Managing Refractory Angina in **Absence of Options**

Professor Shmuel Banai

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Professor Shmuel Banai is an interventional cardiologist at the Tel Aviv Medical Center, affiliated with the Tel Aviv University Sackler School of Medicine, Israel. He is interested in vessel wall biology and physiology and in exploring therapies and interventions to obstructive diseases of the heart blood vessels. Professor Banai has recently validated a new heart device for the treatment of refractory angina.

To begin, can you tell the readers how did you start your career in medical research and why did you choose Cardiology as a domain?

During the years 1988 and 1992, I was a visiting research fellow at the Cardiology Branch of the National Heart, Lung and Blood Institute of the National Institutes of Health in Bethesda, USA. There, under the guidance of Dr. Stephan Epstein and Dr. Ellis Unger, I pursued the early stages of my career in Cardiology research. Since I was a medical student, I have been fascinated by the physiology of the heart, the amazingly engineered organ that is in constant movement to pump the blood throughout our bodies. Understanding the mechanistic events underlying heart diseases and developing solutions to circumvent them has been gratifying to me. In addition, I have a particular empathy for heart disease patients and their families, who are fighting some life-threatening disease conditions.

As we will come to later, you have recently demonstrated the benefits of a new heart device in the treatment of refractory angina. But first, can you explain what is refractory angina and to what extent it affects the patient's health and lifestyle?

Angina is a common clinical problem, which results from the insufficient blood flow to some regions of the heart muscles (ischemia). This often occurs as a complication of coronary artery disease, in which one or more of the coronary arteries, which nourish the heart, become occluded. However, a growing number of patients who suffer from coronary artery disease continue to experience severe angina, despite optimal medical therapy, and despite the surgical interventions aimed to overcome the coronary occlusion. This resistant condition is referred to as refractory angina, while the patients suffering such a type of angina are often labeled as 'no option' patients.

Patients with refractory angina are usually severely disabled, experience marked limitation in their ability to perform ordinary physical activities, and have poor quality of life. In contrast to what was previously reported and believed, the life expectancy of patients with refractory angina is not significantly inferior to that of other patients with stable/chronic ischemic heart disease. Therefore, the goal of refractory angina therapy is mostly directed at improving these patients' quality of life rather than extending their lifespan.

According to your publications, the new heart device is described as a 'coronary sinus reducer'. What is the nature of this device, and how does it alleviate refractory angina?
The coronary sinus reducer is a balloon-expandable hourglass-shaped metal mesh designed to be implanted in the coronary sinus, which drains blood out of the heart muscles. Placement of the Reducer creates a controlled narrowing of the lumen of the coronary sinus, which leads to an increase in backward pressure and dilatation of small blood vessels supplying blood to the heart muscle. As a result, more blood is forced into the areas of the heart muscle which lack sufficient blood supply.

What about the safety of the Reducer™? Were there any major complications or adverse effects of the implantation or the operation of the stent?

There are no safety issues with the Reducer. In the COSIRA trial, which was designed to evaluate the safety and efficacy of the Reducer, no difference in the rate of adverse events was observed between the treatment and the sham-treatment groups.

Does the implantation of the coronary sinus reducer require special care prior administration or long period of hospitalisation afterwards?

Implantation of the Reducer is a very simple and straightforward procedure. It does not require any special care. Patients can go home on the same day of the procedure or on the next morning. Implantation of the Reducer is done under local anaesthesia through a vein in the neck.

Throughout your therapeutic studies on the coronary sinus reducer, have you collaborated with other research groups or institutes?

Absolutely, the earliest clinical trial (First-In-Human) was conducted in one medical centre in Germany and two medical centers in India. The COSIRA trial was conducted in 11 medical centers in western Europe and Canada. The two principal investigators of the COSIRA trials were Dr. Stefan Verheye from Antwerp Cardiovascular Centre, Belgium, and Dr. Marc E. Jolicoeur, from the Montreal Heart Institute, Canada.

Are you planning to extend your research on the management of refractory angina? What might be the scope of the next step?

Currently, the Reducer™ is routinely in use in several clinical centres in Europe. A multicentre observational clinical study is currently undergoing in Europe. Patients with severe chronic refractory angina, confirmed for heart ischaemia, and have 'no options' for other surgical interventions are being enrolled.

