Rev Bras Cardiol Invasiva.
2014;22(3):245-51

Original Article

Comparison of Drug-Eluting Stents with Durable or Bioabsorbable Polymer: Intracoronary Ultrasound Results of the BIOACTIVE Trial

J. Ribamar Costa Jr.[1], Breno de Oliveira Almeida[2], Ricardo Costa[1], Daniel Chamié[1], Andrea Abizaid[1], Marco Perin[2], Rodolfo Staico[1], Fausto Feres[1], Dimytri Siqueira[1], Mateus Veloso[1], Jorge Guimarães[1], Juliano Rasquin Slhessarenko[1], Luiz Fernando Tanajura[1], Amanda Sousa[1], Alexandre Abizaid[1]

ABSTRACT

Background: The everolimus-eluting stent with durable polymer or biolimus A9-eluting stent with bioabsorbable polymer were designed to minimize local inflammatory response providing better endothelial coverage of the struts. The aim of this study was to report the intravascular ultrasound results at 6 months comparing these devices, a secondary endpoint of the BIOACTIVE study. **Methods**: The BIOACTIVE trial is a multicenter, randomized trial (1:1), whose primary endpoint was to compare coronary endothelial function and the percentage of strut coverage of the BioMatrix™ and Xience V™ stents using optical coherence tomography. Patients with single de novo lesions in native coronary arteries, between 3.0 and 3.5 mm, and maximum length of 20 mm were included. Diabetic patients or patients with ST segment elevation myocardial infarction, ostial lesions, bifurcation lesions or lesions with thrombus were excluded. **Results**: Intracoronary ultrasound was performed in 35 (87.5%) of 40 patients included in the study (BioMatrix™ = 21, and Xience V™ = 14). Vessel volume (339.8 ± 149.4 mm^3 vs. 343.0 ± 118.6 mm^3; p = 0.95), stent volume (174.9 ± 73.6 mm^3 vs. 166.2 ± 53.6 mm^3; p = 0.70), intimal hyperplasia volume (3.7 ± 2.6 mm^3 vs. 4.5 ± 5.9 mm^3; p = 0.57) and percent intimal hyperplasia volume (2.3 ± 2.0% vs. 2.4 ± 2.8%; p = 0.90) did not show statistically significant differences. **Conclusions**: In this randomized comparison, both stents proved to be effective in suppressing neointimal response in medium-term follow-up and did not show indirect signs of local toxicity.

DESCRIPTORS: Drug-eluting stents. Polymers. Treatment outcome.

RESUMO

Comparação de Stents Farmacológicos com Polímero Durável ou Biorreabsorvível: Resultados do Ultrassom Intracoronário do Estudo BIOACTIVE

Introdução: Os stents farmacológicos eluidores de everolimus com polímero durável e de biolimus A9 com polímero bioabsorvível foram concebidos para minimizar a resposta inflamatória local e propiciar melhor cobertura endotelial das hastes. Nesta análise, objetivamos apresentar os resultados do ultrassom intracoronário de 6 meses da comparação desses dispositivos como desfecho secundário do estudo BIOACTIVE. **Métodos**: O BIOACTIVE foi um estudo multicêntrico, randomizado (1:1), que teve como objetivo primário comparar a função endotelial coronária e o porcentual de cobertura das hastes dos stents BioMatrix® e Xience V®, por meio da tomografia de coerência óptica. Foram incluídos pacientes com lesão única, de novo, em coronárias, entre 3,0 e 3,5 mm e com extensão até 20 mm. Foram excluídos pacientes diabéticos ou na fase aguda de infarto agudo do miocárdio com supradesnivelamento de ST, lesões ostiais, em bifurcações ou com trombo. **Resultados**: O ultrassom intracoronário foi realizado em 35 (87,5%) dos 40 pacientes incluídos, sendo 21 pacientes com BioMatrix® e 14 com Xience V®. Os volumes do vaso (339,8 ± 149,4 mm^3 vs. 343,0 ± 118,6 mm^3; p = 0,95) e do stent (174,9 ± 73,6 mm^3 vs. 166,2 ± 53,6mm^3; p = 0,70) não mostraram diferenças, bem como o volume de hiperplasia (3,7 ± 2,6 mm^3 vs. 4,5 ± 5,9 mm^3; p = 0,57) e o porcentual de obstrução intimal intra-stent (2,3 ± 2,0% vs. 2,4 ± 2,8%; p = 0,90). **Conclusões:** Nesta comparação randomizada, ambos os stents mostraram-se efetivos em suprimir a resposta neointimal no médio prazo, e não mostraram sinais indiretos de toxicidade local.

