



# In-stent restenosis: COMBO stent may guarantee a proper healing

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## Key words:

in-stent restenosis (ISR), sirolimus-eluting stent, COMBO dual-therapy stent (COMBO - SES), neointimal regression, drug-eluting balloon (DEB), second generation drug-eluting stent (DES).

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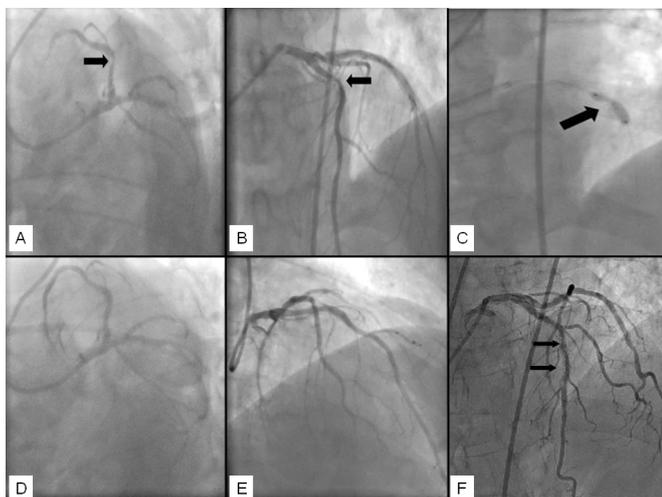
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A 55-years-old man with coronary risk factors hypertension, hypercholesterolemia, history of smoking, diabetes mellitus in insulin treatment with poor control of blood glucose levels was admitted at our department for non-ST elevation myocardial infarction (NSTEMI).

On January 2014 following anterior non ST elevation myocardial infarction (NSTEMI), coronary angiography showed a critical stenosis of middle left anterior descending (LAD) artery, so he had a II generation drug eluting stent (DES) implantation. On May 2014, for unstable angina (UA), on repeat coronary angiography a subocclusive in-stent restenosis (ISR) of previous II generation DES was seen (ISR diffuse type II)<sup>1</sup> on middle LAD (Fig. 1A, B).

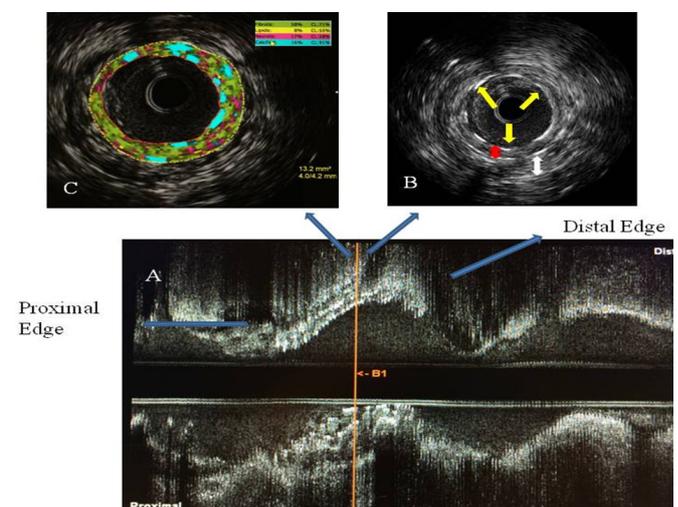
## Figure 1:

- A.** caudal left view, subocclusive ISR on middle LAD (black arrow)  
**B.** anteroposterior cranial view.  
**C.** DES expansion (focal difficult expansion in the middle portion because deep resistance of subocclusive restenosis)  
**D.** Control CVG after 5 months, good result in left caudal view and E) anteroposterior view.  
**F.** right cranial view, partial subexpansion in correspondence of resistant restenosis during COMBO stent apposition (black arrow).



## Figure 2:

- A.** longitudinal IVUS view of LAD with COMBO stent  
**B.** under expansion of II generation DES (white arrow), excessive neointimal and fibrotic tissue harnessed within the struts of COMBO stent (red arrow), and a homogeneous coverage of COMBO stent (blue arrows).  
**C.** iMap assessment with a description of plaque and in-stent restenosis components.



We decided to perform a compliant balloon predilation and a 3.5 x 18 mm COMBO stent (OrbusNeich) implantation with an excellent final result, despite the subocclusive ISR was very resistant both during predilation and stent implantation (Fig. 1C).

