

Expert Consensus (SBC/SBHCI) on the use of Drug-Eluting Stents. Recommendations of the Brazilian Society of Interventional Cardiology/Brazilian Society of Cardiology for the Brazilian Public Single Healthcare System

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Abstract

The authors review percutaneous coronary intervention (PCI) evolution and its growing application in myocardial revascularization for patients with coronary heart disease in Brazil and worldwide. PCI was introduced in 1977 using only the catheter balloon. Limitations of this method (acute occlusion and coronary restenosis) led to the adoption of coronary stents and more recently the advent of drug-eluting stents², which were developed to drastically reduce restenosis rates. These developments allowed the exponential growth of percutaneous coronary intervention (PCI) procedures in Brazil which have replaced many bypass surgery procedures and have become the gold standard for the majority of symptomatic patients suffering from coronary artery disease. The preference for this procedure gained new dimensions in 2000 when the Brazilian Public Healthcare System (SUS) began reimbursing for stent procedures. This measure exemplified the importance of the Public Healthcare System's participation in incorporating medical advances and offering a high standard of cardiovascular treatment to a large portion of the Brazilian population. It is emphasized that prevention of in-stent restenosis is complex due to its unpredictable and ubiquitous occurrence. Control of this condition improves quality of life and reduces the recurrence of angina pectoris, the need to perform new revascularization procedures and hospital readmissions. The overall success of the drug-eluting stents has proven to be reliable and consistent in overcoming restenosis and has some beneficial impact for all clinical and angiographic conditions. This paper discusses the adoption and criteria for the use of drug-eluting stents in other countries as well as the recommendations established by the Brazilian Society of Interventional Cardiology for their reimbursement by SUS.

The incorporation of new healthcare technology involves two distinct stages. During the first stage, the product is registered with the National Health Surveillance Agency (ANVISA). During this stage the interested company submits to the regulatory agency, results from clinical studies that demonstrate the efficacy and safety of the new device or pharmaceutical product. Frequently, in addition to clinical studies, approval records for clinical use

from the regulatory agencies of other countries, mainly the United States of America and the European Community are also submitted. The successful completion of this stage means that the medication or device may be prescribed or used by the physicians in Brazil.

The second stage in the incorporation of new healthcare technology involves the reimbursement or financing of the treatment that was approved in the previous stage based on its efficacy and safety. This stage can be more complex than the first one since the new technology, whether a substitution for established treatment methods or the introduction of a new treatment concept, are usually more expensive.

The incorporation of new technology requires a cost-effectiveness analysis so that fund administrators can make decisions based on the universal scenario of limited resources to finance healthcare with treatments that are more and more burdensome. The difficulties of funding management are aggravated by medical and social ethical implications that arise when a treatment is approved based on its efficacy and safety but is not made available to patients who could benefit greatly from it.

In Brazil, assessment methods for the incorporation of new technology based on reimbursement or financing have not been fully developed for either the private healthcare plans or the Brazilian Public Healthcare System (SUS). The implementation of new technology in both healthcare systems is a slow process and frequently the implementation is a result of the requirements of patients or the organizations that represent them and at times is the result of legal proceedings or political pressure imposed by physicians and their respective scientific societies.

Our objective is to review the evolution of percutaneous coronary intervention (PCI) in Brazil and its current status in view of the advent of drug-eluting stents, the growing participation of drug-eluting stents in myocardial revascularization to treat patients with coronary heart disease, as well as, to compare the regulatory standards from Brazil and other countries regarding the incorporation and recommendations for the use of this new technology.

Key words

Angioplasty, stents, restenosis, coronary artery bypass surgery.

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Percutaneous coronary intervention: The evolution from balloon catheters to drug-eluting stents

Since its introduction in 1977, the clinical efficacy of PCI has been limited due to the possibility of an uncontrollable acute occlusion of the vessel being treated and the late reoccurrence of an obstruction, a clinical condition known as coronary restenosis. Using only the balloon catheter, 30% to 50% of the patients suffered from restenosis, which used to occur between one and six months after the procedure. It is important to emphasize that these rates were observed with a clinical and angiographic profile that had a significantly lower complexity in comparison to contemporary patients. All the resources investigated to reduce the occurrence of restenosis, especially systemic administration of drugs were unsuccessful.

The first percutaneous device that promoted significant reduction in coronary restenosis rates was the stent, an expandable metallic endovascular prosthesis. Stents reduced restenosis by 30% to 35% as demonstrated in three major controlled multi-center studies (Benestent¹ and II² Stress³).

