very well documented in the cancer setting, and later, in coronary intervention. Some drugs, such as sirolimus and paclitaxel, may present the so-called pharmacological resistance by genetic expression, characterized mainly by mutations in genes encoding proteins implied in the metabolism of these drugs.¹²

Resistance to the metal platform is another important aspect to be considered, and was well studied and described in platforms that today are obsolete, such as gold and molybdenum.¹³ Resistance to the platforms used today, although it has been theorized and speculated, has not been proven so far. Polymer hypersensitivity is a well-studied and proven factor in the DES era. Drug-eluting stents have polymers for drug storage and release, which promoted delayed vessel hypersensitivity. Although the inflammatory reaction that occurs shortly after arterial injury from stent deployment is a critical factor for the neointimal response, the persistence of the inflammatory response after 90 days, caused mainly by non-biocompatible polymers of the first generation DES, is a factor strongly associated with ISR and very late thrombosis in these devices.¹⁴⁻¹⁶

Neoatherosclerosis

Neoatherosclerosis is defined as the presence of atherosclerotic disease within the neointima in a segment treated with stent. The pattern found can range from abnormal intimal thickening with presence of intercellular lipid accumulation, to a ruptured thin-layer fibroatheroma, which usually presents with acute coronary syndrome (Figure 3). The incidence of neoatherosclerosis is higher in DES as compared to bare-metal stents (31 vs. 16%).¹⁷⁻²⁰ The mechanism in DES can be explained since it reduces the capacity for re-endothelialization, leading to a neoatherosclerotic cascade with monocyte adhesion, neointimal migration, and increased permeability of the endothelium to circulating lipids, which end up migrating to the subendothelial matrix. This phenomenon is the main responsible for late catch-up, more common with DES. While the primary mechanism of bare-metal stents ISR is NIH, presenting clinically usually between the third and sixth month after PTCA, neoatherosclerosis most commonly occurs after the sixth month and is often symptomatic, because it is an injury with unstable morphological features (thin-layer fibroatheroma), very associated with acute coronary syndrome. Clinical differentiation with in-stent thrombosis is sometimes challenging.

Initially, neoatherosclerosis appeared to be a phenomenon only seen with first-generation DES, as a reaction to durable polymers. However, even with second generation DES, with biocompatible and even biodegradable polymers,

this finding is seen. Moreover, since this is a lesion of unstable aspect, with a high lipid content, its treatment with new angioplasty may lead to an increased periprocedural infarction rate.²¹ Although neoatherosclerosis is usually a late finding after DES implantation, some angioscopy studies showed that even during the first year after deploying a DES, yellow plaques, corresponding to this phenomenon, may be present and impact in adverse cardiac events.²² We see, therefore, that it is a totally different process from NIH, by its composition, and by form and time of variable clinical presentation.

Figure 3. A 69-year-old female patient with non-ST segment elevation myocardial infarction 13 months after circumflex artery angioplasty. Optical coherence tomography shows a pattern of in-stent restenosis by neoatherosclerosis with heterogeneous tissue, abundant in lipids, and poor visualization of the struts of the previously implanted stent, by signal dissipation (bottom center). This region contrasts with a pattern of mild neointimal hyperplasia at the distal edge of the stent (bottom right). In the proximal region, there is a small and calcified plaque.

INTRACORONARY IMAGE AS ADJUNCT TOOL IN DIAGNOSIS AND TREATMENT OF IN-STENT RESTENOSIS

The use of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are crucial in the mechanistic evaluation of ISR promoting factors. NIH pattern, stent underexpansion or edge dissection are easily demonstrated by these methods. Although IVUS is more widely used because of its historical role and accessibility, its limited axial resolution (more than 100 μ) may make luminal and neointimal delimitation difficult in some cases. OCT, with a 12 to 15- μ resolution, can provide accurate information about the vessel-lumen interface, neointimal tissue, and distribution of stent structures, evaluating its expansion and apposition accurately.²³

Accurate OCT resolution enabled the differentiation of ISR patterns, depending on the structure implanted. In bare-metal stent IRS, the characteristic pattern found is NIH, demonstrated by tissue with homogeneous hypersignal, rich in smooth muscle cells. In ISR of DES, the most commonly found pattern is neoatherosclerosis, which presents as a heterogeneous, multifaceted material with some characteristic aspects, such as intimal rupture, lipid lakes, thin-layer fibroatheroma, and macrophage agglomerates.

