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DRUG-ELUTING STENTS: STATE-OF-THE-ART

STENTS FARMACOLÓGICOS: ESTADO ATUAL

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ABSTRACT

Stents farmacológicos foram desenvolvidos para reduzir a resposta proliferativa neointimal e, consequentemente, a reestenose, a mais frequente limitação da intervenção coronária percutânea com balão e stents não farmacológicos. O desenvolvimento desses dispositivos baseia-se no maior entendimento da biologia da reestenose, na seleção de fármacos antiproliferativos adequados para os diversos mecanismos envolvidos nesta complicação e no uso de plataformas/polímeros adequados para a entrega do fármaco. Consequentemente, o desempenho destes dispositivos depende da perfeita interação de todos estes elementos. As abordagens atuais para minimizar a reestenose são revisados neste capítulo. Embora a primeira geração dos stents farmacológicos tenha sido focada na eficácia em reduzir a reestenose, questões relacionadas à sua segurança surgiram, comprometendo seu uso mais disseminado. As novas gerações de stents farmacológicos, com polímeros duráveis ou bioabsorvíveis, conseguiram reduzir as taxas de nova intervenção e de trombose. Embora o modelo ideal de stent farmacológico ainda esteja em investigação, é certo que esta tecnologia já se estabeleceu como primeira linha na intervenção coronária percutânea contemporânea.

Keywords: Coronary restenosis; Polymers; Drug-eluting stents; Thrombosis.

RESUMO

Stents farmacológicos foram desenvolvidos para reduzir a resposta proliferativa neointimal e consequentemente a reestenose, mais frequente limitação da intervenção coronária percutânea com balão e stents não faramcológicos. O desenvolvimento destes dispositivos baseia-se no maior entendimento da biologia da reestenose, na seleção de fármacos anti-proliferativos adequados para os diversos mecanismos envolvidos nesta complicação e no uso de plataformas/polímeros adequados para entrega do fármaco. Consequentemente o desempenho destes dispositivos depende da perfeita interação de todos estes elementos. As abordagens atuais para minimizar a reestenose são revisados neste capítulo. Embora a primeira geração dos stents farmacológicos tenha sido focada na eficácia em reduzir a reestenose, questões relacionadas à sua segurança surgiram, comprometendo seu uso mais disseminado. As novas gerações de stents farmacológicos com polímeros duráveis ou bioabsorvíveis conseguiu reduzir as taxas de nova intervenção e de trombose. Embora o modelo ideal de stent farmacológico ainda esteja em investigação, é certo que esta tecnologia já se estabeleceu como primeira linha na intervenção coronária percutânea contemporânea.

Descritores: *Stents farmacológicos; Polímetros; Reestenose coronária; Trombose.*

INTRODUCTION

Pharmacological stents (PS) were developed to reduce neointimal hyperplasia and minimize restenosis, which occur following balloon angioplasty and use of non-pharmacological stents.

An understanding of the histopathological mechanisms of coronary restenosis suggested the use of controlled-release drug-eluting stents with anti-inflammatory and antiproliferative effects. The clinical benefits of these stents are directly related to their components and to the interaction within the platform-drug-polymer complex.

EVOLUTION OF PHARMACOLOGICAL STENTS AND PHARMACOLOGICAL STENTS WITH DURABLE POLYMERS

The proven efficacy of first-generation PS that eluted sirolimus (SES) or paclitaxel (PES) was observed in initial studies and confirmed in subsequent randomized trials. However, there was concern about safety related to late and very late stent thrombosis.[1-3] The suboptimal biocompatibility of polymers, late endothelialization, and adverse responses in the healing, treated vessel were described and included in

the histopathological mechanisms of intrastent thrombosis, the most feared complication of percutaneous coronary intervention.[4-7] To minimize inadequate endothelial responses to first-generation PS and to overcome the technology of their predecessors, new devices have been developed and specific modifications have been implemented. The new generation of PS incorporated more efficient elution mechanisms, structures with smaller profiles, and more biocompatible polymers. The polymers are the central elements of PS, and act as the reservoirs and carriers of controlled release of antiproliferative drugs. In some cases, the first polymers developed for PS generated excessive local inflammation, resulting in late thrombosis and restenosis.[8,9] However, biocompatible polymers generate less inflammatory response, use new elements, are applied to the outer abluminal surface of the metal structure, and contain less polymer mass. The current trend is the development of polymer-free or biodegradable polymer systems. The three most commonly used PS employ a durable polymer, and include the everolimus-eluting (EES) Xience® and Promus®, and the zotarolimus-eluting (ZES) Resolute. As there is robust scientific evidence for their efficacy and safety, these stents are used as a "gold standard," and their benefits are similar to those of new devices. Compared to other PS using first-generation durable polymers, EES and ZES incorporate more biocompatible polymers and have changed their stainless steel metal platform to chromium-cobalt or chromium-platinum. Therefore, they use thinner stems with a low crossing profile, without significant loss of radial strength and opacity. Such characteristics are essential to improve the delivery of the platform with a lower degree of endothelial injury and to avoid the phenomenon of elastic recoil. Widely tested in various clinical settings and anatomical complexities, the results using these stents were sustainable and highly reproducible.

