Interview

Interventional Cardiology

Current developments in drug-eluting stent technologies

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Q Can you tell us about your career background to date?

I graduated from the University of Catania Medical School, Catania, Italy in 1982 and went on to my postdoctoral fellowships and to train in internal medicine and cardiology. I then become a research fellow at the Pitiè-Salpetriere Facultè Medical School of Paris in France, and I was involved in clinical and research activities focusing on cardiomyopathies and heart failure management. At that time, I learned to perform endomyocardial biopsy. Back in 1990, in my Institution there was a development in cardiac intervention, thus my interest in structural and coronary intervention continued to grow and after completing my research I undertook 2 years of training in interventional cardiology at Saint Antoine Medical School of Paris and at the Center Medico-Chirugicale Parly-Grand Chesnay, Le Chesnay in France, where I gained skills in both coronary and structural interventions. After this training, I have been working for many years at the University Hospital in Catania where I have been performing a large number and a wide range of interventional coronary and structural procedures. The volume of the cath-lab I have been working in and of which I am the director is progressively increasing and now we are among the major referral centers in Italy for both coronary and structural percutaneous interventions. For the last ten years our unit has been pioneering a relevant number of innovative device technologies and interventional procedures.

Q What lead to you deciding to pursue cardiology as a career path?

In general, there are many factors that contribute to a career choice for a specialty and a further subspecialty. Indeed, job opportunities, potential professional satisfaction, family circumstances, local demand, geographical restraints, scientific and clinical interest, personal attitudes, and finally money and prestige are all important considerations that guide decision-making. After I graduated from medical school, among the nonsurgical specializations, cardiology was considered one of the most esteemed, as it allowed to practicing a specific noninvasive medicine demanded in several surroundings and offered several invasive subspecializations in blooming development, especially interventional cardiology. By the mid 1980s, the time when I had to choose a career path, new technological advances, such as steerable guidewires, monorail catheters had made angioplasty easier and more successful, rapidly increasing the number of procedures. Thus, there was a relevant demand that was likely to grow across the cardiology community considering the tremendous technological development of new tools other than the balloons and premounted stent, potentially leading to expand indications. On this background, interventional cardiology was really a 'hot', exciting and flourishing area of cardiology, with the potential to save lives and to be an effective treatment option for a large spectrum of coronary and structural heart disease. Finally, when I firstly tested myself in the field, I demonstrated very handy with catheters and I felt to be a 'cath-guy'.

Q What do you feel have been the most influential developments in the field of interventional cardiology over the past 5 years?

The field of interventional cardiology has become increasingly more technologically sophisticated and the rate of scientific advancement is accelerating, leading to percutaneous treatment of more and more complex patients with coronary artery disease and of additional structural heart disease. In the setting of coronary interventions, in the past years, it has been substantial the introduction of several newer generations drug-eluting stents (DES) with more favorable mechanical, material and design features. These latter new devices have been associated with higher efficacy and an improved safety profile, which was similar or even better to that of bare-metal stents, across all the wide spectrum of coronary artery disease, including acute myocardial infarction. Nevertheless, late thrombotic events and in-stent neo-atherosclerosis remain issues with contemporary DES. On this background, important progresses have been focusing on technologies, as the Combo stent, creating a low vessel injury, promoting an early and predictive vessel healing, without losing long-term efficacy, expecting to further optimize clinical outcome of STEMI patients, while minimizing duration of dual antiplatelet therapy. Furthermore, the fact that these conventional stents still leave a permanent metal implant inside the vessel, potentially leading to future issues and late events, has prompted the influential development of bioresorbable stents. These latter are commonly referred as scaffolds, as they provide a temporary support to the vessel wall (similar to a stent) for a defined period after implantation, but are subsequently resorbed. Although bioresorbable scaffolds have not overtaken the conventional stents, they are considered as fourth revolution in coronary intervention due to their potential additional advantages. Finally, besides to devices developments, relevant scientific evidences have been built to define the best treatment strategy, the optimal antithrombotic regimen, and the role of intravascular imaging in specific angiographic and clinical settings.

Q You recently presented data from the REMEDEE first in man & EGO COMBO trials examining stent healing at the Joint Interventional Meeting 2015 in Rome, could you please outline for us the headline findings of the studies?

The REMEDEE was a first-in-man study in which 183 patients with a single de novo native coronary artery lesion ≤20 mm in length in a native coronary artery ranging in diameter from ≥2.5 to ≤3.5 mm were randomized 2:1 to Combo stent or paclitaxeleluting Taxus Liberté stent implantation. In the Combo group, the angiographic in-stent late lumen loss at 9 months (primary end point) was 0.39 ± 0.45 mm, which was noninferior to the in-stent late lumen loss of 0.44 ± 0.56 mm in the paclitaxel-eluting stent group (pnoninferiority = 0.0012). The distribution of instent late lumen loss in the paclitaxel-eluting stent group showed a bimodal appearance resulting in a larger standard deviation, compared with the Combo group. This latter finding suggests a diminished antiproliferative response to the stent in a particular patient subgroup and has been reported before for first generation DES. Of note, the numerically lower late-lumen loss of the Combo stent seems to be leveraged in a disproportionally lower target lesion revascularization rate with Combo (4.8% at 12 month, 5.7% at 24 and 36 months) in comparison with the paclitaxel-eluting stent (8.5% at 12 and 24 months and 10.2% at 36 months). This cannot be explained by the mean difference alone but more likely is the result of the bimodal nature of the late lumen loss distribution in the paclitaxel-eluting stent group. No stent thrombosis was reported in either group up to 3 years. The EGO COMBO was a study evaluating the evolution over time of strut coverage assessed in by the optical coherence tomography in 61 patients. In this study, the Combo stent had adequate coverage even at 2 months, approaching almost 100% at 9 months. A neo-intimal regression between 9 and 24 months was documented.