The stents reduced the immediate elastic recoil and negative vessel remodeling, physical phenomena that are responsible for two thirds of the coronary lumen loss after balloon PCI. Besides reducing restenosis, stents increased the safety and immediate PCI prognosis, reducing the occurrence of acute coronary occlusions from between 4% and 11% to between 0.5% and 2%⁴. Based on these two benefits, coronary stents were incorporated as the preferred technique for percutaneous coronary revascularization. The stent was approved for clinical use in 1994 and since that time worldwide usage has continually increased reaching the mark of 85% to 90%⁵⁻⁷.

In relation to SUS, the number of patients treated with PCI since the year 2000 exceeded the number of bypass surgery, which coincides with the start of coronary stent reimbursement (fig.1). This information must not conceal the fact that under funding seriously limit patient access to cardiovascular procedures in Brazil. Estimates show that in Brazil, a mere 251 coronary angioplasties are performed per million of inhabitants

on a yearly basis (CENIC www.sbhci.org.br and DATA-SUS www.datasus.gov.br). This is an extremely low number when compared to the number of these procedures offered in other countries such as Uruguay (836), Porto Rico (728), England (894), Canada (900), Spain (580), Portugal(530) and Poland (484) (http://www.solaci.org/docs/registro_1998_2003.ppt#1, www.bcis.org.uk). It is important to emphasize that the prevalence of heart disease in Brazil is not lower than that of the countries mentioned.

In-stent restenosis: A major limitation of PCI

Vascular trauma caused by dilation of the artery and the permanent presence of the stent, lead to variable degree of intimal tissue proliferation. When the intimal proliferation reaction is exaggerated, the coronary lumen is drastically reduced⁸⁻¹³. Clinical experience with stents has enabled the identification of the main predictors of this phenomenon, now known as in-stent restenosis. These factors are grouped according to those related to the patient (diabetes mellitus), those related to lesion characteristics such as length (>15 mm) or small vessel diameter (<3 mm), and those related to the procedure (residual stenosis >30%). Patients with one or more of these factors have significantly higher restenosis rates, which can be as high as 50% for patients with a combination of these unfavorable aspects. It is important to emphasize that its occurrence is unpredictable and its incidence is ubiquitous.

Clinical restenosis, also called target-vessel revascularization, is comprised of the association of a reoccurrence of significant stenosis (>50%) with the presence of angina symptoms or myocardial ischemia demonstrated by functional tests. On average, the occurrence of clinical restenosis is 50% lower than angiographic restenosis. Clinical restenosis usually require hospital readmission for a new revascularization procedure, either percutaneous or at times bypass surgery^{6,7}.

The advent of drug-eluting stents

Drug-eluting stents combine the mechanical support supplied by the stent implant (suppression of negative remodeling) with a controlled local release of antiproliferative drugs.