EVEROLIMUS-ELUTING PHARMACOLOGICAL STENTS

In EES, the drug has a concentration of 100 pg/cm^2 and is stored in a biodegradable polymer. The fluorine base has a thickness of 7.8 μm and is coated with a thin (81 μm) and flexible chromium-cobalt platform. The pharmacokinetics of EES are similar to those of SES, with release of 80% of the drug within 30 days, and with no drug detectable after 120 days. Preclinical studies have shown that the coverage of the EES metal stems is faster and that functional endothelialization is more effective when compared to the eluates of sirolimus, paclitaxel, and zotarolimus.[10]

Several randomized studies have concluded that EES are more effective and safer. The SPIRIT IV study included 3,867 patients undergoing angioplasty using EES or PES. In both groups, guided by ischemia during the first year of follow-up, there was a significant reduction in target vessel revascularization rates. The mortality and infarction rates related to the treated vessel were similar. EES reduced rates of myocardial infarction and definite/probable stent thrombosis. After three years, EES patients had a significant reduction in mortality when compared to PES patients.[11] The COMPARE study included 1,800 patients submitted to angioplasty using EES or PES. This study showed a reduction of combined major cardiovascular events (death from all causes, acute myocardial infarction [AMI], and target vessel revascularization), in patients treated with both EES (6.2%) and PES (9.1%) ($p = 0.02$).[12] The BASKET-PROVE study included 2,314 patients treated with EES, SES, or FNS. The reduction of target vessel revascularization in the EES and SES groups was less than in the FNS group. However, after two years of follow-up, the reduction in mortality, infarction, or stent thrombosis was similar in all three groups.[13] The EXCELLENT[14] and ISAR-TEST IV[15] studies compared EES and SES, and found that the rates of late luminal loss at 9 and 24 months were similar.

Recently, EES were compared to left internal mammary grafts in patients submitted to left coronary trunk revascularization. In the EXCEL randomized clinical trial, there were no significant differences in death from all causes, AMI, and cerebrovascular accidents (15.4% vs. 14.7%; hazard ratio [HR] 1.00; 95% confidence interval [CI]: 0.79-1.26; $p = 0.98$). This result confirmed that EES is a valid option for this type of treatment, a niche that until recently was exclusively occupied by myocardial revascularization surgery.[16]

ZOTAROLIMUS-ELUTING PHARMACOLOGICAL STENTS

ZES, originally designed as second-generation stents, contain 10 μg of the drug per mm of stent, stored in a thin layer of polymer (5.3 μm) that covers the thin (91 μm) and flexible chromium-cobalt stem. Zotarolimus is the most lipophilic antiproliferative drug and its release is faster than that of other drugs, with 90% elution in seven days and complete elution in the first 30 days. Initial studies of the ENDEAVOR series showed low vessel failure rates, even though late luminal loss is higher compared to other drugs. In the ENDEAVOR II study, which included 1,197 patients, ZES were compared to a conventional metallic equivalent, and showed better rates of target vessel revascularization in nine months, a result maintained after five years of follow-up. When compared to first-generation stents, ZES had discouraging results regarding target vessel revascularization, although target vessel failure rates did not increase when revascularization was guided by ischemia. To solve the problem of a high rate of late luminal loss, the company modified the polymer, and started using a hydrophilic component in the endoluminal side and a hydrophobic component adjacent to the surface of the stent. These changes reduced the elution rate of the drug to 60% in the first 30 days and 100% at 180 days, so that this device had the slowest release within that category. The RESOLUTE study (*single arm*) evaluated ZES with a new polymer composition. In this model, the late luminal loss was 0.22 mm and the binary restenosis rate was 2.1%. This was notably lower when compared to previous studies with ZES and metal stents. The RESOLUTE study (*all comers*) included 2,292 patients and compared EES versus ZES. The rates of failure and target vessel revascularization in the first year of follow-up were comparable. However, there was a lower definitive thrombosis rate in favor of EES. After

two years, there was a trend in favor of EES regarding probable/definitive thrombosis (p = 0.77).[17] On the other hand, in the TWENTE study, results differed and there was no significant difference in target vessel revascularization rates or other clinical outcomes (including device thrombosis) between the two stents.