It is essential to define the ISR pattern found, and OCT also plays a key role in the morphological differentiation between ISR and in-stent thrombosis. Since neoatherosclerosis may manifest clinically as acute coronary syndrome, which may be due to ISR or thrombosis, the correct definition of stent failure with OCT may guide different forms of approach and treatment. For example, a neoatherosclerosis pattern in a poorly expanded stent area suggests that better expansion at high pressures, and optimization of stent deployment may lead to better long-term outcome. On the other hand, the presence of thrombus in an area of bad apposition suggests that the balloon or stent size to be employed needs to be revised.²⁴

Kang et al. demonstrated that in a series of patients presenting ISR in DES during a 32-month follow-up, 52% of lesions had at least one thin-layer fibroatheroma, 58% in-stent neointimal rupture, and 58% intraluminal thrombus,¹⁹ rendering understandable the unstable clinical presentation of these patients.

TREATMENT OF RESTENOSIS

The treatment of ISR still presents obstacles and challenges. Although the use of bare-metal stents has been drastically reduced in developed countries, its use in Brazil and in emerging countries is still frequent due to economic reasons, even with high failure rates. The wide introduction of DES significantly reduced the occurrence of ISR, since it interfered with the NIH process, a major cause of restenosis after stent implantation, directly impacting the clinical need for another revascularization.²⁵

The evolution of these devices brought greater efficacy and safety. Nevertheless, even with the advance of platforms, polymers and drug elution, these devices still cause ISR, which occurs in just over 10% in several clinical series.²⁶

TREATMENT MODALITIES

Balloon angioplasty

Plain old balloon angioplasty (POBA) was one of the first methods used to treat ISR. Although it is a method of treatment with easy applicability and good acute results, POBA has favorable results only in patients with focal ISR.²⁷ In patients with diffuse ISR, there is often recurrence, especially in diabetic patients.²⁸

By and large, when this treatment modality is employed, some premises must be obeyed: dilate only the

segment with stenosis, and not all the extension of the stent; if there is constriction at the mid-point of the lesion (dog-bone effect), use non-compliant balloons at high pressure, complying with the nominal rate to the arterial diameter; avoid high pressures in semicompliant balloons, in order not to expand them longitudinally and injure the edges of the stent.

The major limitation of POBA in the treatment of ISR is subacute re-intrusion of the hyperplastic tissue into the lumen, a phenomenon that occurs minutes after balloon dilatation and explains the early luminal loss with this method.²⁹

Angioplasty with cutting/scoring balloons

Cutting balloons are another option for treating ISR and they have the advantage of not sliding longitudinally (watermelon seeding), preventing edge injury. Some initial small studies showed potential benefits as compared to conventional balloon angioplasty, but the RESCUT study, with 428 patients, showed no difference in clinical and angiographic results when making this comparison. In this study, only patients with bare-metal stents ISR were included.³⁰

Scoring balloons are very similar to cutting balloons, but present greater flexibility and deployment capacity, with good results in selected cases, as found in some publications; however, they lack consistent and comparative randomized studies.³¹

Neointimal debulking: laser and rotational atherectomy

The techniques of neointimal ablation (debulking) aim at extrusion of the intimal tissue inside the stent using laser or mechanical atherectomy. The rationale for using these techniques proposes that, in cases of ISR in adequately expanded stents, removal of tissue that obstructs the arterial lumen would be more efficient than conventional balloon angioplasty, since this causes endothelial injury and potentiates the recurrence of proliferative response. Excimer laser showed good results in selected cases (Figure 4), although with lower ablative capacity than rotational atherectomy.³²

Rotational atherectomy was evaluated as treatment of ISR in bare-metal stents by means of randomized trials. The ROSTER study demonstrated that in diffuse ISR, excluding cases of underexpansion of the stent using IVUS, the use of rotational atherectomy reduced the rate of target lesion revascularization (TLR) as compared to POBA.³³ The ARTIST study, in turn, despite being more robust in number of patients, failed to demonstrate superiority of rotational atherectomy in comparison to balloon, even presenting unfavorable short- and long-term results.³⁴ Atherectomy should, therefore, be reserved as a treatment strategy of IRS only for cases with lesions where balloon dilatation is not possible, or else for neoatherosclerosis with significant calcification.