Reducer™: A New Treatment For Refractory Angina

A new heart device (Reducer™) for the treatment of refractory angina has been recently validated in a multicenter international clinical trial. Reducer™ provides a safe and effective treatment option for patients who are neither responsive to medical therapy, nor admissible to surgical or other interventions.

REFRACTORY ANGINA & THE 'NO OPTION' PATIENTS

Angina pectoris – better known as angina – is a clinical symptom in which the patient suffers chest pain accompanied by a feeling of tightness in the chest and shortness of breath. Angina symptoms typically manifest in patients suffering shortage in the supply of oxygen-rich blood to a considerable area of the heart muscles (cardiac ischemia). This shortage is often a direct result of a partial occlusion of one or more of the coronary arteries that nourish the heart muscle, a condition most commonly encountered by patients with atherosclerotic coronary artery disease. The latter involves the accumulation of atheroma (a waxy substance composed of cholesterol and cells) within the walls of the coronary arteries, leading to a significant narrowing of the lumen. Patients with atherosclerosis of the coronary arteries are at a high risk of experiencing heart attacks, which is potentially life-threatening. Patients with angina experience marked limitation in their ability to perform ordinary physical activities and have a poor quality of life. Those patients continue to have debilitating symptoms that keep them from climbing stairs or even walking longer than 100 feet, Professor Banai said.

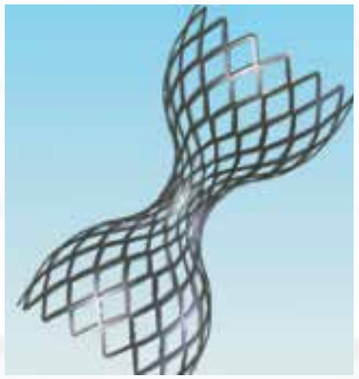
The majority of patients with angina are responsive to medical treatment or to revascularization with by-pass surgery or with stent implantation. However, a significant number of patients continue to suffer from angina, despite the proper medical care and despite revascularization. Moreover, some of these patients might not be amenable to surgical or interventional procedures. 'These patients continue to suffer from angina, commonly referred to as refractory angina, and are clinically labelled as 'no option' patients', says Professor Banai. According to some studies, patients with refractory angina constitute around 25% of total angina patients. The number of these patients is currently growing, especially in aging populations. For example, in the United States, 1,000,000 people are estimated to suffer refractory angina. With the current lack of curative options, managing cases of chronic refractory angina has been a tough challenge for cardiologists.

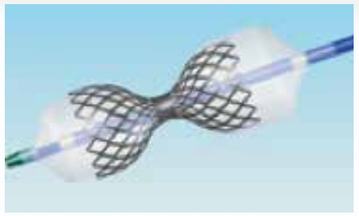
REDUCER™: THE CORONARY SINUS REDUCER TECHNOLOGY

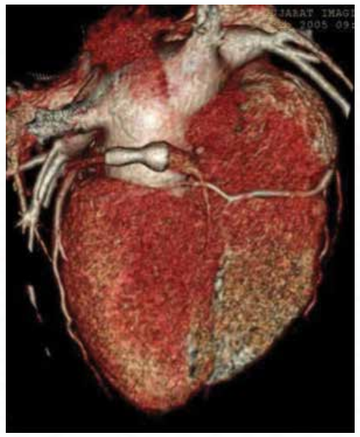
The Coronary Sinus reducer (Reducer™) is a balloon-expandable hourglass shaped stainless-steel mesh, developed by the specialty medical device company, Neovasc Inc. The Reducer™ is designed for implantation in the coronary sinus, the terminal vein through which the blood is drained out of the heart, to create a controlled narrowing in the sinus. As a result, coronary sinus pressure is elevated. These events favour the redistribution of oxygenated blood through the coronary arteries towards ischemic areas of the heart muscles, according to Professor Banai. The implantation of the Reducer™ is performed via a catheter, which is introduced through a large vein at the right side of the neck by a painless procedure under local anesthesia.

