

Myocardial Revascularization in Patients With Multivessel Disease

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The treatment of patients with multivessel disease aims at relieving the symptoms of ischemia, reducing the rate of cardiac events (infarction, arrhythmias), and preserving or restoring left ventricular function, resulting in a greater long-term survival. Important studies carried out during the 1970s comparing coronary artery bypass graft with the medicamentous therapy¹⁻³ led us to believe that such objectives were better achieved with surgery, especially when indicated to patients with a lesion in the left main coronary artery, three-vessel disease or ventricular dysfunction.

Great advances in clinical (statins, potent antiplatelet agents) and surgical (greater use of arterial grafts, better myocardial protection, procedures without extracorporeal circulation) therapy have occurred, resulting in an undeniable improvement in the prognosis of those patients. In recent years, percutaneous transluminal coronary angioplasty has become the most common form of myocardial revascularization used for the treatment of coronary artery disease. The improvement in the techniques and instruments allowed such less invasive form of revascularization to be offered to patients with multivessel disease with safety and efficacy similar to those of surgical revascularization reported in several studies. Silva et al⁴ have reported the results of a randomized study carried out in a single center in our country, assessing the long-term advantages of both strategies of revascularization regarding the clinical evolution of patients with multivessel coronary disease.

The first case series, published in the 1990s, compared coronary artery bypass surgery with balloon-catheter coronary angioplasty⁵⁻¹². Those studies showed in a uniform way that the mortality and infarction rates did not statistically differ between the 2 forms of treatment (fig.1); patients undergoing the percutaneous coronary intervention, however, more often required a new revascularization in the long run, due to the occurrence of restenosis. Although those studies had limitations regarding the selection of patients (inclusion of patients with one-vessel disease, clinical and angiographic differences between the populations), they confirmed the safety of coronary angioplasty and its indication to patients with one- or two-vessel disease and less complex lesions.

Initially used for managing complications of angioplasty (acute occlusions, vessel dissections), the implantation of coronary stents

has become frequent and has been recommended due to their mechanical properties of preventing elastic recoil and negative remodeling of the vascular wall, which are determinant factors in the process of coronary restenosis after balloon angioplasty. By reducing the occurrence of restenosis and acute complications, stent implantation produced results even closer to those obtained with surgery.

A meta-analysis¹³ comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty involving 2,643 patients and comprising the ARTS¹⁴, ERACI II¹⁵, and SOS¹⁶ studies showed no difference in the mortality and non-fatal infarction rates between the 2 groups at the end of one year. The need for a new revascularization in the group undergoing percutaneous transluminal coronary angioplasty with stents was 15%, half of the incidence reported for balloon angioplasty in patients with multivessel disease. The indices of new revascularization, however, continued significantly greater than those of coronary artery bypass graft, mainly due to intra-stent restenosis.

The article by Silva et al⁴ corroborated those results: the combined-event-free survival in 5 years reported in the study in question (82% for the surgical group, and 55% for the PTCA group, $P < 0.001$) was similar to that reported in the ARTS I study for the same follow-up period (tab. I)¹⁷.

We face a new era in the percutaneous treatment of coronary artery disease. The use of stents coated with antiproliferative drugs, carried and released in a controlled way in the vascular wall from biocompatible polymers proved effective in reducing neointimal hyperplasia, which is the major determinant of the occurrence of intra-stent restenosis. Since the first clinical use of sirolimus-eluting stents here in Brazil¹⁸, several studies have shown the safety and efficacy of that new technology for the treatment of *de novo* coronary lesions¹⁹⁻²². In a meta-analysis involving 5,103 patients²³, the angiographic restenosis rate and the adverse cardiac event rate (mainly revascularization of the target lesion) were significantly lower in patients treated with sirolimus- and paclitaxel-eluting stents as compared with those in patients treated with conventional stents (8.9% vs 29.3% and 7.8% vs 16.4%, respectively).

Although initially applied to selected patients with single lesions in larger-caliber vessels, the drug-eluting stents proved to be effective also in more adverse situations. In the RESEARCH study²⁴, including individuals with more complex lesions (bifurcations, venous grafts, impairment of the left main coronary artery, or long lesions requiring more than one stent), the evidenced angiographic restenosis rate (7.9%) was smaller than that reported for conventional stents. The observation that the type of intra-stent restenosis

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with drug-eluting stents is predominantly focal is of great clinical importance, because it allows the taking of a new percutaneous approach with a lower recurrence rate ²⁵.