Table 1 presents the main PS with durable polymers currently in clinical use.

PHARMACOLOGICAL STENTS WITH BIORESORBABLE POLYMERS

The understanding that durable polymers with greater thickness and lower biocompatibility perpetuated the local anti-inflammatory response and potentiated the occurrence of late and very late thrombosis led to the development of bioresorbable polymers. This concept is attractive. For the required time, the polymer could fulfill its function of storing and controlling the elution of the drug, with subsequent bioresorption and disappearance from the metal platform. Most of the reabsorbed devices composed of poly-L-lactic acid (PLLA) and poly-DL-lactic acid (PDLLA) are progressively metabolized into ester chains and subsequently degraded into lactic acid. The first stent using this new concept was the Biolimus A9-eluting stent, with a highly lipophilic drug, placed in a thin layer of stainless steel at a concentration of 15.6 μg/mm. *In vivo* studies have shown that the polymer is completely converted into lactic acid after six to nine months. The FIM study, conducted in two centers in Germany and one center in Brazil, compared 80 patients treated with this device with 40 patients who used the conventional metallic equivalent. In this study, there was a significant reduction of late luminal loss (0.26 vs. 0.74, p = 0.001) in patients treated with the new device after six months. The randomized LEADERS clinical trial included 1,707 patients and compared the Biolimus A9-eluting stent with first-generation SES. In this study, there was no significant difference in the combined primary outcome (death, AMI, and target vessel revascularization) or in any of the cardiovascular outcomes analyzed individually, after nine months of follow-up. Late luminal loss, as well as the rate of definitive/probable intrastent thrombosis, were also equivalent. Meta-analysis of the randomized studies ISAR-TEST 3, ISARTEST 4, and LEADERS showed that pharmacological stents with biodegradable polymer are associated with very low rates of intrastent thrombosis and AMI when compared to SES. As the effectiveness of durable polymer stents was confirmed, contemporary studies have aimed at improving the safety profile of these new devices.

The processes that lead to the perpetuation of inflammation are the same as those that delay tissue healing after stent implantation. Reduced inflammatory activity and hypersensitivity reactions, imputed to polymers, theoretically accelerate the tissue repair process, allowing the antithrombotic strategy to be less aggressive. Therefore, the potential reduction in thrombosis rates of bioresorbable stents reduces the number of bleeds related to antiplatelet therapy. The GLOBAL LEADERS study is recruiting patients to evaluate antiplatelet therapy in those with the Biolimus A9-eluting stent. During the first month, all patients receive double antiplatelet therapy (DAPT). Then, for 23 months, they receive ticagrelor monotherapy or undergo standard treatment for 12 months. Both groups switch to aspirin monotherapy after the established follow-up time. This study aims to include 16,000 patients for adequate statistical power to determine the combined outcome of death from all causes or non-fatal AMI for two years after randomization.

Table 1. Most common drug-eluting stents with durable polymers in clinical use.

Stent	Manufacturer	Antiproliferative drug (dose) and release time	Metal alloy, thickness	Polymer, thickness, location	Late luminal loss	Clinical study
Endeavor™	Medtronic	Zotarolimus (10μg/mm), 100% released in 14 days	CoCr, 91μm	Phosphorylcholine, 3 μm, abluminal	0.61mm (12 months)	ENDEAVOR II
Promus Element™	Boston Scientific	Everolimus (1μg/mm^2), 87% released in 3 months	PtCr, 81μm	Copolymer of co-hexafluoropropylene fluoride polyvinylidene, and poly n-butyl methacrylate (PBMA), 6 μm, circumferential	0.17mm (9 months)	PLATINUM QCA
Resolute Integrity™	Medtronic	Zotarolimus (10 μg/mm), 85% released in 2 months	CoCr, 91μm	BioLinx (C19 hydrophilic polymer/polyvinyl pyrrolidinone/C10 hydrophilic polymer), 4.1 μm, abluminal	0.22mm (9 months)	RESOLUTE FIM
Xience V/ Prime/ Expedition /Alpine	Abbott Vascular	Everolimus (1μg/mm^2), 80% released in 1 month and 100% in 3 months	CoCr, 81μm	Copolymer of co-hexafluoropropylene fluoride polyvinylidene and poly n-butyl methacrylate (PBMA), 7,6 μm, circumferential	0.10mm (9 months)	SPIRIT I

CoCr = cobalt-chromium; PtCr = platinum-chromium.

