

The first absorbable metal stents

Biotronik GmbH is developing absorbable metal stents for the treatment of coronary and peripheral artery diseases. The first human implants of Biotronik's absorbable metal stents took place in December 2003 at the AZ St-Blasius Hospital in Dendermonde, Belgium, and the Imelda Hospital in Bonheiden, Belgium, in patients with critical limb ischaemia (Rutherford 4-5) and with infrapopliteal pathology. Speaking at Advanced Angioplasty 2004, Dr Carlo di Mario of the Royal Brompton Hospital, London, said that trials in coronary arteries are to begin shortly.

BIOTRONIK has developed a new magnesium absorbable metal stent. This new stent is made of an alloy consisting of over 90% magnesium in combination with different rare earth elements. Dr Carlo di Mario, who spoke on behalf of Biotronik at the recent Advanced Angioplasty 2004 meeting in London, said: "In vitro tests and animal experiments suggest that this magnesium alloy can make great bioabsorbable stents which allow rapid endothelialisation and reduced intimal hyperplasia." He continued by stating that the first implants in peripheral arteries have already been performed and that clinical studies in the coronary arteries are planned to begin in the first half to 2004.

The rationale behind these absorbable metal stents is as follows: Stents reduce recoil but as a result of the permanent presence of the stent material, unwanted reactions of the vessel wall are induced and the vessel may become narrowed again. As an approach to decrease restenosis, stents have been coated with certain drugs that prevent the harmful reaction of the vessel to the stent. However, once the coating has dissolved from the stent the abnormal growth may occur and the vessel may become narrowed once again. Similar to the typical metal stents, the absorbable metal stents prevent vessel recoil and keep the vessel open after angioplasty. However, unlike other stents, the absorbable metal stents should disappear before long-term effects occur and the abnormal growth pattern and re-narrowing should therefore not occur. Once the stent is gone, the inner part of the vessel regains its normal smooth surface and blood flow improves. Also, unlike other metal stents, the absorbable metal stents does not cause artefacts on magnetic resonance angiography. A prospective multi-centre study with

absorbable metal stents in diseased coronary arteries is planned to start during the first half of 2004 and will enrol 63 patients with single-vessel disease. According to di Mario, "Combinations of absorbable metal stent and antiproliferative drugs are in the pipeline." In answer to what happens to the magnesium, di Mario explained, "If you think how much magnesium there is in your diet, one of these stents is just 100th of your daily intake"

First clinical results in the periphery

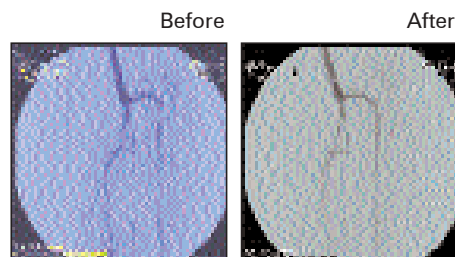
Cardiovascular News talked to Dr Marc Bosiers, Head of Vascular Surgery at the AZ St-Blasius Hospital, and Dr Patrick Peeters, Head of Vascular Surgery at the Imelda Hospital, as the first results of absorbable metal stents in peripheral applications were being released.

In December 2003, absorbable metal stents were implanted in patients with critical limb ischaemia (Rutherford 4-5) and with infrapopliteal pathology. According to Bosiers "We treated vessels with focal lesions, vessels that had one short occlusion or high-grade stenosis."

The stent is completely absorbed by the



Biotronik's absorbable metal stent



surrounding vessel wall. Previous animal tests revealed an absorption time of approximately two months. "These results convinced us this alloy has the adequate strength to support the vessel wall as long as necessary and that it fully absorbs after this time frame, consequently lowering the intimal hyperplasia", Bosiers said.

Furthermore, the animal tests described a complete covering of the expanded stent with a thin layer of tissue after four days. This complete embedding of the stent with endothelial tissue yields low rates of thrombotic events and supports a

homogenous degradation process of the stent without any risk of particle migration and subsequent microembolism.

After pre-dilatation of the short infrapopliteal lesions, Bosiers and Peeters implanted the absorbable metal stent. "Nevertheless, the stent is not visible on standard angiography, it is easy to implant as it behaves like all the stents available on the market today" Bosiers said. "To control stent placement, we used peroperative IVUS," Peeters continued.

On the first day post-procedure, MR angiography and duplex scans were performed. "On MR angiography normally a metal stent creates an artefact so you see a black image, which prevents you seeing the vessel. With the absorbable metal stent there is no artefact so that you can see the blood flow and the vessel and therefore will not compromise physicians' options," explained Peeters.