The impact of the use of drug-eluting stents in patients with multivessel disease has been investigated in the ARTS II study ¹⁷, which compares, by use of paired analysis, the evolution of patients treated with sirolimus-eluting stents with that of the population in the ARTS I study, which had undergone surgery or implantation of conventional stents. Preliminary results referring to a 6-month follow-up have revealed that, although with a greater percentage of diabetic patients, greater quantity of treated lesions per patient, and use of longer stents in narrower vessels (all predictive factors of restenosis), the individuals treated with sirolimus-stents had a longer event-free survival than that of the patients assessed in the ARTS I protocol (93.6% vs 91% in the surgical group and 80% in the percutaneous coronary artery intervention group). The occurrence of death, infarction, and stroke was smaller in the sirolimus group (tab. II).

Patients with diabetes mellitus and multivessel coronary disease have a poorer prognosis in the short and long run as compared with that of nondiabetic patients, independently of the type of myocardial revascularization used. Restenosis is one of the major factors implicated in the worst prognosis of diabetic patients undergoing percutaneous coronary intervention. The presence of neointimal hyperplasia and the greater negative remodeling of the vessel after angioplasty, in addition to the increase in platelet aggregation and the reduction in the mechanisms of fibrinolysis explain the

greater tendency of diabetic patients towards recurring coronary artery obstruction in the previously treated site. Although the use of stents has reduced the incidence of restenosis, most studies comparing the results of the use of stents with those of surgery point to greater rates of new revascularization even when those devices are used ²⁶. In the ARTS I study, at the end of the first year of follow-up, the diabetic patients treated with percutaneous coronary angioplasty more often required a new revascularization when compared with the diabetic patients undergoing surgery (22.3% vs 3.1%; $P < 0.001$) ²⁷. That stresses the influence of the excessive neointimal hyperplasia in that subgroup as a determinant factor of intra-stent restenosis.

The benefits obtained with the use of drug-eluting stents may be extended to diabetic patients, who have a lower incidence of angiographic restenosis and revascularization of the target lesion when treated with sirolimus-eluting stents as compared with those receiving conventional stents. The results of a subanalysis of the SIRIUS study ²⁸, which specifically assessed diabetic patients, have shown that revascularization of the target lesion is significantly lower when sirolimus-eluting stents are used (22.3% vs 6.9%; $P < 0.001$). When these results are compared with those of the ARTS study, the occurrence of cardiovascular events is significantly lower in the sirolimus group (fig. 2).

The evidence of greater mortality in the long run in diabetic patients undergoing coronary angioplasty is found in 2 studies (CABRI ⁶ and BARI ⁷), which were carried out in the pre-stent era. In a non pre-specified subanalysis of the BARI study ²⁹, the diabetic patients with multivessel disease who underwent coronary artery bypass grafting showed, after 5 years, a lower overall mortality than those who underwent balloon angioplasty (19.4% x 34.5%; $P = 0.0024$). This benefit of surgery over angioplasty was restricted to diabetic patients revascularized with implantation of the internal thoracic artery to the anterior descending artery, and the evolution of those who received exclusively venous grafts was similar to that of those treated with angioplasty. Such observation has not been corroborated by the large registers (including the BARI study) and other more contemporary case series. In the ARTS study ³⁰, when the subgroup of diabetic patients is considered (208 patients), the mortality rate after 3 years of follow-up is 7.1% in the group undergoing angioplasty and 4.2% in the surgical group ($P = NS$).

In the era of drug-eluting stents, a better clinical evolution will certainly be experienced by the patients with multivessel disease undergoing percutaneous intervention, due to longer-lasting revascularization. However, important questions should still be analyzed before extending the results to clinical practice.

The inclusion criteria in most studies of patients with multivessel disease was the need for obtaining complete myocardial revascularization both for percutaneous coronary intervention and coronary artery bypass graft. Individuals with more extensive and complex coronary anatomy and left ventricular dysfunction, who had already undergone previous revascularization through percutaneous intervention, were systematically excluded. Similarly, patients with acute coronary syndromes, renal failure, and cerebrovascular disease were the minority of the population studied, which, therefore, comprised patients with multivessel disease with a less severe clinical and angiographic profile. The best strategy of revascularization in more critically ill patients has not yet been defined.