Figure 4. A 70-year-old male patient, with multiple comorbidities and ischemic heart disease. Optical coherence tomography showed a pattern of in-stent restenosis with homogeneous tissue in the mid-shaft of the left main coronary artery (left). In the center, the lesion after laser. On the right, after stent deployment, with good apposition and expansion.

Source: Dallan LA, Pereira GT, Bezerra HG. In-stent treatment of left main coronary artery with laser atherectomy guided by intracoronary optical coherence tomography. *J Transcat Interv.* 2019; 27eA20180002.

Bare-metal stents

When compared to conventional angioplasty, the use of bare-metal stents reduced ISR due to greater acute gain in relation to balloon. The phenomenon of acute luminal loss could result in better angiographic outcome in the long run. However, the immediate benefit was not followed by persistence in the late outcome. The RIBS I study compared 450 patients with ISR in BMS treated with balloon vs. angioplasty with bare-metal stenting. Although the immediate results were favorable to bare-metal stent, due to a greater acute gain, at the 6-month follow-up, the late luminal loss was significantly higher when compared to POBA. Minimal luminal diameter and stenosis diameter were not significantly different with both techniques after 6 months.³⁵ Bare-metal stents should therefore be avoided in the treatment of ISR.³⁶

Drug-eluting stents

DES have undoubtedly revolutionized the outcome of coronary angioplasty. If DES initially proved their efficacy in *de novo* lesions, it would be reasonable to apply them in the ISR scenario. The initial results with DES are observed in the long-run, unlike those with bare-metal stents. The first observational studies with first-generation DES demonstrated that they were safe and effective when used in ISR.³⁷

The ISAR-DESIRE study compared the use of balloon with first-generation stents in the treatment of ISR. With 300 patients included, the ISR recurrence rates were 14.3% for patients treated with sirolimus-eluting stents, and 21.7% for those treated with paclitaxel-eluting stents, as compared to 44.6% in patients treated with balloon.³⁸ In the RIBS II study, the treatment of ISR of bare-metal stent was significantly more effective with the use of siroli-

mus-eluting stents, leading to a reduced rate of long-term restenosis (11%), with less need for reintervention, when compared to the use of balloon, with consistent results after 4-year follow-up.^{39,40}

The treatment of ISR in DES remains a challenge. Interestingly, the use of DES in the treatment of ISR in drug-eluting stents has worse results as compared to the use of DES in the treatment of ISR with bare-metal stents.⁴¹ Even though, since it still presents better results than any other technique studied, the treatment of ISR in DES with a new DES has become standard in this scenario. What leads to extensive discussion and debate is whether, when ISR occurs in one DES, it should be treated with DES eluted by another drug or this exchange is exempt of benefit. The rationale for switching is based on the hypothesis of individual resistance to the drug present in the first stent, or problems related to its polymer. Nonetheless, the results to date are inconclusive.

The ISAR-DESIRE 2 study randomized 450 patients with ISR in sirolimus-eluting stent to be treated again, using the same stent or paclitaxel-eluting stent. There was no significant difference between the two groups regarding angiographic (late loss and ISR) and clinical (new revascularization) outcomes, with no difference in thrombosis rates either.⁴² In the same context, in the RIBS III study, a prospective multicenter registry, the use of a different drug DES to treat IRS in DES resulted in better clinical outcomes. In particular, the outcome was better in patients treated with second generation DES and with intracoronary imaging-guided procedures.⁴³

Drug-eluting balloons

Although the use of drug-eluting balloons remains controversial in native lesions, it showed to be effective in ISR in bare-metal stents or DES. Initially, better results were found as compared to the use of conventional balloons to treat ISR in bare-metal stents.⁴⁴

A more challenging scenario is the comparison of drug-eluting balloons with DES in the treatment of ISR. The RIBS V study compared the use of drug-eluting balloons with second generation everolimus-eluted stents in the treatment of ISR in bare-metal stents.⁴⁵ In that study, there was no statistically significant difference in the rate of ISR and clinical events in 1-year follow-up. Regarding angiographic outcomes, the minimum luminal diameter obtained with DES was larger when compared to the drug-eluting balloon (2.36mm vs. 2.01 mm; $p < 0.001$).