"Immediately after implantation and one day after the procedure a whole range of blood sample parameters were run, and none of them revealed any toxicity of the implanted material," said Bosiers.

According to Bosiers, the toxicity tests at one-month follow-up also turned out to be negative. At one month with MR angiography and duplex on eight patients, no restenosis is diagnosed and all the arteries are patent. Furthermore the duplex investigation already revealed the start of the absorption process: the magnesium alloy became less visible after one month compared to one day.

Bosiers said, "There seems to be a good balance between the absorption process and the function of the stent supporting the vessel wall to keep the vessel open."

Bosiers and Peeters summarised the preliminary outcome of their first peripheral implants as: 1) the efficacy of the stent at one month has been confirmed as all vessels remained patent with no restenosis, 2) the implantation of this magnesium alloy is safe as all toxicity tests were negative and 3) the absorption process has started as seen on duplex.

According to Biotronik, the plan is to have an absorbable metal stent on the market in 2005.

Carlo di Mario



Patrick Peeters



Marc Bosiers



Edwards buys PVT

EDWARDS LIFESCIENCES has completed its acquisition of Percutaneous Valve Technologies (PVT), a privately held medical technology company that has developed an innovative, percutaneous approach for replacing aortic heart valves. Under terms of the agreement Edwards is paying the shareholders of PVT \$125 million cash, plus up to an additional \$30 million in payments upon the achievement of key milestones.

"We are pleased at how smoothly this transaction has been completed, and we're looking forward

to bringing this technology to market quickly," said Michael A. Mussallem, Edwards' Chairman and CEO. "Our due diligence on PVT's products, people and intellectual capital has reinforced our enthusiasm about the promise that this technology holds for patients."

The acquisition of PVT reinforces Edwards Lifesciences' leadership role in replacement and repair of heart valves through catheter-based technologies. PVT's technology is an innovative, catheter-based (percutaneous) approach for replacing aortic heart

valves, a proprietary combination of a percutaneously delivered balloon-expandable stent technology integrated with a tissue heart valve. Unlike conventional open-heart valve replacement surgery, this less invasive procedure can be performed under local anaesthesia, and is a breakthrough for patients who are not candidates for surgery today. Edwards estimates that total sales of catheter-based valve repair and replacement products could exceed \$1 billion over the next decade.

The first human implant of PVT's valve was performed in April 2002 by Dr Alain Cribier, Charles Nicolle Hospital, University of Rouen, France, who has treated 17 patients to date and is conducting a

prospective clinical trial in France. Edwards plans to file for a Humanitarian Device Exemption (HDE) with the FDA in 2005, which would allow for commercial use in a limited number of patients. A CE Mark also is anticipated in Europe in 2005.

In addition, Edwards Lifesciences plans to sell off its Lifepath AAA endovascular graft system. The company announced that it will explore "strategic alternatives" for its Lifepath system and that it intends to focus its resources on its heart valve technologies and haemodynamic monitoring devices. The Lifepath system is currently sold in Europe and Australia and is in clinical trials in the US.



Alain Cribier

Profile **Sigmund Silber**

Sigmund Silber, Professor of Medicine, University of Munich, is a noninvasive and invasive cardiologist with additional licences in nuclear cardiology, Cardio-CT and endovascular radiation therapy, who also has extensive experience with drug-eluting stents. He talked to *Cardiovascular News* about his career and the problems facing cardiologists in Germany.

SIGMUND SILBER was born in 1949 in Passau, Bavaria, Germany, and his interest in medicine started at an early age. "During school, I was very interested in biology," said Silber, "and of course the top of biology is the human body. I was interested in how it works, and, believe it or not – although it sounds a bit old-fashioned, I was also interested in helping other people."

Silber explained, "When I started medicine, one of my professors said, 'When you come to my exam, I will ask you why you started medicine and why do you want to become a doctor.' The professor said, 'Don't tell me that you want to help people because I don't believe it.'" However, Silber believes that there are physicians who want to help people and "I am one of those," he said.

Silber then described how he found his vocation as a cardiologist. "I decided to become a cardiologist during medical school. Why? Maybe because I like to see reproducibility. I like to see numbers. I like to see tests and qualifications, and cardiology was one of the very few specialties in medicine in which you can actually measure something. I like to focus on specific problems and cardiology was always fascinating."