According to the high cardiovascular risk of the patient and his particularly aggressive atherosclerotic disease (ISR after three months DES implantation) we programmed an angiographic control five months later showing good result of COMBO stent (Fig. 1D, E), confirmed by intra-vascular ultrasound (IVUS) images with an appropriate apposition of COMBO on the previous DES and an adequate and homogeneous endothelialization, even where the restenosis showed a greater resistance (Fig. 2)

In particular, in correspondence of middle portion, whereas the previous stent showed a subexpansion with excessive neointimal and fibrotic formation (the likely cause of subocclusive restenosis), the stent COMBO allowed to trap the fibrotic tissue between the two layers of struts still allowing adequate endothelialization and coverage of the stent (Fig 1F).

12 months after ISR treatment by COMBO stent, clinical evaluation of the patient confirmed the absence of symptoms and no myocardial ischemic signs during stress test. The treatment of ISR is one of the most ambitious challenges for both interventional cardiologist during percutaneous revascularization, as well as for companies offering new devices able to improve this treatment.

The risk of ISR appears to be related to several factors which cooperate synergistically; among these factors an important role is played by: the metal struts of the stent and the consequent inflammatory stress on the vascular wall which favors an excessive neointimal proliferation that "attacking" the stent struts, progressively and critically reduce the vessel lumen. This is the reason because the drug eluting balloons (DEBs) have made progress in the treatment of ISR, starting from the previous guidelines (indication only for the treatment of bare metal stent (BMS) ISR, class IIa, level of evidence B)<sup>2</sup>, today they have indication for the treatment of BMS and DES ISR (class Ia, as the use of DES for the ISR treatment)<sup>3</sup>.

The concept that increasing the metal struts during the ISR treatment with a second stent implantation, it determines a higher mechanical stress on the vessel wall, exponentially increasing the inflammatory response and an excessive and not homogeneous neointimal formation, is the reason that DES are losing out to DEB in the treatment of this complication COMBO stent could be a viable alternative which may properly compare to DEB in the ISR treatment: one of a kind, because it has a dual therapy action, synergistically combining the effect of sirolimus with the presence of CD34+ antibodies on the surface of its struts, capturing circulating endothelial progenitor cells (EPCs), so mobilized EPCs differentiate into functional endothelium and allowing a homogeneous neointimal formation. In fact EPCs are naturally elevated due to the response to injury and significant increases their plasma concentration both in course of stable angina that during acute coronary syndromes<sup>4</sup> contributing to an excessive and inhomogeneous struts coverage if not controlled.

Therefore, the unique association between an antimitotic as sirolimus in a biodegradable abluminal matrix and antibodies anti CD34+ may be the right formulation to reduce the rate of restenosis giving an healing profile of the stent struts. In this manner, during the ISR treatment, the presence of a second metal structure has the task to contain the neointima formation and the presence of a dual therapy enhance the formation of a homogeneous and controlled neointima. Granada J. et al shows as COMBO stent implantation in de novo lesions, compared to the second generation DES, presents a homogeneous coverage with a smaller neointimal thickening assessed at 28 days in animal models using OCT and histological evaluation ( $p < 0.00001$ )<sup>5</sup>.

In vivo evaluation provides even more surprising data: in the EGO-COMBO study, OCT images after COMBO stent implantation demonstrate a full coverage after five months and in the following months, from nine months to 24 months, neointima evaluating by OCT image, in-stent neointimal volume percentage, which is an important surrogate marker

for neointima assessment, declined by 11.9% during that time (9-month median, 17.76; interquartile range [IQR], 12.21- 21.22; 24-month median, 15.65; IQR, 11:17 to 19:35;  $P = .004$ ), the first time that has been demonstrated in a DES<sup>6</sup>.

In literature there are not yet available data on the COMBO efficacy in the treatment of ISR, in particular if their dual therapy may bring benefits greater than second generation DES and/or DEB.

In our case report, the patient had many cardiovascular risk factors, including diabetes mellitus treated with insulin, with a high cardiovascular risk, contributing to a particular aggressive atherosclerosis disease, both as de novo disease and short time ISR (subocclusive ISR type II, within three months of II generation DES implantation).

COMBO stent in this case was effective in ISR treatment, as well as to determine a rapid and homogeneous endothelialization, especially in the subexpansion struts of the previous DES, where the restenosis was particularly difficult to treat, demonstrating by IVUS images after about five months a homogeneous coverage of the struts in the absence of new atherosclerotic disease.

## Statement of ethical publishing

The authors state that they abide by the statement of ethical publishing of the International Cardiovascular Forum Journal<sup>7</sup>.

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The authors have nothing to declare.

## Conflict of interest:

The authors declare that there is no conflict of interest.

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