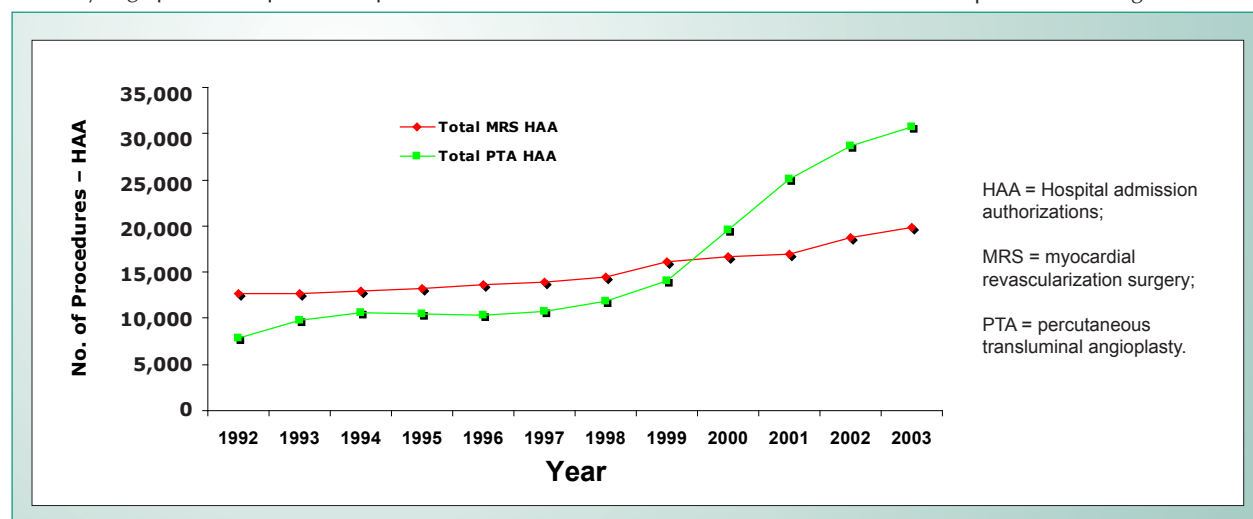


Fig. 1 - Chronological analysis of myocardial revascularization procedure payments made by the Brazilian Single Health Care System (SUS).

Success of this new technology is based on effective antiproliferative drugs (cytostatic or cytotoxic mechanism) with minimal or no level of toxicity, a predictable and programmable release system (polymers), and a low thrombosis rate.

Up to 2004, only two medications, sirolimus and paclitaxel, which are released from the Cypher_{TM} and Taxus_{TM} stents, respectively, had achieved extensive successful clinical investigation. The common factor between these two drug-eluting stent systems is that the medication is stored and released in a controlled manner from polymers.

Clinical studies with the sirolimus (Cypher_{TM}) coated stent were based on an approximately 50% reduction of intimal tissue proliferation in balloon angioplasty porcine models with oral or intramuscular administration. The first clinical study was conducted by Sousa and associates in Brazil, with excellent angiographic, ultrasonic and clinical follow-up¹⁵⁻¹⁶. In this initial series of 30 patients, neointimal hyperplasia was reduced by roughly 80% with late target vessel lumen loss rate of less than 0.20 mm, that was maintained in serial angiographic assessments during the four years after the initial implant.

Various other controlled clinical trials followed this initial series testing larger patient groups and a spectrum of increasing risk for the occurrence of in-stent restenosis, or in other words, recruiting patients with more serious disease and more unfavorable angiographic pattern. All the studies consistently and homogeneously demonstrated the efficacy of this technology in reducing clinical in-stent restenosis from 15% to less than 5% (RAVEL¹⁷, SIRIUS¹⁸, C-SIRIUS¹⁹ and E-SIRIUS²⁰). This stent was approved for clinical use in Europe, the United States and Brazil in 2002.

The safety and efficacy of the stent coated with paclitaxel (TAXUS_{TM}) was comparable as demonstrated in various studies (TAXUS I²¹, II²², III²³, IV^{24,25}). These series have incorporated new data revealing that both immediate and late safety and efficacy are maintained. Other more complex studies have been conducted and should be published in the near future.

The rates for a new target vessel revascularization were reduced from 19.2% to 6.4% in the Sirius¹⁸ study and from 12% to 4.7% in the TAXUS IV²⁴ study.

Extensive investigations comparing the performance of these two drug-eluting stents are ongoing. Some studies have been presented at conferences but to date have not been published.

In conclusion, we can mention the most recent systematic revision that incorporated the analyses from 11 major controlled drug-eluting stent clinical studies (n=5,103 patients). This meta-analysis clearly demonstrates the efficacy of drug-eluting stents in comparison to bare metal stents to reduce clinical in-stent restenosis. Clinical in-stent restenosis rates were reduced with the paclitaxel-coated stents from 21% to 6.8% and the sirolimus-coated stents from 14.2% to 4.8%²⁶.

One controversial aspect should be mentioned when discussing the clinical effectiveness and incorporation of drug-eluting stents in medical practice. Equivocally, the importance of this technology is occasionally questioned based on the argument that that it does not reduce the two major adverse cardiovascular events: myocardial infarction and death. Drug eluting stents were developed to reduce in-stent restenosis

and not to modify these major events that are related to the natural history of coronary atherosclerosis. The control of in-stent restenosis promotes an improvement in quality of life by reducing the risk of having to perform new revascularization procedures by 70%^{18,24,26,27}.

Adjunctive pharmacotherapy to drug-eluting stent use implantation

Antiplatelet therapy is mandatory after a PCI intervention and has been established since the balloon era when it was proven that aspirin reduced the occurrence of myocardial infarction associated with the procedure from 6.9% to 1.5%²⁸. With the advent of stents it was proven that a combination of aspirin with a thienopyridine, initially ticlopidine, was more effective. The efficacy of this combination was demonstrated in three randomized clinical trials (STARS²⁹, MATTIS³⁰, FANTASTIC³¹).