DESCRITORES: Stents farmacológicos. Polímeros. Resultado do tratamento.

[1] Instituto Dante Pazzanese de Cardiologia, São Paulo, SP, Brazil.
[2] Hospital Santa Marcelina, São Paulo, SP, Brazil.

Correspondence to: J. Ribamar Costa Jr. Av. Dr. Dante Pazzanese, 500 – Vila Mariana – CEP: 04012-180 – São Paulo, SP, Brazil
E-mail: rmvcosta@uol.com.br

Received on: 06/19/2014 • Accepted on: 08/30/2014

Rev Bras Cardiol Invasiva.
2014;22(3):245-51

Second-generation drug-eluting stents (DES) were developed aiming to maintain the anti-restenotic efficacy of first-generation stents, reducing reintervention rates in the target lesion after percutaneous coronary intervention (PCI) and improving the safety profile of these devices.

As their most striking features, the new generation of drug-eluting stents incorporated derivatives or analogues of sirolimus, an antiproliferative drug with remarkable effectiveness, and more biocompatible polymers (and even bioabsorbable) to carry and control the release of this drugs.[1]

The Xience V™ (Abbott Vascular, Santa Clara, United States), a cobalt-chromium (605L) everolimus-eluting stent with low durable polymer load, and the BioMatrix™ (Biosensors International, Singapore), a stainless steel (316L) biolimus-eluting A9 stent with bioabsorbable polymer derived from polylactic acid (PLA) are two of the main representatives of the current generation of DES in clinical use.

Although comparative studies have demonstrated the superiority of the new stents over those of the first-generation, particularly in the reduction of late and very late thrombosis,[2-5] it is still unclear whether there are differences between them. This analysis aimed to compare the results of intravascular ultrasound (IVUS) of two second-generation stents with durable or bioabsorbable polymer.

METHODS

Design and study population

BIOACTIVE is a two-center (Instituto Dante Pazzanese de Cardiologia and Hospital Santa Marcelina, São Paulo, SP, Brazil), randomized (1:1) trial, whose primary objective was to compare coronary endothelial function through the peri-stent luminal diameter difference before and after stimulation with cardiac pacemaker, using quantitative angiography and the percentage of strut coverage, by optical coherence tomography, of the Xience V™ and BioMatrix™ stents at 6 months of evolution. Secondary objectives consisted of comparing the IVUS and quantitative coronary angiography variables at six months, and combined adverse cardiac events (death, myocardial infarction, and target vessel revascularization) at 12 months.

This analysis reports the comparison of IVUS variables between these two drug-eluting stents, which represented one of the secondary endpoints of the study.

Individuals with *de novo* lesions in native coronary arteries with a diameter of 3.0-3.5 mm and maximum lesion length of 20 mm were included in the study. Diabetic patients or those treated in the acute phase of acute myocardial infarction (AMI) with ST-segment elevation (< 72 hours), as well as those with ostial lesions, bifurcation lesions, presence of thrombi, or lesions with severe calcification were excluded.

This study was approved by the Research Ethics Committees (REC) of both participating institutions, and all selected patients signed the informed consent before randomization.

Procedure

PCI procedures were performed according to the routine of the institutions and according to recommendations.[6,7]

Direct stenting without pre-dilation was allowed and the use of post-dilation was at surgeons' discretion.

