

Can coronary artery bypass surgery provide equivalent outcomes after percutaneous coronary interventions?

Walter J. Gomes¹, Enio Buffolo²

The number of patients previously submitted to percutaneous coronary interventions with the implantation of stents and subsequently referred for coronary artery bypass graft surgery (CABG) has increased considerably and is already a substantial part of the surgical cases. However, corresponding concerns have increased about the short-term and long-term results of patients undergoing CABG after PCI with stent implantation [1]. New scientific evidence seems to reinforce this apprehension, with recent publications highlighting findings of coronary endothelial dysfunction over the long term, induced by new generation of drug-eluting stents (DES).

Endothelial function, which is unequivocally impaired by the insertion of bare metal stents (BMS) [1], seems to be additionally injured by the use of DES. Initially, Togni et al. [2] demonstrated that sirolimus eluting stents (SES) (Cypher; Cordis, J&J) were associated with exercise-induced paradoxical coronary vasoconstriction, suggestive of endothelial dysfunction induced by the drug as a subjacent mechanism. Subsequently, Hofma et al. [3] comparatively evaluated the coronary endothelial function six months after BMS and DES implant. The conclusion was that Cypher stent implantation compromised the endothelial-dependent coronary vasomotor response compared to BMS implantation, even over the long term; the real clinical consequences of these findings remain unknown.

The exacerbation of endothelial dysfunction induced by DES may have several implications. Firstly, low efficacy in the relief of the symptoms of angina as endothelial dysfunction is involved in the mechanisms triggering angina. Surprisingly, there are inconsistent data in medical publications on the efficiency of the use of DES in the relief of angina. The next consequence of endothelial dysfunction is thrombosis. The rates of

subacute and long-term thrombosis associated to the use of BMS and DES were initially reported as being similar. In the first studies, the accumulated incidence of thrombosis with DES over 9 to 12 months varied from 0.4% to 0.6% [1].

However, preliminary evidence of an increase of subacute and long-term thrombosis with DES has been found in metanalysis comparing the results of BMS and DES [4]. Although clinical studies did not have the statistical power to detect differences in the rates of thrombosis, metanalysis suggests an increased risk. Thus, the risk of acute myocardial infarction (AMI) increased by 1.94 times with the use of DES (95% CI from 0.89 to 4.23, p-value = 0.096). DES have also been associated with a greater risk of thrombosis at a similar degree to the risk observed for AMI [4].

Subsequent works showed that the incidence of thrombosis with the use of DES in the real world was at least double the first reported rate; close to 1.3%. In a multivariate analysis, an early interruption of antiplatelet use, renal insufficiency, coronary lesions at bifurcations, diabetes and low ejection fraction were identified as risk factors for thrombosis with the use of DES. The mortality rate observed in patients with DES thrombosis was 45% [5].

Recently, data from other studies showed that the incidence of thrombosis with the use of DES is increasing. In the ERACI III study [6] over a follow up period of 18.3 ± 8.8 months (varying from 5 to 36 months), of 225 patients with DES implantation, 3.1% presented with thrombosis. The time between stent implantation and the occurrence of thrombosis varied between 3 and 927 days. Thrombosis after stent implantation was always associated to more significant events such as death or AMI; late thrombosis was identified after the cessation of antiplatelet medication.

This finding was reinforced by data reported in the BASKET-LATE study [7]. This study compared

the long-term results (up to 18 months of follow-up) in patients submitted to either BMS or DES implantation, analyzing the incidence of clinical events related to late thrombosis. The incidence of thrombosis was twice as high in DES patients, with clinical events related to thrombosis being two times more frequent in patients treated with DES. The clinical events related to thrombosis (defined as nonfatal AMI and death) were 3.3 times higher. Thrombosis with BMS tended to occur in the first 150 days after cessation of clopidogrel, while events related to DES occurred evenly throughout the study period.

In the recent World Congress of Cardiology in Barcelona, presentations of new meta-analyses analyzing the data published on the long-term use of the DES brought important revelations.

