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A RANDOMIZED COMPARISON OF THE CORONARY VASOMOTOR FUNCTION AND MYOCARDIAL FLOW IN PATIENTS TREATED WITH EVEROLIMUS-ELUTING BIORESORBABLE SCAFFOLDS AND EVEROLIMUS-ELUTING METALLIC STENTS

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1. Summary of the project

Background

Around 25-50% of patients with stable coronary artery disease treated with metallic stents remain with effort angina despite optimal medical treatment and the absence of restenosis after one year. The most likely cause of symptom persistence is microvascular dysfunction. Coronary circulation has the function of balancing coronary flow with the oxygen needs of the myocardium. Metallic stents have been associated with endothelial dysfunction and altered coronary reserve flow (the ratio between resting coronary flow and those at maximal hyperemia) of the treated vessel at one year. Bioabsorbable intracoronary devices (BVS) have shown improvement in endothelial function and angina pectoris compared to metal stents after one year. However, coronary flow of BVS-treated arteries has not been investigated so far.

Main objective

To determine differences in the maximum mid-speed peak (APM) with maximal hyperemia through adenosine infusion between patients treated with bioabsorbable and metal stents after one year post-implantation.

Methods

A total of 70 patients with stable coronary artery disease were 1:1 randomized to be treated with Everolimus-eluting bioabsorbable stents (BVS) versus Everolimus-eluting metallic stents (EES) at three Catalan hospitals (Bellvitge, Clínic and Mar). At 13 months, all patients underwent coronary angiography to perform a coronary artery function study using an intracoronary pressure / Doppler wire. The wire was advanced proximally to the stent segment and then endothelium-dependent (acetylcholine infusion) and non-endothelial-dependent (adenosine and nitroglycerin) vasomotor function were measured. The Doppler wire uses ultrasound to evaluate the blood speed of the target coronary artery. As per protocol, a baseline measurement was performed (with the patient relaxed without any vasomotor drug) followed by a new measurement at maximal hyperemia under adenosine infusion that simulates a situation of maximum exertion. During the study, several external questionnaires on the patient's symptoms (Seattle angina questionnaire) were also performed before stent implantation and in the following months.

Sample size

A difference of 12.0 cm / sc. in the average peak velocity (APV) value of blood passing through the target coronary artery, as assessed by intracoronary Doppler at maximal hyperemia, was expected between study devices at 13-month. The study has statistical power to demonstrate superiority of patients treated with BVS.

Working plan

Each center has a principal investigator in charge of examining patients, explaining the protocol, signing the informed consent form, and conducting the angiographic and clinical controls at 13-month follow-up. In addition, the study has an assistant specifically contracted for the study who carries out the supervision and coordination with the centers. The original plan spent a total of 18 months completing the inclusion of patients (n = 70), followed by 13 months of clinical follow-up and coronary angiography, and with a final 6 months to analyze the study data and write the article.

2. Results

Fifty-nine patients (30 BVS and 29 EES) underwent invasive examination. Angiographic lumen loss was larger with BVS (-0.30±0.43 mm *vs.* -0.11±0.16 mm; p=0.03). Vasomotor changes to acetylcholine in the scaffold segment were numerically small but significantly larger with BVS (-4.9±5.7% *vs.* -1.9±3.5%; p=0.03). Coronary blood flow (97.4±53.5 *vs.* 88.3 ± 46.7 ml/min; p=0.51) and coronary flow reserve (2.6±0.9 *vs.* 2.7±0.8; p=0.84) at maximal hyperemia were similar between groups. The APV (49.0±17.5 *vs.* 49.3±18.3 cm/sc., respectively; 0.947) were also similar in both groups the study being negative for the primary end-point. Self-reported angina was also similar between groups at 1 year of the stent implantation (20.7% with BVS vs. 33.3% with EES; p=0.275). One patient treated with BVS died due to intracranial hemorrhage not related with the study device. Other patient treated with BVS presented with periprocedural coronary perforation treated with additional stent implantation. This patient had periprocedural myocardial infarction. There was no patient with stent thrombosis.

3. Study relevance and future implications

Bioabsorbable intracoronary devices (bioabsorbable stents) have been discussed worldwide during the study. A clinical impact study published in 2017 in the New England Journal of Medicine (Bioresorbable Scaffolds versus Metallic Stents in Routine PCI; Wykrzykowska JJ) revealed an increased risk for stent thrombosis with BVS during the first 3 years after implantation. This increased risk of stent thrombosis has been attributed to the progressive dismantling of the stent, which can lead to stent fractures that protrude into the lumen and cause thrombosis. For this reason, polymer bioabsorbable stents were withdrawn from the world market in 2018. A number of studies are currently underway (ABSORB IV study) which will evaluate the long-term effectiveness of these devices (10 years after implantation) taking into account that the devices disappear at 3-4 years of implantation and therefore the risk of stent thrombosis must be conceptually 0 after the bioabsorption period, whereas it is well known that conventional metallic stents continue to have an annual percentage of stent thrombosis even in the very long term of implantation.

The data of this study adds information regarding the vasomotion and microcirculatory changes observed in patients treated with bioresorbable devices. The main results of the study have already been evaluated and they conclude:

- Bioabsorbable devices exhibit greater vasomotion than conventional stents to endothelial-mediated stimuli at 13 months. Bioabsorbable stents exhibit greater vasoconstriction within the stent-treated segment than conventional stents. This response is similar to that presented by the segments not encompassed by the stent, meaning that the global artery (segment of the stent and not the stent) recovers vasomotor functionality to endothelial-mediated stimuli.

- However, this increased vasomotion is not reflected by an increase in coronary flow measured by intracoronary Doppler guidance nor by a greater decrease in the degree of residual angina than those observed with conventional metallic stents at 13 months of implantation.

The clinical relevance of the study is remarkable because the clinical characteristics of our patients are unique: young patients, without a high burden of coronary heart

disease or cardiovascular risk factors. In this selected group of patients BVS was unable to recover the "normal" vasomotor function as compared to metallic stents. This may also favor a higher number of cardiovascular events. However, no stent thrombosis of the device occurred during the study (at 1 or 2 years of clinical follow-up, which is currently available to most patients).

4. Bibliography

The study has been published in EuroIntervention journal. The article is available online with the following DOI reference: 10.4244/EIJ-D-18-01203.