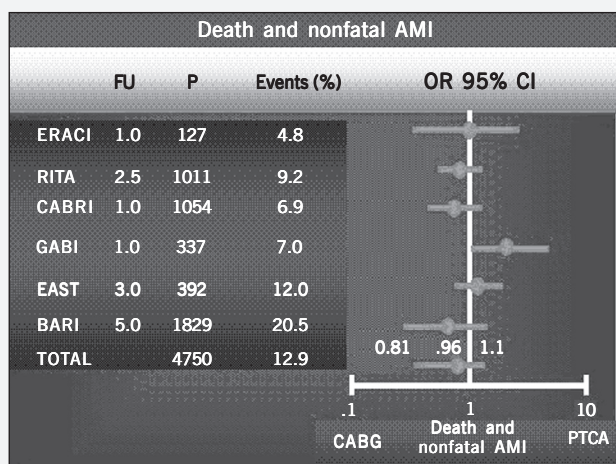


Fig. 1 - Occurrence of death and nonfatal acute myocardial infarction (AMI) in studies comparing coronary artery bypass graft and percutaneous transluminal coronary angioplasty ¹³. CABG - Coronary Artery Bypass Graft; PTCA - Percutaneous Transluminal Coronary Angioplasty; FU - Follow-up in years; P - Patients.

Outcome	CABG (n=605)	Stent (n=600)	Risk relative	P
Survival (%)	92.4	92.0	1.05	0.83
Death/Infarction/Stroke-free survival (%)	85.1	81.8	1.22	0.14
Death/Infarction/Stroke/ New revascularization-free survival (%)	78.2	58.3	1.91	<0.001

CABG- coronary artery bypass graft.

**Table II - Clinical outcome after a 6-month follow-up in the ARTS I and II studies**

Outcome	ARTS II - SES (%) N=606	ARTS I - CABG (%) N=605	ARTS I - PTCA (%) N=600
Death	0.5	1.8	2.3
Stroke	0.5	1.2	1.5
Myocardial infarction	0.7	3.8	4.5
New CABG	1.6	0.5	3.8
New PTCA	3.1	2.0	7.8
Combined events	6.4	9.0	20

SES- sirolimus-eluting stents; CABG- coronary artery bypass graft; PTCA- percutaneous transluminal coronary angioplasty.

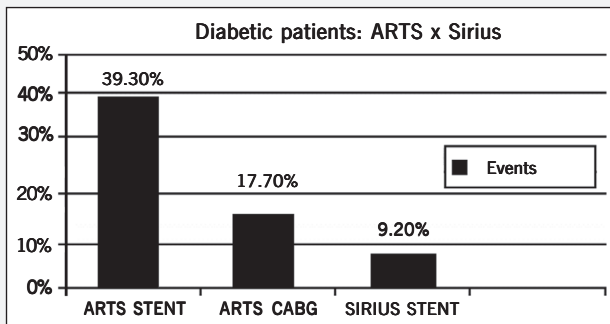


Fig. 2 - Cardiovascular events (death, acute myocardial infarction, and revascularization of target vessel) in 12 months in diabetic patients included in the ARTS and SIRIUS studies. CABG - coronary artery bypass graft.

The SINTAX study¹⁷ aims at randomizing 1,500 patients with left main coronary artery or multivessel disease for percutaneous intervention with implantation of paclitaxel-eluting stents and coronary artery bypass graft. By including individuals with a more severe clinical profile (presence of ventricular dysfunction, renal failure, and previous stroke), as well as patients with complex lesions, such as chronic occlusions, the population studied will near that of the real world.

Although nonuniform, the observation of greater mortality in

the long run in diabetic patients undergoing coronary angioplasty is still controversial. The FREEDOM study¹⁷, multicentric and randomized, aims at assessing the evolution of 2,400 diabetic patients undergoing coronary artery bypass graft (with or without extracorporeal circulation) and coronary intervention with the use of sirolimus- and paclitaxel-eluting stents. With a clinical 3-year follow-up, the comparison of the occurrence of primary outcomes (death, infarction, and stroke) will provide relevant information for the management of that subgroup of patients.

When approaching patients with multivessel coronary disease, the limits defining the strategy to be used have become less strict. The clinical presentation, extension, and severity of the coronary artery disease, and the presence of left ventricular dysfunction and comorbidities continue to influence the choice of the initial treatment. In the era of drug-eluting stents, indication for percutaneous transluminal coronary angioplasty will be widened, because restenosis will not be the major limitation. In such context, the reduction in cardiac events (death, infarction) is established as the primary objective to be achieved. In addition to the medicamentous treatment, the development and refinement of methods to identify vulnerable individuals and coronary artery lesions, and the evaluation of the therapy recommended (including the approach of lesions prone to instability with drug-eluting stents) will be required.