A Brazilian company developed chromium-cobalt SES with ultrafine stems (75 μm) and a bioresorbable polymer composed of PLLA and poly(d,l-lactic-co-glycolic acid) (PDLLGA) (INSPIRON®). This national device was compared to its non-pharmacological equivalent in a randomized *"first-in-man"* study, with a significant reduction of late luminal loss and the percentage of neointimal obstruction.[18] A report with 470 patients followed up for one year further confirmed the efficacy and the good safety profile of the device, presenting very low target vessel failure rates.[19] The multicenter REPAIR study is currently being performed in four Brazilian centers with the aim to determine, through optical coherence tomography, the moment when the stems of the bioresorbable polymer stent (INSPIRON®) present complete endothelialization. This hypothesis-generating clinical trial aims at identifying an ideal theoretical period for discontinuation of DAPT, serving as the basis for the development of clinical studies addressing this topic.

Although the concept of bioresorbable polymer stents is attractive, its advantage over the excellent results with durable polymer stents still needs to be confirmed. A meta-analysis involving 126 randomized clinical trials and 258,544 patients treated with conventional metal stents, first- and second-generation pharmacological stents, and biodegradable polymer stents failed to show superiority of biodegradable polymer stents over stents with durable polymers. In addition, durable state-of-the-art stents with a chromium-cobalt platform showed the best combination of efficacy and safety.[20]

Table 2 shows the main PS with bioresorbable polymers currently in clinical use.

PHARMACOLOGICAL STENTS WITHOUT POLYMERS (NON-POLYMERIC)

To end the exposure of the endothelium to the exacerbated inflammatory process, alternatives were created to store the drug in the metallic structure of the stent without the need for the polymer. This potential benefit occurs to the detriment of the ability to control the elution time of the drug, and the dynamics of the release of the drug becomes faster and may affect its therapeutic efficacy. Therefore, modifications in the metal structure, such as micropores or microcracks, are required to carry the antiproliferative agent. Alternatively, the drug can be directly attached to the metal surface through covalent bonds, crystallization/chemical precipitation, or dissolution in biodegradable non-polymeric carriers (nanoparticles).[21]

Given the excellent results of new generation PS, regardless of the type of polymer used, the development of non-polymeric stent technology is focused on the reduction of DAPT time after percutaneous intervention. The absence of the polymer accelerates tissue repair due to the lower inflammatory response, and there may be complete endothelialization of the stent stems within 30 days after the procedure, if the implant is technically optimized.

The randomized LEADERS FREE clinical trial had the greatest impact in this area. This trial evaluated a stainless steel platform with selective microstructures on the abluminal surface that eluted Biolimus A9 (Biofreedom®) (Figure 1) in patients with at least one criterion of high risk for bleeding (age ≥ 75 years, oral anticoagulant use, anemia, thrombocytopenia, previous bleeding, stroke, etc.). At the end of 12 months, the group treated with the non-polymeric

Table 2. Most common drug-eluting stents with bioresorbable polymers in clinical practice.

Stent	Manufacturer	Antiproliferative drug (dose) and release time	Metal alloy, thickness	Polymer, thickness, location	Late luminal loss	Clinical study
BioMatrix/ NOBORI™	Biosensor/ Terumo	Biolimus A9 (15.6 µg/mm), 45% released in 1 month and 100% released in 3 months	SS, 112µm	PLA, 10µm, abluminal, absorption in 9 months	0.11 – 0.13mm (9 months)	LEADERS/ NOBORI I
Biomime™	Meril Life Science	Sirolimus (1.25 µg/mm2), 100% released in 1 month	CoCr, 65µm	PLLA/PLGA, 2µm, abluminal, absorption N/A	0.15mm (8 months)	MERIT I
Excel™	Biosensors	Sirolimus (195-376 µg), release profile not reported	SS, 119µm	PLA, 10-15µm, absorption in 6 to 9 months	0.21mm (6-12 months)	CREATE
INSPIRON™	SCITECH	Sirolimus (1.4 µg/mm2), 80% released in 1 month	CoCr, 75µm	PLA, PLGA, 5µm, abluminal, absorption in 6 to 9 months	0.19mm (6 months)	INSPIRON I
ORSIRO™	Biotronik	Sirolimus (1.4 µg/mm2), 50% released in 1 month	CoCr, 60µm	PLLA with silicon carbide layer, 7 µm, circumferential, absorption in 12 to 24 months	0.10mm (9 months)	BIOFLOW II
SYNERGY™	Boston Scientific	Everolimus (5.6 µg/mm), 50% released in 2 months	PtCr, 71µm	PLGA, 4 µm, abluminal, absorption in 4 months	0.10mm (6 months)	EVOLVE I
Ultimaster™	Terumo	Sirolimus (3.9 µm/mm), 100% released in 3 to 4 months	CoCr, 80µm	PDLLA/PCL, abluminal, Thickness not reported, absorption in 3 to 4 months.	0.04mm (6 months)	CENTURY I

CoCr= cobalt-chromium; N/A = not available; PCL = poly (L-lactic-co-caprolactone); PDLLA = poly (D-L-lactic acid); PLA = polylactic acid; PLGA = poly (lactic acid-co-glycolic acid); PLLA = L-polylactic acid; PtCr = platinum-chromium; PVP = polyvinylpyrrolidone; SS = stainless acid.