A more current issue is the role of the drug-eluting balloons in the treatment of ISR in DES. The efficacy of drug-eluting balloon in this scenario, compared to the conventional balloon, was initially demonstrated in a single center randomized study.⁴⁶ The treatment of ISR in DES obtained better clinical and angiographic results with the use of drug-eluting balloon. The ISAR-DESIRE 3 study compared three different ISR treatment techniques: conventional balloon PTCA, drug-eluting balloon PTCA and angio-

plasty with DES. There were no differences in efficacy when comparing the uses of drug-eluting balloon and first-generation DES, both of which were better than conventional balloon.⁴⁷

The PEPCAD clinical program confirmed good results using drug-eluting balloon as compared to a new angioplasty with DES in cases of ISR in DES.⁴⁸ Other clinical studies confirmed these findings, raising the degree of recommendation of the use of drug-eluting balloon to treat ISR in DES.^{49,50} Although the use of a new DES may result in better acute luminal gain and consequent advantage in terms of angiographic outcomes, a learning curve using drug-eluting balloons to achieve favorable results in this scenario has been described. Careful preparation of the lesion with non-compliant balloons, and especially scoring balloons, prior to the use of the drug-eluting balloon results in a better angiographic result in the short- and long-run, as demonstrated in the ISAR-DESIRE study 4.⁵¹

Several advantages can be listed in the treatment of ISR in DES with drug-eluting balloons, instead of a new stent: it avoids multiple metal layers, reduces the time of antiplatelet use, enables new procedures, and may present lower thrombosis rates in the long run. The acute angiographic disadvantage can be minimized with adequate preparation of the lesion.

In sum, drug-eluting balloon angioplasty is an effective technique in the treatment of ISR in bare-metal stent and DES, being at least as effective as first-generation DES, without entailing additional deposition of metallic platform in the target vessel.

CONCLUSION

The advent of drug-eluting stents led to reduced cases of in-stent restenosis, but the increased use of new-generation drug-eluting stents in clinical practice still makes this complication relevant. In addition, today the in-stent restenosis cases are more challenging, because there is no consensus about the best strategy and treatment in this context. Biological and mechanistic phenomena may be involved. The former are immutable; the latter can be duly clarified and corrected.

Whenever possible, intracoronary imaging is key to elucidate the mechanism of stent failure, and may guide the new intervention to minimize this or other factors found. After the correct definition of the mechanism of in-stent restenosis, the use of drug-eluting balloons and new-generation drug-eluting stents is paramount in the therapeutic armamentarium, and coronary artery bypass graft is an option to be reserved for patients with in-stent restenosis associated with complex multivessel disease.

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CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF THE AUTHORS

Conception and design of the study: CNZ and MR; data collection: CNZ and MR; data interpretation: CNZ and MR; writing of the text: CNZ and MR; approval of the final version to be published: CNZ and MR.