The first meta-analysis focused on double-blind controlled randomized trials comparing DES and BMS. In overall were studied 1685 patients submitted to Cypher implantation versus 1675 cases with BMS from the Ravel, Sirius, E-Sirius and C-Sirius studies; while 878 patients with Taxus versus 879 with CS were included in the Taxus II, IV, V and VI studies. The analysis concentrated in the main results of death (from any cause), Q-wave AMI and combined death and Q-wave AMI to reflect the incidence of stent thrombosis. For studies of Cypher stents, the incidence of combined death and AMI-Q was significantly greater with drug-eluting Cypher stents than with BMS over 3 years (6% versus 4%) giving an relative risk increase of 33%.

In the Taxus studies, the death rate plus AMI-Q yielded a 1% higher relative risk with Taxus compared with BMS over 3 years (3.5% versus 3.1%). Subsequently, on analyzing the data over a longer term, the incidence of death from any cause or AMI-Q was 2.4% greater with the Cypher stent compared to BMS (6.3% versus 3.9%) and 0.3 greater with Taxus stents versus BMS (2.6% versus 2.3%). Additional analysis of the data showed an increase of 38% in the relative risk of events combined with death (for all causes) and AMI-Q in patients with Cypher stents compared to BMS and an increase of 16% in patients implanted with Taxus stents versus the group with CS [8].

Thus, the incidence of death together with AMI-Q occurs is higher in patients with DES compared with those with BMS, although the level of clinical events observed with DES still needs to be clearly defined. These findings reinforce the need of careful evaluation of the risks and benefits with the indiscriminate use of DES. Long-term thrombosis of the stent can determinate AMI or death, both sudden or as a

consequence of secondary heart failure due to AMI.

Nordmann et al. [9], in another meta-analysis, presented important data about the total mortality rate examining cardiac related and non-cardiac related deaths separately. The odds ratio (OR) for death at 3 years was 1.25 for the combined data of both types of DES, 1.25 for Cypher and 1.10 for Taxus when compared with BMS.

Preliminary evidence suggests that Cypher, but not Taxus, is associated to an increase in the incidence of non-cardiac death. A long-term follow up and reevaluation of specific causes of deaths in patients who received Cypher stents is essential to determine the safety of these devices. The commonest causes of deaths in patients who received Cypher stents were cancer (mainly lymphomas), sepsis, pneumonia and other infections, strokes and pulmonary embolism. The suggested explanation would be a rapid deterioration of the immune system after stent implantation with the drugs and the prothrombotic systemic effects.

Clearly, satisfactory results after DES implantation are strongly dependent on the long-term use of antiplatelet drugs. However 25% of the patients taking clopidogrel are resistant to the drug, without an adequate platelet antiaggregation response. These patients are at continual risk of increased thrombotic complications after PCI [10].

Other consequences of endothelial dysfunction are graft failure, the progression of coronary atherosclerotic disease and heart failure. These critical aspects remain little studied and are still relatively unknown. From the early concerns [1, 11], a growing amount of evidence suggests that patients who were previously submitted to PCI/stent may not fully benefit of further CABG.

Kamiya et al. [12] compared the immediate and late patency of grafts in patients with and without previous PCI. Graft patency of the left internal thoracic artery anastomosed to the left anterior descending artery in patients who had previously undergone PCI tended to be lower than in patients who had not been submitted to this procedure. Gaudino et al. [13] performed a prospective randomized study to evaluate graft patency in patients with stent restenosis who were subsequently submitted to CABG. After 5 years of follow-up, the venous grafts had a higher incidence of occlusion among patients who had previously been submitted to coronary stent implantation.

Subsequently, Hassan et al. [14] assessed the impact of prior PCI on the in-hospital death of patients submitted to CABG. Using multivariate analysis, prior PCI emerged as an independent predictor for

postoperative hospital mortality ($p=0.003$). Comparing the two groups of patients, the in-hospital mortality rate was higher among patients previously submitted to PCI (3.6% versus 1.7%; $p=0.01$). The long-term results remain unknown, as does the impact of this factor on the benefits of the surgery.