The antithrombotic protocol followed current guidelines and consisted of the administration of dual antiplatelet therapy with acetylsalicylic acid (ASA) and a thienopyridine (clopidogrel). The pre-treatment included ASA at a dose of 100 to 200 mg per day in case of chronic use (> 7 days) or loading dose of 200 to 300 mg given > 24 hours prior to PCI; for clopidogrel, the loading dose of 300 mg was given > 24 hours before the intervention in elective cases, or 600 mg > 2 hours before the procedure, in cases of acute coronary syndrome. After the procedure, the use of ASA (100-200 mg daily) was recommended indefinitely and clopidogrel (75 mg daily) was administered for a minimum period of 12 months. Regarding antithrombin therapy during the procedure, intravenous heparin was administered at the dose of 70 to 100 U/kg, in order to maintain the activated clotting time > 250 seconds (> 200 seconds in case of concomitant administration of glycoprotein IIb/IIIa inhibitor, at the surgeon's discretion).

OBJECTIVES AND INTRAVASCULAR ULTRASOUND METHODOLOGY

The primary endpoint of this analysis was to compare the volume of in-stent intimal hyperplasia and the percentage of in-stent volume obstruction at 6 months.

IVUS was performed per protocol, only during angiographic re-evaluation at 6 months post-PCI. Image acquisition was performed using a single rotating transducer, with a frequency of 40 MHz and a 2.6 F sheath, with an automatic pullback system at a velocity of 0.5 mm/s and commercial scanners (i-Lab, Boston ScientificCorp., Nattick, United States).

The images were digitized for off-line quantitative analysis according to the criteria of the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement, and Reporting of Intravascular Ultrasound.[8]

To perform the volumetric analysis, three-dimensional image reconstruction was performed using a commercially available computerized planimetry program (echoPlaque

3.0; INDEC Systems Inc., Mountain View, United States). The lumen, stent, and vessel (external elastic membrane) areas in the analyzed segment were determined at each millimeter by computerized planimetry. The neointimal hyperplasia area was calculated as the stent area minus the lumen area. Then, volumes (lumen, stent, and vessel) were calculated by Simpson's rule. The percentage of in-stent intimal volumetric obstruction was calculated as the ratio between the hyperplasia volume and the stent volume × 100.

All IVUS analyses were performed in an independent laboratory (Cardiovascular Research Center, São Paulo, Brazil) by examiners who were blinded to the type of stent implanted.

Statistical analysis

Categorical variables were expressed as absolute and percentage frequency, and continuous variables as mean and standard deviation. Student's *t*-test was used for the comparison of continuous variables and the chi-squared test or Fisher's exact test was used for categorical variables, as appropriate. The level of significance was set at $p < 0.05$.

RESULTS

Between July 2011 and April 2014, a total of 40 patients were included in the BIOACTIVE trial and randomized to receive the BioMatrix™ stent with bioabsorbable polymer (n = 22) or the Xience V™ stent with durable polymer (n = 18).

Figure 1 shows the flowchart for study inclusion. Among the 35 (87.5%) patients evaluated with IVUS at 6 months, the mean age of both groups was 58 years, and 42.8% were females. The treated vessels showed similar distribution between the groups and B2/C-type lesions were treated in 40% of patients (Table 1).

Table 2 shows the comparison of the main IVUS results at 6 months between the two stents. No significant differences were observed between the groups, emphasizing the minimal formation of neointimal tissue with both stents. Figure 2 shows the distribution of luminal obstruction percentage in the assessed stents. It is observed that both stents, in most cases, produced luminal obstruction < 5%.

Regarding the presence of stent malapposition, only three cases were observed at six months, of which two were with the BioMatrix™ stent. The absence of IVUS in the index procedure did not allow for the identification of malapposition as chronic or acquired. However, in all cases, the volume of malapposition was quite low and did not differ between the stents. As for the neointimal pattern (qualitative assessment) through IVUS, one neoatherogenesis case was observed in this population, manifested as clinical restenosis in a patient who had received a Xience V™ stent.