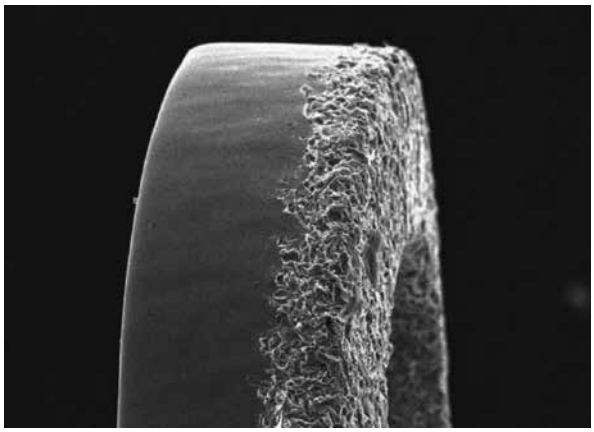

Figure 1. Biofreedom® drug-eluting stent: Microscopic visualization of the selective microstructures on the abluminal surface of the stainless steel structure that will be filled by the antiproliferative drug Biolimus A9.

drug-eluting stent had a lower incidence of the primary safety outcome in terms of cardiac death, AMI, or stent thrombosis (9.4% vs. 12.9%; HR 0. 71; 95% CI: 0.56-0.91; $p < 0.001$), and efficacy in terms of ischemia-guided reference lumen area (5.1% vs. 9.8%; HR 0.50; 95% CI: 0.37-0.69; $p < 0,001$).[22] The two-year follow-up was published in 2016, confirming previous results regarding safety (12.6% vs. 15.3%; HR 0.80; 95% CI: 0.64-o 0.99; $p = 0.039$) and efficacy (96.8% vs. 12.0%; HR 0.54; 95% CI: 0.41-0.72; $p < 0.0001$). A pre-specified substudy involving only patients with acute coronary syndrome (LEADERS FREE ACS)[23] confirmed the findings of the main study, demonstrating the superiority of non-polymeric stents over non-pharmacological stents. Another pre-specified substudy (LEADERS FREE OAC) involving patients receiving chronic oral anticoagulation did not show such strong results; the trend was toward a better efficacy outcome, with no significant difference in safety outcome after a two-year follow-up.[24]

CONCLUSIONS AND PERSPECTIVES

Althugh first-generation PS have placed great emphasis on the efficacy profile, problems with safety outcomes have resulted in their replacement in clinical practice. More recent PS with durable biocompatible polymers or bioresorbable polymers have been shown to significantly reduce the risk of further vessel revascularizations and stent thrombosis.

The ideal "design" of the platform, the ideal polymer (or its absence), and the antiproliferative drugs and their release kinetics are under intense investigation; thus, with the evidence currently available, it is not possible to determine the superiority of one in relation to others. In addition, there is no doubt that modern PS will continue to play a key role in the treatment of coronary artery disease and that devices under development should incorporate mechanisms to reduce thrombosis rates and promote endothelialization.

The focus of studies in this area has been to reduce the time of DAPT and thus reduce the time that patients are exposed to an increased risk of bleeding. This will be theoretically possible when we are able to promote high rates of tissue repair in the shortest time possible, avoiding excessive tissue proliferation. Endothelial healing depends directly on the stent used, the technique implemented and, mainly, the degree of inflammation generated throughout this process. It was initially thought that the efficacy of antiproliferative drugs was the key to resolving unwanted events in the treatment of coronary disease with stents. The basis of this concern has changed with the understanding of the histopathology of these events and the polymer is the key factor to be developed. The polymers perpetuate the inflammatory response and trigger hypersensitivity reactions, factors that delay effective endothelialization of the metal structures of the devices.

First-generation PS were largely replaced by new generation PS, and PS with durable polymers are the most commonly used. Devices with bioresorbable polymers and non-polymeric stents are attractive alternatives and represent the current focus of scientific development in this area.

CONFLICTS OF INTEREST

The authors declare that they do not have conflicts of interest in this work.

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