Thielmann et al. [15] studied the relationship between the perioperative risks during elective coronary artery bypass graft surgery in patients with prior multiple PCI. The multivariate analysis by logistic regression revealed that multiple PCI were strongly associated with hospital mortality ($p < 0.001$).

Fragomeni et al. [16] studied left ventricular function (LVEF) in patients initially submitted to PCI/stent and afterwards submitted to CABG, with a mean time interval of 9.5 months between the two procedures. Comparing the pre-PCI ventricular function with the LVEF obtained just before surgery, demonstrated that 39.2% of patients had significant reductions. The drop in the LVEF is associated to a worse long-term prognosis.

The morphological, structural and physiological alterations of the myocardium and coronary artery induced by the inflammatory reaction consequent to DES implantation have been little studied and are not well understood [1]. DES implantation causes intense structural alterations in the wall of coronary arteries, both at the site of implantation and in the surrounding region. The wall of the coronary artery close to the stent is almost completely replaced by collagen (fibrosis) with intense leukocyte infiltration [11,17]. This histological alteration of the coronary artery structure is in consonance and helps to explain the long-term endothelial dysfunction. Both the inflammatory reaction and the induced endothelial dysfunction are probably irreversible, at least for some patients.

Joner et al. [18] studied the effects of DES on the repair mechanisms of the coronary artery in autopsies and the correlation of these with late stent thrombosis (LST). LST was observed in 61% of cases with DES implants. After 60 days of Cypher stent implantation, the the coronary artery wall showed inflammatory reaction with infiltration of eosinophils and giant cells, while with the Taxus stent implantation, deposits of fibrin and less inflammatory cells infiltrate predominated. After 120 days, patients implanted with Cypher stents showed focal deposits of fibrin and a reaction of giant cells, while Taxus implants demonstrated greater inflammatory reactions, consisting in the infiltration of lymphocytes, eosinophils and macrophages. Deficient healing of coronary artery lesions with

incomplete endothelialization was found in all cases with LST. Incomplete endothelialization is one of the pathological substrates involved in the emergence of LST.

Thus, there is evidence of irreversible involvement of the structure and endothelial function of the coronary artery wall. Based on this evidence, the procedure of stent implantation is characterized as the most paradoxical method for treatment of coronary artery disease (CAD). That is, to treat a condition (coronary artery disease) that is first and foremost an inflammatory disease (and progressed due to the associated endothelial dysfunction), the result is an aggravation of the inflammatory disease and worsening of the endothelial function. Currently, CAD is no longer characterized as merely a hydraulic problem but as a metabolic disease, where the inflammatory process and endothelial dysfunction have prime importance in its genesis and progression.

However, the complications originating from coronary stent implantation (stent failure) is characterized as a new clinical entity. Will the medications and surgical procedures now used have the same effectiveness in the treatment of this new disease? Due to the progression of the induced endothelial dysfunction, can relief of the angina (both using medicines and surgery) be as effective in this patient?

As CAD is a progressive disease and the number of patients submitted to stent/PCI and subsequently referred to coronary artery bypass graft surgery is increasing, there is a necessity to reassure that these events will not put long-term results provided by coronary artery bypass graft surgery at risk. Additionally, the best operative method and the impact of the intensive use of arterial grafts are still to be identified, as is the effect of the intensive use of statins and angiotensin converting enzyme inhibitors.

Moreover, as new types of stents, specifically DES and absorbable stents (so-called second generation DES), are ready to arrive on the market, specific complications related to each one of them should be expected. The identification of these complications can contribute to a reduction in associated adverse events with a consequent improvement in clinical results.