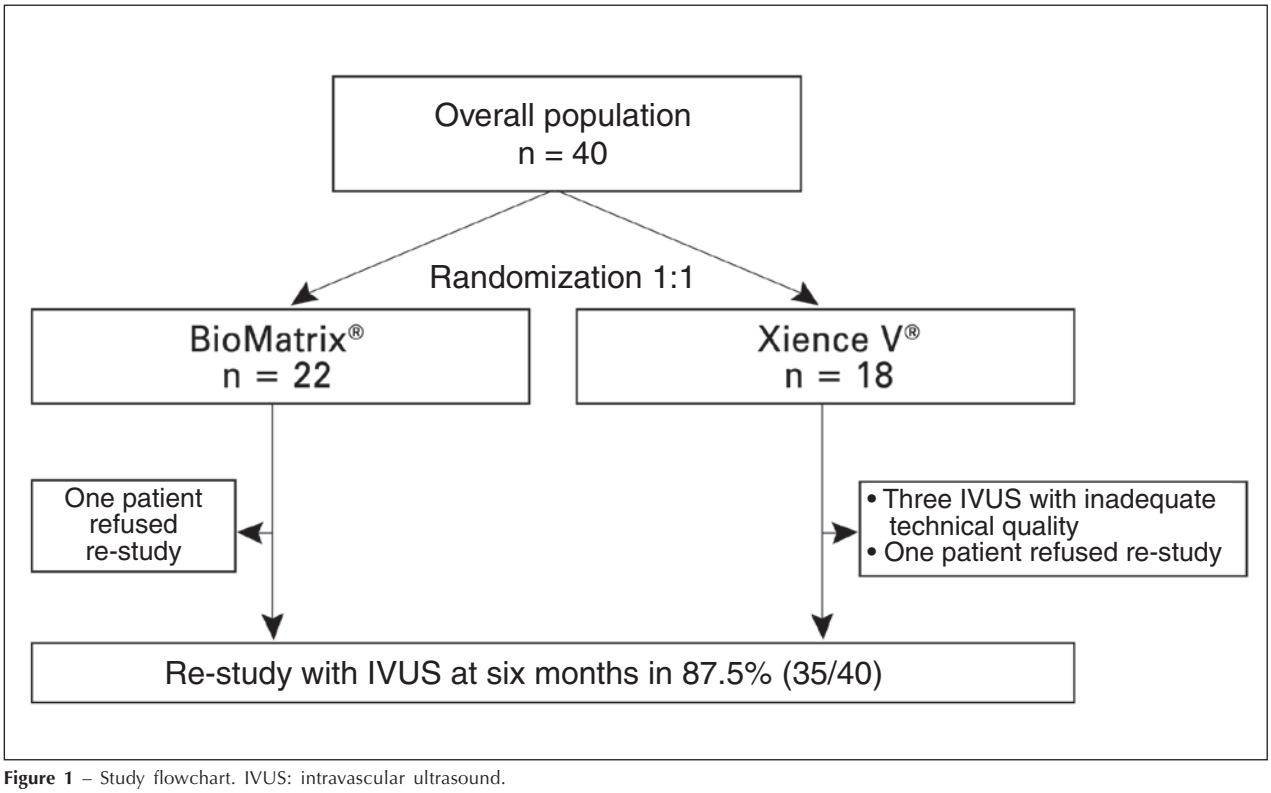

Figure 1 – Study flowchart. IVUS: intravascular ultrasound.

Rev Bras Cardiol Invasiva.
2014;22(3):245-51

TABLE 1
Basal clinical and angiographic characteristics.

Variable	BioMatrix™ (n = 21)	Xience V™ (n = 14)	*p*-value
Age, years	57.0 ± 8.3	59.0 ± 6.5	0.45
Female gender, n (%)	11 (52.4)	4 (28.6)	0.30
Hypertension, n (%)	19 (90.5)	12(85.7)	> 0.99
Dyslipidemia, n (%)	13 (61.9)	10 (71.4)	0.72
Smoking, n (%)	14 (66.7)	8 (57.1)	0.72
Previous AMI, n (%)	11 (52.4)	6 (42.9)	0.73
Previous PCI, n (%)	3 (14.3)	2 (14.3)	> 0.99
Clinical picture, n (%)			> 0.99
Silent ischemia	1 (4.8)	1 (7.1)	
Stable angina	20 (95.2)	13 (92.9)	
Target vessel, n (%)			0.72
Left anterior descending	5 (23.8)	5 (35.7)	
Left circumflex artery	8 (38.1)	5 (35.7)	
Right coronary artery	8 (38.1)	4 (28.6)	
B2/C lesions, n (%)	8 (38.1)	6 (42.9)	> 0.99

AMI: acute myocardial infarction; PCI: percutaneous coronary intervention.