Q What properties distinguish the COMBO within the crowded field of DES?

In order to produce more biologically compatible devices, current generation of DES have thinner and absorbable polymer layers or no polymer, thinner stent struts, alternative drug compounds and lower doses of drugs. The Combo dual therapy stent has a thin strut stainless steel metallic platform, which combines a sirolimus elution from an abluminal biodegradable polymer matrix for control of neo-intima hyperplasia, along with a covalently bound layer of CD34 antibodies to capture circulating endothelial progenitor cells to promote vessel healing with accelerated and stable stent strut tissue coverage should address early and predictive healing with neointimal stent strut coverage, allowing a significantly shorter duration of DAPT without losing the efficacy and with potential to reduce inflammation and neo-atherosclerosis, factors underlying late thrombotic events.

Q What are the aims of the ongoing research program of the COMBO stent in terms of the number of patients to be included & how the trials compare with previous studies in this field?

The Combo stent has been investigated in a large research program. Similarly to previous studies for contemporary DES, two large 'all-comers' postmarketing registries are ongoing, the REMEDEE (n = 1000) and the MASCOT (n = 2500), with the objective to evaluate the long-term safety and performance of Combo in routine clinical practice. The HARMONEE is a prospective, multicenter, randomized study for Japan and US Approval planning to enroll 572 patients. An influential research novelty with the Combo stent is represented by the REDUCE large trial, in which all-comers patients (n = 1500) with acute coronary syndrome successfully treated with the Combo stent will be randomized 1:1 at discharge to 3 months or to 12 months of dual antiplatelet therapy.

Q While all of the trials of the COMBO stent have yet to report, what future implications might we expect based on the results already seen?

In my opinion, in general, a future main implication from Combo studies could be that in the long run patients benefit more from an adequately healed stent than from an initially lower late-lumen loss. Indeed we can expect the Combo stent to be associated with stable vessel healing and durable results with the potential of lower late thrombotic events. The REDUCE trial, in particular, besides to demonstrate the safety of Combo with a shorter dual antiplatelet duration in the high-risk setting of acute coronary syndrome, will have influential implications on the management of this challenging setting. In consideration of the increasing age and risk of treated patients, the availability of a stent requiring a short dual antiplatelet therapy even after an acute coronary syndrome has the potential to remarkably improve overall net clinical outcomes.

Q In your view, what are the greatest changes currently facing interventionalists practicing today?

In general, interventionalists are currently dealing with a more and more complex patients and lesions, which have been often excluded from trials or there is scarce evidence, and thus their management is still a matter of debate. In particular, a relevant current change across the board is the increasing number of primary percutaneous coronary intervention for ST-elevation myocardial infarction due to the implementation of local networks. An amount of evidence is emerging on the optimal management of these high-risk patients, including antithrombotic regimen, stent selection and revascularization strategies of culprit and con-culprit lesions. Another important change in current interventional practice is the increasing need of adjunctive assessment with intravascular imaging techniques, especially functional, with which operators have to get more familiar. In this regard more sophisticated imaging technologies are in development. An additional great change regards the introduction in clinical practice of bioresorbable scaffolds, which require an accurate patient and lesion selection and specific implantation techniques. Finally, dynamic changes involve the stenting strategies of specific anatomic subsets, such us coronary bifurcations, calcified lesions, angiographically intermediate lesions, diffuse and small vessel disease.

Q In your view, what does the future hold in terms of new technology/techniques for stenting?

Coronary stents are developed and brought into clinical practice at an impressively high speed, and before one product has been thoroughly evaluated, a newer generation or alternative is already available. Therefore in the next future a relevant number of coronary stents will be available, and it will be more and more challenging to identify the best devices for the specific settings. Nevertheless, the devices in development, associated with low vessel injury, superior conformability, early endothelialization, without increasing neo-intimal hyperplasia, and requiring a short period of dual antiplatelet therapy, even when used in the acute coronary syndrome setting, have a great potential to prevail over current generation stents. However, long-term net clinical end points associated with the unrestricted use of these devices are warranted. Although workhorse permanent metallic stents will have a central role in percutaneous coronary intervention, in my view, as more randomized and nonrandomized data at long-term follow-up will come available a relevant part, to be defined, of the next future will be 'bioresorbable'.

Q Amongst the other results presented at the Joint Interventional Meeting 2015, what studies do you think present the most exciting possibilities for cardiologists in the coming years?

In the field of coronary intervention, all studies on the several novel DES technologies that are being developed are very exciting and promising, although most available results are still preliminary. Among those studies, at the moment, stands out the LEADERS Free, which is a large multicenter trial with the polymer-free Biofredom DES and only 1 month of dual antiplatelet

therapy after stenting in patients at high risk for bleeding. The results of the this trial, that will be presented soon this year, beyond to demonstrating the efficacy and safety of the novel DES with a very short period of dual antiplatelet therapy, will provide important insights into the management of a challenging subset of patients with high bleeding and thrombotic risk, including those with acute coronary syndrome. Other discussed stimulating and potentially impacting studies for coming years are those regarding the imaging techniques to characterize the plaque vulnerability and guide revascularization. Finally all registries data presented on bioresorbable scaffolds are very promising and open the possibility for the increasing use of these devices.

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