Thus, the morphological and physiological alterations caused by the use of stents in coronary arteries and the clinical repercussions have been little studied. It is evident that CABG cannot offer the ideal results to patients with immediate and long-term complications caused by PCI and coronary stent implantation. Moreover, there is a necessity to

accurately monitor, by an independent organization, the adverse effects and events resulting from the use of DES.

1 - Livre Docent; Adjunct Professor of EPM, Unifesp

2 - Titular Professor of EPM, Unifesp

REFERENCES

1. Gomes WJ, Buffolo E. Coronary stenting and inflammation. Implications for further surgical and medical treatment. *Ann Thorac Surg.* 2006;81(5):1918-25.
2. Togni M, Windecker S, Cocchia R, Wenaweser P, Cook S, Billinger M, et al. Sirolimus-eluting stents associated with paradoxical coronary vasoconstriction. *J Am Coll Cardiol.* 2005;46(2):231-6.
3. Hofma SH, van der Giessen WJ, van Dalen BM, Lemos PA, McFadden EP, Sianos G, et al. Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. *Eur Heart J.* 2006;27(2):166-70.
4. Katritsis DG, Karvouni E, Ioannidis JPA. Meta-analysis comparing drug-eluting stents with bare metal stents. *Am J Cardiol.* 2005;95(5):640-3.
5. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA.* 2005;293(17):2126-30.
6. Rodriguez AE, Mieres J, Fernandez-Pereira C, Vigo CF, Rodriguez-Alemparte M, Berrocal D, et al. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. *J Am Coll Cardiol.* 2006;47(1):205-7.
7. Pfisterer ME, for the BASKET-LATE Investigators. BASKET-LATE: late clinical events related to late stent thrombosis after stopping clopidogrel: drug-eluting vs bare-metal stenting. In: American College of Cardiology 55th Annual Scientific Session. March 11 - 14, 2006;Atlanta.
8. Camenzind E. Safety of drug-eluting stents: a meta-analysis of first generation of drug-eluting stent programs. In: World Congress of Cardiology 2006; Sept. 2-6, 2006;Barcelona.
9. Nordmann AJ, Briel M, Bucher HC. Safety of drug-eluting stents: insights from a meta-analysis. In: World Congress of Cardiology 2006; Sept. 2-6, 2006;Barcelona.
10. Matetzky S, Shenkman B, Guetta V, Shechter M, Bienart R, Goldenberg I, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation.* 2004;109(25):3171-5.
11. Gomes WJ, Giannotti-Filho O, Hossne NA Jr, Catani R, Buffolo E. Inflammatory reaction after sirolimus-eluting stent implant. *Ann Thorac Surg.* 2005;80:1903-4.
12. Kamiya H, Ushijima T, Mukai K, Ikeda C, Ueyama K, Watanabe G. Late patency of the internal thoracic artery graft in patients with and without previous successful percutaneous transluminal coronary angioplasty. *Interact Cardiovasc Thorac Surg.* 2004;3(1):110-3.
13. Gaudino M, Cellini C, Pragliola C, Trani C, Burzotta F, Schiavoni G, et al. Arterial versus venous bypass grafts in patients with in-stent restenosis. *Circulation.* 2005;112(9 suppl):I-265-9.
14. Hassan A, Buth KJ, Baskett RJF, Ali IS, Maitland A, Sullivan JA, et al. The association between prior percutaneous coronary intervention and short-term outcomes after coronary artery bypass grafting. *Am Heart J.* 2005;150(5):1026-31.
15. Thielmann M, Leyh R, Massoudy P, Neuhäuser M, Aleksic I, Kamler M, et al. Prognostic significance of multiple previous percutaneous coronary interventions in patients undergoing elective coronary artery bypass surgery. *Circulation* 2006;114(1 Suppl):I-441-7.
16. Fragomeni LSM, Falleiro RP, Hoppen G, Krahl G. Coronary artery bypass grafts in patients with coronary stents. *Braz J Cardiovasc Surg.* 2005;20(4):371-6.
17. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol.* 2006;47(1):175-81.
18. 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(1):193-202.