REFERENCES

- Holmes DR Jr., Vlietstra RE, Smith HC, Vetrovec GW, Kent KM, Cowley MJ, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol.* 1984;53(12):77C-81C.
- Cutlip DE, Chauhan MS, Baim DS, Ho KK, Popma JJ, Carrozza JP, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol.* 2002;40(12):2082-9.
- Serruys PW, Kay IP. I like the candy, I hate the wrapper: the (32)P radioactive stent. *Circulation.* 2000;101(1):3-7.
- Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2006;113(6):e85-151. Erratum in: *Circulation.* 2006;113(14):e696. *Circulation.* 2006;114(23):e630.
- Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation.* 1999;100(18):1872-8.
- Corbett SJ, Cosgrave J, Melzi G, Babic R, Biondi-Zoccai GG, Godino C, et al. Patterns of restenosis after drug-eluting stent implantation: Insights from a contemporary and comparative analysis of sirolimus- and paclitaxel-eluting stents. *Eur Heart J.* 2006;27(19):2330-7.
- Kastrati A, Dibra A, Mehilli J, Mayer S, Pinieck S, Pache J, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circulation.* 2006; 113(19): 2293-300.
- Lemos PA, Hoye A, Goedhart D, Arampatzis CA, Saia F, van der Giessen WJ, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation.* 2004;109(11):1366-70.
- Bainey KR, Norris CM, Graham MM, Ghali WA, Knudtson ML, Welsh RC; APPROACH investigators. Clinical in-stent restenosis with bare metal stents: is it truly a benign phenomenon? *Int J Cardiol.* 2008;128(3):378-82.
- Sianos G, Hofma S, Ligthart JM, Saia F, Hoye A, Lemos PA, et al. Stent fracture and restenosis in the drug-eluting stent era. *Catheter Cardiovasc Interv.* 2004;61(1):111-6.
- Canan T, Lee MS. Drug-eluting stent fracture: incidence, contributing factors, and clinical implications. *Catheter Cardiovasc Interv.* 2010; 75(2):237-45.
- Huang S, Houghton PJ. Mechanisms of resistance to rapamycins. *Drug Resist Updat.* 2001;4(6):378-91.
- Köster R, Vieluf D, Kiehn M, Sommerauer M, Kähler J, Baldus S, et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet.* 2000;356(9245):1895-7. Erratum in: *Lancet.* 2001;357(9252):316.
- Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol.* 2006;48:193-202.
- Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation.* 2005;112(2):270-8.
- Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, et al. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol.* 2007;27(7):1500-10.
- Takano M, Yamamoto M, Inami S, Murakami D, Ohba T, Seino Y, et al. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents extended late-phase observation by intracoronary optical coherence tomography. *J Am Coll Cardiol.* 2009;55(1):26-32.
- Habara M, Terashima M, Nasu K, Kaneda H, Inoue K, Ito T, et al. Difference of tissue characteristics between early and very late restenosis lesions after bare-metal stent implantation: an optical coherence tomography study. *Circ Cardiovasc Interv.* 2011;4(3): 232-8.
- Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation.* 2011;123(25):2954-63.
- Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol.* 2011;57(11):1314-22.
- Grines CL, Schreiber TL. Neoatherosclerosis detection and clinical consequences. *JACC Cardiovasc Interv.* 2015;8(6):822-3.
- Ueda Y, Matsuo K, Nishimoto Y, Sugihara R, Hirata A, Nemoto T, et al. In-stent yellow plaque at 1 year after implantation is associated with future event of very late stent failure: the DESNOTE study (Detect the Event of Very late Stent Failure From the Drug-Eluting Stent Not Well Covered by Neointima Determined by Angioscopy). *JACC Cardiovasc Interv.* 2015;8(6):814-21.
- Byrne RA, Joner M, Tada T, Kastrati A. Restenosis in bare metal and drug-eluting stents: distinct mechanistic insights from histopathology and optical intravascular imaging. *Minerva Cardioangiol.* 2012;60(5):473-89.
- Alfonso F, Fernandez-Viña F, Medina M, Hernandez R. Neo-atherosclerosis: the missing link between very late stent thrombosis and very late in-stent restenosis. *J Am Coll Cardiol.* 2013;61(12): e155.
- García Del Blanco B, Rumoroso Cuevas JR, Hernández Hernández F, Trillo Nouché R. Spanish Cardiac Catheterization and Coronary Intervention Registry. 22nd official report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990-2012). *Rev Esp Cardiol.* 2013; 66(11):894-904.
- Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med.* 2013;368(3):254-65.
- Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med.* 2007;356(10):1030-9.
- Cassese S, Byrne RA, Tada T, Pinieck S, Joner M, Ibrahim T, et al. Incidence and predictors of restenosis after coronary stenting in 10,004 patients with surveillance angiography. *Heart.* 2014; 100(2):153-9.