THE COSIRA TRIAL TO VALIDATE THE CONCEPT

The earliest study exploring the validity of the Reducer™ was conducted by Professor Banai and his research team in 2007, on a limited number of refractory angina patients who were not suitable candidates for revascularisation procedures. The study gave the first evidence on the safety and efficacy of Reducer™, which resulted in no adverse reactions and relieved the angina symptoms in the majority of the patients over a six-month period of follow up. However, despite the promising outcomes, a subsequent study was required to confirm these preliminary results in a larger group of patients, while taking stronger control measures to ensure their reliability. Hence, Professor Banai, together with a panel of international collaborators has conducted a large clinical







Reconstruction of the back of the heart and the Reducer in the coronary sinus

trial to evaluate the safety and efficacy of the Reducer™ in 14 clinical centres in Canada, Belgium, England, Scotland, Netherlands, Sweden and Denmark. The study, which is better known as COSIRA, lasted from April 2010 to April 2013 involved a total number of 104 patients of with refractory angina. Selected patients were >18 years old, and belonged to class III or IV angina, according to a four-class scale of physical disability adopted by the Canadian Cardiovascular Society (CCS). Importantly, these patients suffered from angina despite optimal medical therapy and were not amenable to revascularization procedures ('no option' patients).
During the COSIRA study, strict measures were taken to circumvent biases related to the patient or the staff's prior knowledge of the group assignments. The participants were randomly divided into two study groups, one of which was assigned the Reducer™ implantation (treatment group), while the other was assigned the same procedures, with no Reducers being placed (sham control group). None of the patients were aware with the group allocation throughout the study. 'Participants were offered either headsets playing music or conscious sedation to mask the conversation in the room regarding the randomisation and the procedure', says Professor Banai. Similarly, except for the cardiologists performing the implantation procedures, none of the investigators responsible for assessing the angina at follow-up, the laboratory staff and the statisticians analysing the data were aware of the group assignments.

The patients were assessed on various measures reflecting both the safety and efficacy of the Reducer™. Efficacy measures included the proportion of patients with an improvement of two or more CCS angina classes from baseline to 6 months after implantation, as a primary measure, while the proportion of patients with an improvement of one or more CCS classes from baseline to 6 months and exercise tolerance was set as a secondary measure. Safety measures included any adverse effects during a six-month follow-up.

The Reducer™ device offers a safe and efficacious therapeutic option for alleviation of refractory angina in patients who are neither responsive to therapy nor admissible to revascularisation procedures

REDUCER™ IS A PROMISING TREATMENT OPTION

At 6 months, 35% of the patients in the treatment group had improved by at least two CCS classes versus only 15% of the control group. In addition, 71% of the patients in the treatment group versus 42% in the control group improved by at least one CCS class. Quality of life, has improved by 17.6 points in the treated group versus 7.7 points in the control group, as measured by a validated questionnaire.

Overall, 76 adverse events were reported in the treatment group and 93 in the control group. Three cases have suffered complications of cardiac ischemia, and one death (due to multiorgan failure) in the control group, and there was one case of ischemic complications and no deaths in the treated group.

'The COSIRA trial demonstrated that implantation of the Reducer™ device to narrow the coronary sinus significantly improved symptoms and quality-of-life in refractory angina patients', says Professor Banai.

THE FUTURE OF THE REDUCER™ TECHNOLOGY

Parallel to the evidence provided by COSIRA on the validity of Reducer™ as a curative option in cases of refractory angina, the device has already obtained a CE mark in Europe in 2011. Professor Banai and his team have also recently reported the clinical results of the first 23 patients treated with the Reducer implantation under the CE mark. This report combines the results from 2 medical centres in which the Reducer is currently used for the treatment of such 'no option' refractory angina patients. The results show that the implantation of the Reducer™ was associated with a significant improvement in the severity of angina and ischemia, while no associated adverse effects were observed. Currently, Neovasc Inc plans to conduct a trial to obtain approval of the US food and in the United States.

Currently, the Reducer is used in selected medical centers in the United Kingdom, Belgium, The Netherlands, Italy, Switzerland and Germany.

Researcher Profile

Neovasc
Neovasc Inc. is a specialty medical device company that develops, manufactures, and markets products for the rapidly growing cardiovascular marketplace.

Its products include the Tiara™ technology in development for the transcatheter treatment of mitral valve disease, the Neovasc Reducer™ for the treatment of refractory angina and a line of advanced biological tissue products that are used as key components in third-party medical products including transcatheter heart valves.

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