TABLE 2
Comparison of main ultrasound variables at 6 month follow-up.

Variable	BioMatrix™ (n = 21)	Xience V™ (n = 14)	*p*-value
Mean luminal area, mm^2	7.98 ± 2.48	7.39 ± 1.49	0.43
Minimal luminal diameter, mm	2.57 ± 0.45	2.44 ± 0.32	0.36
Mean vessel area, mm^2	15.73 ± 5.06	15.06 ± 2.99	0.66
Minimal vessel diameter, mm	3.76 ± 0.71	3.72 ± 0.41	0.85
Mean stent area, mm^2	8.11 ± 2.42	7.51 ± 1.63	0.42
Minimal stent diameter, mm	2.62 ± 0.47	2.54 ± 0.33	0.59
Neointimal area, mm^2	0.18 ± 0.13	0.19 ± 0.24	0.87
Vessel volume, mm^3	339.80 ± 149.37	343.01 ± 118.57	0.95
Stent volume, mm^3	174.93 ± 73.65	166.16 ± 53.64	0.70
Luminal volume mm^3	172.40 ± 75.12	161.97 ± 50.34	0.65
In-stent hyperplasia volume, mm^3	3.71 ± 2.57	4.55 ± 5.96	0.57
Malapposition volume, mm^3	1.0 ± 2.8	0.3 ± 0.6	0.37
Percentage of neointimal obstruction,%	2.33 ± 1.98	2.43 ± 2.77	0.90

As for the clinical outcomes, there were no deaths or spontaneous AMI in this subgroup submitted to IVUS analysis, and the only documented case of restenosis occurred in the group treated with Xience V™.

DISCUSSION

The present study represents the first randomized comparison of two second-generation drug-eluting stents,