Nevertheless, ticlopidine has limitations such as a low gastrointestinal tolerance and the risk of neutropenia, especially when used for a prolonged period. Its pharmacodynamic properties are also unfavorable, requiring administration for 3 to 5 days before it reaches a significant antiplatelet effect.

Ticlopidine has been progressively substituted by clopidogrel that has comparable effectiveness, better tolerance and clinical safety levels which are associated with more favorable pharmacodynamics. The onset of its antiplatelet effect occurs roughly six hours after the administration of a 300 mg load dosage and within 2 hours after the oral administration of a 600 mg bolus dose. The efficacy and safety of clopidogrel have been demonstrated in randomized clinical trials comparing it to ticlopidine (TOPPS³² and CLASSICS³³), and in a meta-analysis with 13,827 patients³⁴.

With delayed endothelialization, the prevention of late thrombosis with drug-eluting stents requires a longer duration of thienopyridine therapy in comparison to bare-metal stents. Patients that receive the sirolimus-eluting stent should use both antiplatelet medications for at least two months and those that receive the paclitaxel-eluting stent, for six months. Nevertheless, observations of current medical practices reveal that thienopyridines are recommended for a minimum period of six months regardless of the type of drug-eluting stent implanted.

The thrombosis rate for drug-eluting stents in comparison to bare metal stents is also a controversial issue. It is agreed that late stent thrombosis (after the first month) is in fact higher with drug-eluting stents especially in the case of clinical (diabetes) or angiographic (multiple stents with overlapping and bifurcations) adversities. A recent series demonstrated that the premature suspension of the aspirin and thienopyridine therapy is the greatest predictor for late thrombosis³⁵. Therefore, any healthcare program that incorporates the use of drug eluting stents should ensure patient access to these medications for at least six months.

Worldwide drug-eluting stent adoption policies

In September 2003, the government health care system in France set the following criteria for the reimbursement of

Consensus

sirolimus-eluting stents: stenosis in 2.5 to 3.5 mm vessels with a length less than 18 mm, and high risk restenosis patients (diabetics, stenosis in left anterior descending artery and stenosis shorter than < 15 mm in a vessel with a diameter < 3 mm)³⁶.

The following contraindications were considered: left coronary artery stenosis, ostial location, angiographic evidence of thrombus, severe calcification, primary PCI and left ventricular ejection fraction < 50%; antiplatelet or heparin intolerance; contrast agent and/or stainless steel allergies; and women of childbearing age.

In November 2004, reimbursement of the paclitaxel-eluting stent was established for diabetic patients in lesions of vessels with a diameter between 2.5 and 3.5 mm regardless of the length. The reimbursement is limited to one stent per procedure except in the case of a long dissection (maximum 3 stents). Diabetic patients with multi-vessel disease and contraindication for bypass surgery may also receive up to three stents.

In the province of Ontario, Canada, the recommendations for drug eluting stents were outlined by the Cardiac Care Network of Ontario (CCNO)³⁷ and accepted by the Ministry of Health. The recommendations included diabetic and non-diabetic patients with long stenosis (>18 mm) located in vessels with a diameter < 2.75 mm or in patients in whom the occurrence of in-stent restenosis could have serious consequences (unprotected left coronary artery or single remaining vessel).

CCNO estimated that these recommendations would cover 40% of percutaneous treatment target lesions based on Canada's standard percutaneous coronary intervention practices.

In the United Kingdom, the Ministry of Health followed the recommendations published by the National Institute for Clinical Excellence in October, 2003³⁸. Reimbursement covers Cypher_{TM} and Taxus_{TM} stents for patients indicated for revascularization of one vessel with a reference diameter less than 3 mm and a stenosis length greater than 15 mm. Patients who have suffered an acute myocardial infarction with less than 24 hours of evolution and patients with angiographic evidence of thrombosis would not be eligible for reimbursement.

In the United States of America, both drug-eluting stents have been approved for clinical use in patients whose symptoms are related to non-restenotic lesions with a length less than 30 mm in native coronary arteries with a diameter between 2.5 and 3.5 mm. The public system, Medicare has reimbursed these endovascular prostheses since April 2003, offering coverage for 30 million users (one stent per procedure; in cases that require two or more stents the approval of another cardiologist is requested). The reimbursement is also approved by the private health care plans (Blue Cross/Blue Shield, Aetna, Humana, etc.), encompassing 147 million people. The drug-eluting stents usage has already exceeded the 70% mark for patients submitted to PCI.