References

- European Coronary Surgery Study Group. Long-term results of prospective randomized study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1982;2: 1173-80.
- Alderman EL, Bourassa MG, Cohen LS et al. Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. *Circulation* 1990;82: 1629-46.
- Detre KM, Takaro T, Hultgren H et al. Long-term mortality and morbidity results of the Veterans Administration randomized trial of coronary artery bypass surgery. *Circulation* 1985;72(supl 5): 84.
- Silva PRD et al. Estudo comparativo dos resultados da intervenção cirúrgica e da angioplastia na revascularização do miocárdio em portadores de comprometimento multiarterial equivalente. *Arq Bras de Cardiologia* 2005.
- RITA Trial Participants. Coronary angioplasty vs coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. *Lancet* 1993;343: 573-80.
- CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty vs. Bypass Revascularization Investigation). *Lancet* 1995;346: 1179-84.
- The Bypass Angioplasty Revascularization (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;335: 217-25.
- Rodriguez A, Bouillon F, Perez-Balino N et al. Argentine randomized trial of percutaneous transluminal coronary angioplasty vs coronary artery bypass surgery in multivessel disease (ERACI): in-hospital results and 1-year follow-up. *J Am Coll Cardiol* 1993;22: 1060-7.
- Hamm CW, Reimers J, Ischinger T et al. for the German Angioplasty Bypass Surgery Investigation. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. *N Engl J Med* 1994;331: 1037-43.
- King SB, Lembo NJ, Weintraub WS et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. *N Engl J Med* 1994;331: 1044-50.
- BARI investigators. Influence of diabetics on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease. *Circulation* 1997;96: 1761-9.
- King SB, Kosinski AS, Guyton RA et al. Eight-year mortality in the Emory Angioplasty vs Surgery Trial (EAST). *J Am Coll Cardiol* 2000;35: 1116-21.
- Hoffman SN, TenBrook JA, Wolf WP et al. A meta-analysis of randomized controlled trials comparing coronary bypass graft with percutaneous transluminal coronary angioplasty: one to eight-year outcomes. *J Am Coll Cardiol*. 2003;41: 1293-304.
- Serruys PW, Unger F, Sousa JE et al. Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;344: 1117-24.
- Rodriguez A, Bernardi V, Navia J et al. Argentine randomized study: coronary angioplasty with stenting vs coronary bypass surgery in patients with multiple-vessel disease (ERACI-II): 30 day and one-year follow-up results. *J Am Coll Cardiol* 2001;37: 51-8.
- SoS Investigators. Coronary artery bypass vs percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomized controlled trial. *Lancet* 2002;360: 965-70.
- Disponível na internet: <http://www.theheart.org/e/tctmd.com>.
- Sousa JE, Costa MA, Abizaid A et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional ultrasound study. *Circulation* 2001; 103: 192-95.
- Morice MC, Serruys PW, Sousa JE et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346: 1773-80.

20. Moses JW, Leon MB, Popma JJ et al. Sirolimus-eluting stents vs standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349: 1315-23.
21. Stone GW, Ellis SG, Cox DA et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350: 221-31.
22. Park SJ, Shin WH, Ho DS et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. *N Engl J Med*. 2003;348: 1537-45.
23. Babapulle MN, Joseph L, Belisle P et al. A hierarchical bayesian meta-analysis of randomized clinical trials of drug-eluting stents. *Lancet* 2004;364: 557-8.
24. Lemos PA, Hoyer A, Goedhart D et al. Clinical, angiographic and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation on complex patients. *Circulation* 2004;109: 1366-70.
25. Lemos PA, Saia F, Lighart JM et al. Coronary restenosis after sirolimus-eluting stent implantation: morphological description and mechanistic analysis from a consecutive series of cases. *Circulation* 2003;108: 257-60.
26. Abizaid A, Kornowsky R, Mintz GS et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. *J Am Coll Cardiol* 1998;32: 584-9.
27. Abizaid A, Costa MA, Centemero M et al. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary artery disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. *Circulation* 2001;104: 533-8.
28. Moussa I, Leon MB, Baim DS et al. Impact of sirolimus-eluting stents on outcome in diabetic patients. *Circulation* 2004;109: 2273-8.
29. Detre K, Guo P, Holubkov R et al. Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1999;99: 633-40.
30. Legrand VMG, Serruys PW, Unger F et al. Three-year outcome after coronary stenting vs bypass surgery for the treatment of multivessel disease. *Circulation* 2004; 109: 1114-20.