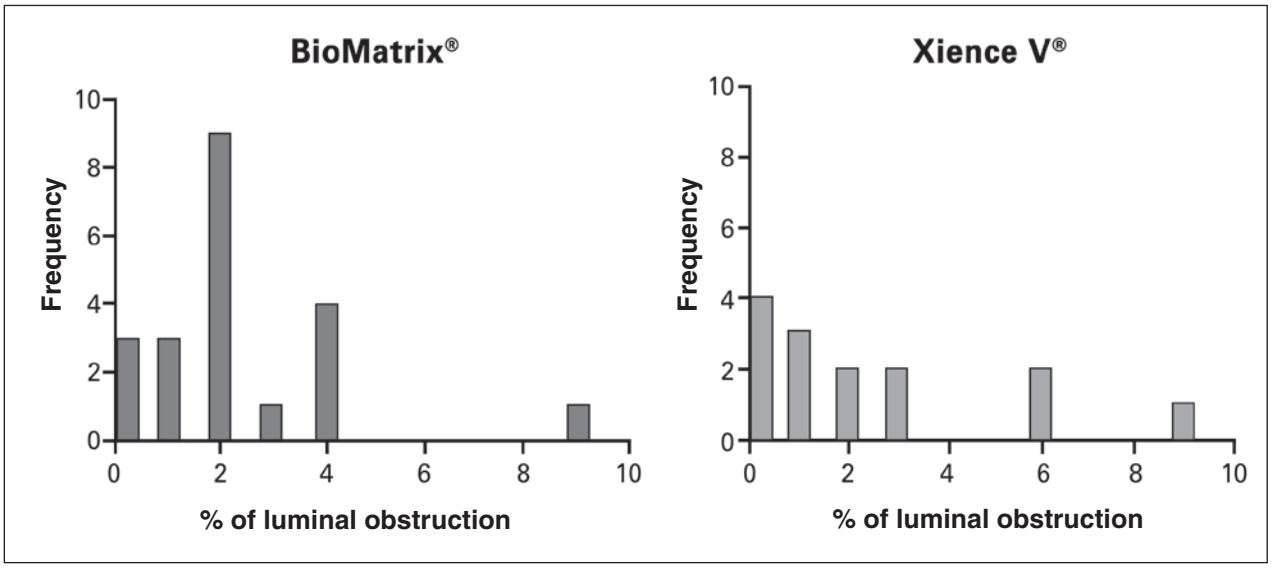

Figure 2 – Individual distribution of neointimal obstruction percentage. Most patients in both groups had less than 5% of luminal obstruction in the previously implanted stent.

using ultrasonographic criteria as surrogate endpoint. As the main finding, it must be highlighted that both stents, with bioabsorbable or durable polymer, showed minimal neointimal response and no signs of local toxicity.

Drug-eluting stents, developed a little over a decade ago, were designed to minimize excessive healing response (exaggerated neointimal hyperproliferation) promoted by previously used bare-metal stents without drug elution. For that purpose, drugs with antiproliferative properties were added to the previously used metal structures, delivered at the site of lesion by means of a polymer, which, in addition to acting as drug carrier and minimizing drug loss during the trajectory to the implant site, also controls its release.[1]

However, the durable polymer present in the first-generation drug-eluting stents appears to have a central role in perpetuating the local inflammatory process in the vascular wall, which may potentially lead to the occurrence of late and very late stent thrombosis.[1]

To minimize the occurrence of these deleterious effects, the new generation of drug-eluting stents started using new, more biocompatible materials for the manufacturing of polymers, or even fully bioabsorbable polymers.

The durable polymers present in the current generation of drug-eluting stents (Xience V™, Xience Prime™, Promus Element™, and Resolute Integrity™) generate minimal inflammatory response, partly due to new elements used in their manufacturing, but also because they are applied only on the abluminal (outer) stent surface, which significantly reduces the polymer load used. Several randomized trials have demonstrated the superiority of these stents compared toBMS and first-generation DES, regarding both effectiveness and safety.[2,3]

Among the DES with bioabsorbable polymers, PLA and polylactic-co-glycolic acid [PGLA]) are used in most cases, which progressively decompose into esters until they are finally degraded into lactic acid. In drug-eluting stents with biodegradable polymer, drug release occurs not only by diffusion but also by degradation of the polymer matrix. The benefit of this new technology was demonstrated in the study Limus Eluted from A Durable versus Erodable Stent Coating (LEADERS), which compared the BioMatrix™ stent with bioabsorbable PLA polymertothe Cypher® stent with a durable polymer.[4] At the end of 5 years of clinical follow-up, the group of patients treated with absorbable polymer stent tended to a lower incidence of adverse cardiac events (22.3% vs. 26.1%; *p* for superiority = 0.071) and a significant reduction in the rate of thrombosis in the first year after the procedure (0.66% vs. 2.5%, *p* for superiority = 0.003).

After the demonstration that both second-generation stents were superior to those of the first generation, especially regarding safety, the first studies comparing second-generation stents with different polymers appeared. The Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent (COMPARE-II) trial compared, in a randomized (2:1) manner; 2,707 patients treated with drug-eluting stents with biolimus A9 and bioabsorbable polymer (n = 1,795) vs. everolimus-eluting stent with durable polymer (n = 912). After 12 months of follow-up, the rate of major combined events (cardiac death, AMI, and new revascularization) was comparable between the stents (5.2% vs. 4.8%; *p* of

non-inferiority < 0.001).[9] Later, the NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial (NEXT) randomized (1: 1) 3,235 patients to receive one of these two second-generation stents. Just as in the COMPARE-II trial, there was no significant difference in the occurrence of restenosis and thrombosis with this prostheses.[10]

As seen so far, no study, individually, has been able to demonstrate superiority between the new drug-eluting stents with bioabsorbable and durable polymers. This is mainly due to the fact that rates of adverse clinical events after use of these devices are currently quite low, requiring studies with thousands of patients, so that there is adequate statistical power for such comparisons. In the absence of such studies, surrogate endpoints can be used in search for indirect signs that disclose differences between such devices.