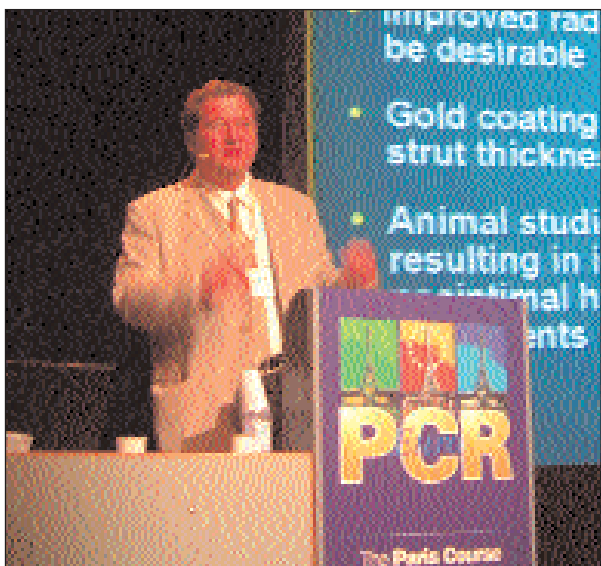
Silber then recalled his start in the profession. "I was very lucky because, when I finished medical school and started as a young physician in my first medical practice, I got an appointment at a new institution in Munich – the German Heart Centre. This was actually the first Heart Centre in Germany. Its first director was Professor Rudolph and from him I learnt a lot. I learnt how to deal with the cardiology problems and also how to create new concepts that didn't exist before. It was a once in a lifetime opportunity."

Silber saw how the German Heart Centre became established. This was a new venture in Germany, because previously, cardiology only existed as departments in major general hospitals.

At the very beginning of his career, Silber became involved in nuclear cardiology, which at the time was a brand new field. "I was lucky as young physician to get involved in a new and noninvasive method of myocardial perfusion imaging, actually I did the second thallium scan in Germany. It was a coincidence because the first was done at Munich University Hospital and they had some thallium left over and they called us and said 'Hey, do you want to try this?'. Myocardial perfusion imaging, testing viability, I was one of the first to get involved, just because I was there at the right time."

Silber was then trained in invasive cardiology. "I was very fortunate to work with people who were involved very early on in PCI. I remember when I started assisting with PCIs – performed in cardiac surgery rooms with big machines for

During EuroPCR



inflating the balloons. It was at a time when many cardiologists were reluctant to do this. They said that it was unethical to put a balloon in a coronary lesion. Today, people can't imagine what it was like then."

Silber then received an offer to work as Associate Professor in the USA from Dr Pohost, who was at Massachusetts General Hospital (MGH) in Boston and became Director of Cardiology in Birmingham, Alabama. During his time in the USA, Silber – besides doing general clinical work – also gained experience in magnetic resonance imaging and spectroscopy.

Having returned to Munich after three years, Silber entered private practice and later became full Professor of Medicine at the University of Munich. "To enter private practice was a major decision and a difficult decision, especially in Germany. I think that without my time in the USA, I would never have done this step," said Silber. "In the USA, even university hospitals are run like a private practice, so it was not too difficult for me." Silber explained, "Most people think either you do private practice or you do specialised, academically oriented medicine. But it is not true, you can do both at the same time."

Silber then focused on building up the private practice. The next step was to initiate a system of "integrative patient care". We actually started doing this in 1991 – long before the German health care ministry demanded it with a new law – starting 2004. Silber built up a strong network with general practitioners, non-PCI hospitals and the Department of Cardiac Surgery at the University of Munich (Director: Professor Dr B. Reichart). In 1999 Professor Silber started the "Heart Diagnostic Centre" in Munich for noninvasive risk assessment including the measurement of coronary calcium scores and non-invasive coronary- and bypass-angiography. In 2003, he also got the licence for endovascular radiation therapy. "Brachytherapy still is a very important tool for treating in-stent restenosis. We have a lot of patients referred to us for radiation therapy of recurrent in-stent restenosis. I decided to get the licence, so I don't need a radiation therapist to be present, which is complicated sometimes", said Silber. According to Silber, "The practice sees about 10,000 patients a year, both invasive and non-invasive. Invasively, we do around 2,500 diagnostics and around 1,000 PCIs. We always try to do all types of PCI – whatever is necessary. In earlier times, we did a lot of laser and rotablation when it was popular."