Assessment of the financial impact on the Brazilian Public Healthcare System (SUS)

In most of the countries where drug-eluting stents were approved, the incorporation strategies were developed to maximize the benefits attained and minimize the ensuing the

financial impact. For this reason the greatest indications were for lesions and patients with a higher restenosis risk³⁹. It is estimated that the implementation of the clinical indications recommended by the Brazilian Society of Interventional Cardiology (SBHCI) will result in the adoption of the drug-eluting stent for roughly 50% of all lesions treated. For SUS in 2005, this would be equivalent to approximately 20,000 units. This estimate of the number of drug-eluting stents does not consider the increase in the number of patients whose surgical indication could have been shifted to PCI indication. It is not possible at this time to make this estimate.

A perspective of bypass surgery can be interpreted from the study conducted by Powel and associates⁴⁰. Analyzing the coronary angiography of a significant series of consecutive patients submitted to surgery⁴¹, the authors confirm that if the inclusion criteria used in the clinical trials for drug-eluting stents had been followed strictly, only 6% would have been candidates for the procedure. However, during 2004, in the medical assessments made by cardiologists, as many as 46% of the patients indicated for surgical procedures would have been converted to PCI with drug-eluting stents. It was also observed that one of the main reasons for maintaining the indication for surgical myocardial revascularization, in this study, was the presence of chronic coronary occlusion.

At this time it is difficult to calculate the financial impact of drug-eluting stents on the SUS budget since the price paid for these endovascular prostheses should be the result of negotiation between the interested parties (SUS and company suppliers). Observations of the international scenario reveals that prices differ considerably among the various countries, particularly in those with strong public healthcare financing systems such as Canada, France, Australia, Portugal, Spain and the United Kingdom.

It is fundamental that in consideration of the current Brazilian scenario, which offers a very limited access to cardiovascular therapeutic procedures, the incorporation of drug-eluting stent procedures should be attained through additional funding and not reallocation of the existing insufficient resources.

Recommendations for the use of drug-eluting stents in the Brazilian Healthcare System (SUS)

The recommendations made by Brazilian Interventional Cardiology Society (SBHCI) are the result of assessments and observations of the clinical studies referred to in this paper as well as the criteria adopted by various other countries with systematic experience in the evaluation and incorporation of new healthcare technologies.

- I. Formal indications based on conclusive evidence, consensus or majority rule of specialists: patients clinically indicated for revascularization of a native coronary artery with:
 - a. Stenosis of the left descending anterior artery with a reference diameter of ≤ 3.5 mm;
 - b. Stenosis in a vessel with a diameter ≥ 2.5 and ≤ 2.75 mm;
 - c. Long stenosis that is ≥ 15 mm and ≤ 30 mm in length in

- a vessel with a diameter ≤ 3.5 mm;
- d. Stenosis in a single remaining vessel;
- e. In-stent restenosis;
- f. Diabetics with stenosis treatable by PCI;

II. Acceptable indications based on medical judgment for special clinical situations that do not have considerable scientific evidence or consensus:

- a. Stenosis of the left main coronary artery not protected by previous revascularization surgery;
- b. Stenosis with angiographic evidence of thrombus;
- c. PCI within the first 24 hours following an acute myocardial infarction;
- d. Stenosis located in bypass venous grafts.

III. Contraindications

- a. Severely calcified stenosis;
- b. Women who are pregnant or childbearing age who intend to become pregnant within six months of the PCI procedure;

c. Intellectual or social incapacity to understand the importance of using the antiplatelet therapy for six months or those that are unable to obtain these medications.

It should be emphasized that a hybrid indication for both bare-metal and drug-eluting stents has been anticipated for patients with more than one stenosis to be treated that have distinct characteristics.

PCI practices have presented a rapid evolution and therefore periodical revisions of these recommendations are imperative in order to implement continual updates.

Conclusions

With this revision, based on scientific documentation and clinical practices, SBHCI has recommended that SUS implement the reimbursement of drug-eluting stents within the shortest timeframe possible. SBHCI has also advised that along with the reimbursement of drug-eluting stents that the systematic offer of clopidogrel for a minimum timeframe of six months be mandatory.

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