29. Alfonso F, Pérez-Vizcayno MJ, Hernández R, Goicolea J, Fernández-Ortiz A, Escaned J, et al. Long-term outcome and determinants of event-free survival in patients treated with balloon angioplasty for in-stent restenosis. *Am J Cardiol.* 1999; 83(8):1268-70.
30. Albiero R, Silber S, Di Mario C, Cernigliaro C, Battaglia S, Reimers B, Frasheri A, Klauss V, Auge JM, Rubartelli P, Morice MC, Cremonesi A, Schofer J, Bortone A, Colombo A; RESCUT Investigators. Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the Restenosis Cutting Balloon Evaluation Trial (RES-CUT). *J Am Coll Cardiol.* 2004;43(6):943-9.
31. Takano M, Yamamoto M, Murakami D, Takano H, Asai K, Yasutake M, et al. Optical coherence tomography after new scoring balloon angioplasty for in-stent restenosis and de novo coronary lesions. *Int J Cardiol.* 2010;141(3):e51-3.
32. Mehran R, Dangas G, Mintz GS, Waksman R, Abizaid A, Satler LF, et al. Treatment of in-stent restenosis with excimer laser coronary angioplasty versus rotational atherectomy: comparative mechanisms and results. *Circulation.* 2000;101(21):2484-9.
33. Sharma SK, Kini A, Mehran R, Lansky A, Kobayashi Y, Marmur JD. Randomized trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-stent Restenosis (ROSTER). *Am Heart J.* 2004;147(1):16-22.
34. vom Dahl J, Dietz U, Haager PK, Silber S, Niccoli L, Buettner HJ, et al. Rotational atherectomy does not reduce recurrent in-stent restenosis: results of the Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-stent Restenosis Trial (ARTIST). *Circulation.* 2002;105(5):583-8.
35. Alfonso F, García P, Fleites H, Pimentel G, Sabaté M, Hernández R, et al. Repeat stenting for the prevention of the early lumen loss phenomenon in patients with in-stent restenosis. Angiographic and intravascular ultrasound findings of a randomized study. *Am Heart J.* 2005;149(2):e1-8.
36. Alfonso F, Zueco J, Cequier A, Mantilla R, Bethencourt A, López-Mínguez JR, et al. Restenosis Intra-stent: Balloon Angioplasty Versus Elective Stenting (RIBS) Investigators. A randomized comparison of repeat stenting with balloon angioplasty in patients with in-stent restenosis. *J Am Coll Cardiol.* 2003;42(5):796-805.
37. Lemos PA, van Mieghem CA, Arampatzis CA, Hoye A, Ong AT, McFadden E, et al. Post-sirolimus-eluting stent restenosis treated with repeat percutaneous intervention: late angiographic and clinical outcomes. *Circulation.* 2004;109(21):2500-2.
38. Kastrati A, Mehili J, von Beckerath N, Dibra A, Hausleiter J, Pache J, Schühlen H, Schmitt C, Dirschinger J, Schömig A; ISAR-DESIRE Study Investigators. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA.* 2005;293(2):165-71.
39. Alfonso F, Pérez-Vizcayno MJ, Hernandez R, Bethencourt A, Martí V, López-Mínguez JR, Angel J, Mantilla R, Moris C, Cequier A, Sabaté M, Escaned J, Moreno R, Bañuelos C, Suárez A, Macaya C; RIBS-II Investigators. A randomized comparison of sirolimus-eluting stent with balloon angioplasty in patients with in-stent restenosis: results of the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) trial. *J Am Coll Cardiol.* 2006;47(11):2152-60.
40. Alfonso F, Pérez-Vizcayno MJ, Hernández R, Bethencourt A, Martí V, López-Mínguez JR, Angel J, Iñiguez A, Moris C, Cequier A, Sabaté M, Escaned J, Jiménez-Quevedo P, Bañuelos C, Suárez A, Macaya C; RIBS-II Investigators. Long-term clinical benefit of sirolimus-eluting stents in patients with in-stent restenosis results of the RIBS-II (Restenosis Intra-stent: Balloon Angioplasty vs. Elective Sirolimus-eluting Stenting) study. *J Am Coll Cardiol.* 2008;52(20):1621-7.
41. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol.* 2010;56(23):1897-907.
42. Mehili J, Byrne RA, Tiroch K, Pinieck S, Schulz S, Kufner S, Massberg S, Laugwitz KL, Schömig A, Kastrati A; ISAR-DESIRE 2 Investigators. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. *J Am Coll Cardiol.* 2010;55(24):2710-6.
43. Alfonso F, Pérez-Vizcayno MJ, Dutary J, Zueco J, Cequier A, García-Touchard A, Martí V, Lozano I, Angel J, Hernández JM, López-Mínguez JR, Melgares R, Moreno R, Seidelberger B, Fernández C, Hernandez R; RIBS-III Study Investigators (under the auspices of the Working Group on Interventional Cardiology of the Spanish Society of Cardiology). Implantation of a drug-eluting stent with a different drug (switch strategy) in patients with drug-eluting stent restenosis. Results from a prospective multicenter study (RIBS III [Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent]). *JACC Cardiovasc Interv.* 2012;5(7):728-37.
44. Scheller B, Hehrlein C, Bocks W, Rutsch W, Haghi D, Dietz U, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med.* 2006;355(20):2113-24.
45. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, García Del Blanco B, Seidelberger B, Iñiguez A, Gómez-Recio M, Masotti M, Velázquez MT, Sanchis J, García-Touchard A, Zueco J, Bethencourt A, Melgares R, Cequier A, Dominguez A, Mainar V, López-Mínguez JR, Moreu J, Martí V, Moreno R, Jiménez-Quevedo P, Gonzalo N, Fernández C, Macaya C; RIBS V Study Investigators, under the auspices of the Working Group on Interventional Cardiology of the Spanish Society of Cardiology. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent in-stent restenosis: the RIBS V Clinical Trial. *J Am Coll Cardiol.* 2014;63(14):1378-86.
46. Habara S, Mitsudo K, Kadota K, Goto T, Fujii S, Yamamoto H, et al. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. *JACC Cardiovasc Interv.* 2011;4(2):149-54.
47. Byrne RA, Neumann FJ, Mehili J, Pinieck S, Wolff B, Tiroch K, Schulz S, Fusaro M, Ott I, Ibrahim T, Hausleiter J, Valina C, Pache J, Laugwitz KL, Massberg S, Kastrati A; ISAR-DESIRE 3 investigators. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet.* 2013;381(9865):461-7.
48. Rittger H, Brachmann J, Sinha AM, Waliszewski M, Ohlow M, Brugger A, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. *J Am Coll Cardiol.* 2012;59(15):1377-82.
49. Rittger H, Waliszewski M, Brachmann J, Hohenforst-Schmidt W, Ohlow M, Brugger A, et al. Long-Term Outcomes After Treatment With a Paclitaxel-Coated Balloon Versus Balloon Angioplasty: Insights From the PEPCAD-DES Study (Treatment of Drug-eluting Stent [DES] In-Stent Restenosis With SeQuent Please Paclitaxel-Coated Percutaneous Transluminal Coronary Angioplasty [PTCA] Catheter). *JACC Cardiovasc Interv.* 2015;8(13):1695-700.
50. Mamuti W, Jiamali A, Rao F, Zhang W, Pei X, Ablimit A, et al. Drug-coated balloon angioplasty for drug-eluting stent restenosis: insight from randomized controlled trials. *Ann Med.* 2014;46(8):679-83.

51. Kufner S, Joner M, Schneider S, Tölg R, Zrenner B, Repp J, Starkmann A, Xhepa E, Ibrahim T, Cassese S, Fusaro M, Ott I, Hengstenberg C, Schunkert H, Abdel-Wahab M, Laugwitz KL, Kastrati A, Byrne RA; ISAR-DESIRE 4 Investigators. Neointimal modification with scoring balloon and efficacy of drug-coated balloon therapy in patients with restenosis in drug-eluting coronary stents: a randomized controlled trial. *JACC Cardiovasc Interv.* 2017;10(13):1332-40.