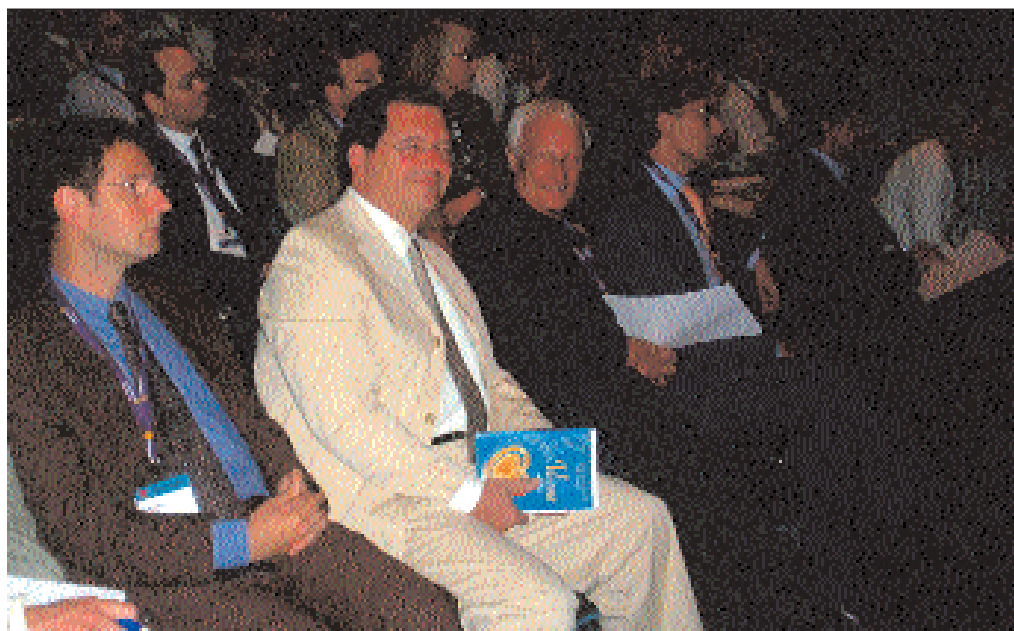
Among the elected positions that he has held, Silber selected out being Chairman of the Committee for PCI guidelines of the European Society of Cardiology (ESC) and being the President of the cardiologists in private practice in Bavaria. In the German Society of Cardiology (DGK) he is the vice president of the interventional cardiologist working group and a member of the project group for quality assurance.



What is your opinion on drug-eluting stents?

Silber and his team gained very early experience with drug-eluting stents. "We participated in the SCORE trial, which was not a good start because it was the wrong stent design and totally overdosed. We also participated in TAXUS I, TAXUS II (where we were number one enrolling centre, and also participating in TAXUS VI and the ENDEAVOR II trials," said Silber.

"Of course everybody knows, I don't have to repeat it, that drug-eluting stents are a major step forward. It is an exciting field and the results are very good, but there is one Achilles' heel for drug-eluting stents: this is that people are getting older and older, so the more drug-eluting stents you put in, the higher the probability is that a patient with a drug-eluting stent will soon have any type of non-cardiac surgery." Silber explained, "We unfortunately have seen some cases, where the surgeons, for non-cardiac surgery, or the dentists, take the patient off clopidogrel four months after DES-implantation resulting in subacute stent thrombosis and a major heart attack. So we have to be very careful



Silber with Eberhard Grube

before we implant a drug-eluting stent to make sure the patient does not have a planned surgery." For at least six months, patients have to be instructed not to discontinue clopidogrel – like after brachytherapy.

According to Silber, the second problem with drug-eluting stents in Germany is the price. Germany is a very low-price country for the bare metal stents and therefore there is a larger difference between the price of bare stents and drug-eluting stents than in many other countries. This has meant that drug-eluting stent penetration in the German market has so far been less than in most of the other countries in Europe. For Germany, drug-eluting stent penetration is estimated to be only around 5%. Silber explained, "If you get 10 bare stents for the price of one drug eluting stent, I think the choice is quite clear – especially if DES are not reimbursed."

"I am involved in politics and reimbursement. It is very difficult to convince the Social Healthcare to reimburse drug-eluting stents. So far there is no official reimbursement for drug-eluting stents for Social

Healthcare insured patients. Why is that?

They main reason they give is that a drug-eluting stent doesn't prolong life. However, mortality is so low with the bare stent already- how can it be improved? What drug-eluting stents do is that they improve quality of life and to convince the healthcare providers of improved quality of life is very difficult. Silber said that he thinks that the recently introduced DRG system will only make things worse because "reimbursement is lower than with the old system".

One possible solution that Silber suggested would be that if a patient wants a drug-eluting stent then he could pay out of his own pocket. However, this is currently not allowed. "If I have a patient and the patient asks 'Can I pay for my drug-eluting stent?' I have to say in theory you could – but I would lose my licence...."