Among the studies with surrogate endpoints, there is an analysis of the NEXT trial, in which 528 patients (biolimus: n = 263; everolimus, n = 265) were assessed with angiographic re-evaluation at nine months. In this study, both devices showed low luminal loss, with no significant statistical difference in relation to the primary angiographic endpoint of late loss in the segment (0.03 ± 0.39 mm vs. 0.06 ± 0.45 mm, *p* for non-inferiority < 0.0001, *p* for superiority = 0.52).[10]

More recently, Tada et al., using optical coherence tomography, compared, in a randomized study (1:1), 34 patients treated with second-generation stents with biolimus and bioabsorbable polymer to everolimus and durable polymer. As main findings, no differences were observed between the rate of tissue coverage (uncovered struts: 479 with biolimus vs. 588 with everolimus; odds ratio – OR 1.54; 95% CI 0.63-3.79; *p* = 0.34) and strut malapposition: 46 with biolimus vs. 32 with everolimus; OR = 1.64; 95% CI 0.21-12.5; *p* = 0.64) of these stents at the end of 6 to 8 months.[11]

These studies, although they used surrogate outcomes that are different from this analysis, are in agreement in terms of results, as they demonstrated a similar safety and efficacy profile between the two types of stent, at least in the medium term.

Limitations

The main limitation of this study concerns the small number of subjects in each group. Still, it represents the largest cohort of subjects randomized to these stents and evaluated by IVUS. Another important limitation concerns the lack of systematic assessment with IVUS atthe end of the index procedure, which prevents the detailed evaluation of malapposition. Finally, a six-month period represents a short period to assess potential differences between these two stents.

CONCLUSIONS

No significant differences were observed between second-generation stents with durable or bioabsorbable polymer regarding the medium-term ultrasound evaluation in the randomized BIOACTIVE trial. Both stents showed to be quite effective in reducing the neointimal tissue formation inside the stent, and no indirect sign of local toxicity was observed in either group.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING SOURCES

None.

REFERENCES

1. Costa Jr. JR. Dispositivos contemporâneos na ICP: stents farmacológicos e suportes vasculares bioabsorvíveis. In: Abizaid A, organizador. Manual de cardiologia intervencionista do Instituto Dante Pazzanese. São Paulo: Elsevier; 2012. p. 191-208.
2. Dangas GD, Serruys PW, Kereiakes DJ, Hermiller J, Rizvi A, Newman W, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). JACC Cardiovasc Interv. 2013;6(9):914-22.
3. Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). JACC Cardiovasc Interv. 2013;6(12):1263-6.
4. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus E Rodable Stent Coating) randomized, noninferiority trial. JACC Cardiovasc Interv. 2013;6(8):777-89.
5. Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, et al. Biodegradable polymerdrug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J.2012;33(10):1214-22.
6. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)1; European Association for Percutaneous Cardiovascular Interventions (EAPCI). Guidelines on myocardial revascularization. Eur Heart J. 2010;31(20):2501-55.
7. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report

of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv. 2012;79(3):453-95.

8. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, et al. American College of Cardiology Clinical Expert Consensus Documenton Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2001;37(5):1478-92.
9. Smits PC, Hofma S, Togni M, Vázquez N, Valdés M, Voudris V, et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. Lancet. 2013;381(9867):651-60.
10. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, et al.; NEXT Investigators. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferioritytrial. J Am Coll Cardiol. 2013;62(3):181-90.
11. Tada T, Kastrati A, Byrne RA, Schuster T, Cuni R, King LA, et al. Randomized comparison of biolimus-eluting stents with biodegradable polymer versus everolimus-eluting stents with permanent polymer coatings assessed by optical coherence tomography. Int J Cardiovasc Imaging. 2014;30(3):495-504.