Silber continued, "The major challenge [in Germany] is to provide state of the art treatment to patients with Social Healthcare Insurance. We hear of all these studies, not just drug-eluting stents but also putting in ICDs and many other innovations. We have so many innovations, important innovations, but the major challenge is how to provide the patients with these treatments within the confines of the system."

Which innovations in cardiology do you regard as pivotal?

Asked what he sees as the current hot topics in cardiology, Silber referred to the top 10 list for 2003, recently published

by the American Heart Association. From this list, Silber highlighted ximelagatran, which he described as "a major step forward getting patients off coumadin", the concept of utilising the patients' own progenitor cells, drug-eluting stents and recently ETC-216, which "appears to be a miracle drug for decreasing coronary lesions."

Silber said that drugs such as ETC-216 could be a "threat" to PCI in the future. "If you diagnose a coronary lesion very early, like we do with the ultra-fast CT, then you give the patient this medication and it takes away the lesion. If a drug can take away the plaques very early, or even later, then we wouldn't need PCI anymore."

He continued, "Heart attack is still the number one killer so there is still obviously a great need for cardiologists, unless, of course, you can make the cardiologist superfluous with miracle drugs. I remember when I was a young physician there were many surgeons that made their living from surgery on gastric ulcers. Today surgery on gastric ulcers is a treatment of the past because we have very effective drugs. Maybe one day cardiology will go the same way."

Asked about the relations between cardiologists and cardiac surgeons in Germany, Silber said that in general they are good. "Most of the cardiologists are conservative – so they leave a lot of surgeries for the surgeons still. However, there are other cardiologists in Germany that dilate everything. The surgeons are a little bit afraid because whereas PCI numbers are still going up in Germany, bypass surgery is going down. This has been the trend for the last two years and with the advent of drug-eluting stents potentially replacing surgery for multivessel disease in diabetic patients, this is set to continue."



Fact File

Sigmund Silber, MD, FACC, FESC

Professional experience

- 1982–1986 Director, Nuclear Cardiology, University of Munich
- 1982–1986 Member, Isotope Committee, University of Munich
- 1982–1986 Director, ST-Segment Holter Monitoring Laboratory, University of Munich
- 1983–1986 Member, Formulary Committee, University of Munich
- 1987–1989 Associate Professor, University of Alabama at Birmingham (UAB), USA
- 1987–1989 Director, Holter Laboratory, (UAB)
- 1987–1989 Director, Cardiac Pharmacology Clinic, (UAB)
- 1987–1989 Member, Pharmacy & Therapeutics Committee, (UAB)
- 1990 Staff, Cardiology Associates at the Red Cross Hospital, Frankfurt/Main, Germany
- 1991 Private Practice Cardiology Associates in Munich and at the Dr Müller Hospital ("integrative patient care")
- 1996 Associate Professor, University of Munich
- 1998 Professor of Medicine, University of Munich

Professional memberships

- German Society of Cardiology and Cardiovascular Research (DGK)
- German Society for Internal Medicine (DGIM)
- Working Group for Interventional Cardiology of the German Society of Cardiology (AGIK)
- Working Group for Nuclear Cardiology of the German Society of Cardiology
- German Society of Internal Medicine (BDI)
- German Society of Cardiologists in Private Practice (BNK)
- Federal Association of Specialists in Private Practice (BNF)
- Federal Association of Specialized Internists in Private Practice (BNFI)
- European Society of Cardiology (ESC)
- American Society of Nuclear Cardiology (ASNC)
- American College of Cardiology (ACC), rank of FACC
- American Heart Association (AHA), Clinical Cardiology
- European Council of Cardiology Practice (ECCP)

Editorial consultant

- HERZ
- MMW – Fortschritte der Medizin
- Klinische Wochenschrift
- Deutsche Medizinische Wochenschrift
- Drugs Safety
- International Journal of Cardiology
- Clinical Cardiology
- Catheterization and Cardiovascular Intervention
- American Journal of Medicine
- American Heart Journal
- American Journal of Cardiology
- Journal of the American College of Cardiology
- Circulation

National and multinational studies

- A.A.C.H.E.N., ACUITY, ARTIST, BETA-CATH, BRIE, CHARISMA, DETECT, EBEAT, ENDEAVOR-II, EVIDENT, IMPULSE, IST, LUSTY, MUNICH, NIRTOP, NUGGET, PETN, RECALL, RENO, RESCUT, SAFE, SCORE, SEAL, START, TAXUS-I, TAXUS-II, TAXUS-VI