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INTERNATIONAL LECTURE

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A Journey in the Interventional Field

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HISTORICAL MILESTONES

On September 16, 1977, the first successful angioplasty was performed by Andreas Gruentzig. Ten years later, the patient underwent recatheterization, which showed that the previously instrumented coronary artery was widely patent (1). The year 1986 marked the beginning of the stent era, with the first implantation of the self-expanding Wallstent by Ulrich Sigwart in Lausanne (2). In 1994, the results from Stent Restenosis Study (STRESS) investigators (3) and the Benestent Study Group (4) became available. The Belgium Netherlands Stent Arterial Revascularization Therapies Study (BENESTENT)-1 demonstrated that the implantation of metallic stents results in a reduction in the restenosis rate from 32% to 22%. Similarly, the occurrence of any adverse event at seven months was reduced from 29.6% to 20.1%.

July 1999 was a fresh new start for me. I had been invited to the headquarters of Cordis Corporation in Warren, New Jersey, where I was introduced to a rapamycin-eluting stent and asked how to begin a Phase II program for it. I was impressed by the molecular biology behind the principles: sirolimus (which is attached to the internal receptor, $FKBP_{12}$), by acting on mTOR, influences the up-regulation and down-regulation of p27 and, therefore, blocks cell proliferation. The original plan of the first-in-human study was to conduct the trial in a country outside the U.S., with safety monitoring (i.e., subacute thrombosis, myocardial infarction, death) for 60 days, and to treat these patients for 60 days with ticlopidine and aspirin. After discussion, the final plan was made to perform quantitative coronary angiography and quantitative intravascular ultrasound (IVUS) motorized pullback in 15 patients in Rotterdam and 30 patients in Sao Paulo (5,6). It was a happy time, commuting between Amsterdam and Sao Paulo on KLM flight 797. One day we succeeded in performing 15 consecutive angiographic and IVUS follow-up studies, with a debriefing at the end of the day. At the end of that memorable day, a bottle of champagne was opened to celebrate the end of an iatrogenic disease: restenosis by intrastent neointimal hyperplasia. The holy grail of 25 years of fighting against restenosis was completed.

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At the Andreas Gruentzig Lecture of the ESC Congress in September 2000, presenting these results, I begged the audience by telling them, "Don't wake me up. Don't pinch me. Let me keep dreaming," because at that time we had the angiographic control of the first 45 patients showing the absence of late loss, restenosis, and target vessel revascularization (7). At the same meeting in September 2000, I presented my vision of the future, the so-called rosy prophecy (Fig. 1). The Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) trial, which was conducted in the early 1990s and compared balloon angioplasty and bypass surgery, showed a gap of 32% in clinical outcome between the two methods of revascularization. In 1999, the gap between the outcome of surgery and the outcome of the percutaneous treatment was reduced to 14% in the Arterial Revascularization Therapies Study (ARTS) trial (8). My rosy prophecy predicted that in the future the Kaplan-Meier estimate of freedom from major adverse events with eluting stents would be even greater that of surgery, which was, and still remains, quite a provocative statement.

In those days, *The Wall Street Journal* interviewed me. I said to the journalists that "we are not talking about some kind of reduction of restenosis. We are talking about the radical abolition of what we normally see. There is basically no tissue visible in the stent." In another very "scientific" publication, *The New York Times*, Dr. Spencer King, III, said that "he was encouraged by the early findings, but wished cardiologists would tone down the rhetoric a little. And that the pilot trials cry out for larger and more rigorously designed studies known as randomized double-blind placebo-controlled trials to provide definitive answers."

The Randomized Study with the Sirolimus-Coated Bx Velocity (RAVEL) trial, presented by Marie-Claude Morice at the European Society of Cardiology Congress of 2001, showed a zero late-loss, a zero restenosis rate, a target lesion revascularization percentage of zero, and an astonishing 97% event-free survival. In 2002, we published the report in the *New England Journal of Medicine*: this was the real beginning of the drug-eluting stent era (9). To date, many trials with sirolimus and paclitaxel have confirmed these first observations (10–15). In all these trials, a treatment effect of approximately 70% to 80% exists: the events at 6 and 12 months are less than the two digits for the

Abbreviations and Acronyms

CABG = coronary artery bypass graft
CT = computed tomography
CTO = chronic tomography occlusion
EEM = external elastic membrane
EPC = endothelial progenitor cell
IVUS = intravascular ultrasound
MACE = major adverse cardiac event
MI = myocardial infarction
MRI = magnetic resonance imaging
OCT = optical coherence tomography
PCI = percutaneous coronary intervention
PTCA = percutaneous transluminal coronary angioplasty
TCFA = thin-cap fibroatheroma

drug-eluting stent. The question is, where are we going now? In this lecture, I will review the future of interventional cardiology.

DRUG-ELUTING STENTS

Where are we heading to? Let's start analyzing what can be expected beyond the published randomized trials on drug-eluting stents. The drug-eluting stent revolution has ushered into clinical practice. In Rotterdam, since April 2002, the implantation of drug-eluting stents has been the default strategy for all patients treated using percutaneous coronary intervention (PCI) in our daily practice, which means more than 3,700 patients and more than 8,000 eluting stents (14,15). In addition, we have shown that there is a 66% relative reduction in the need for clinically driven target vessel revascularization, from 13.9% to 4.8%, which is a major achievement, indeed! We have scrutinized the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry quite intensively, I would say, which has resulted in a large number of publications in well-known peer-reviewed journals. We have summarized our experience in a monograph entitled "From RESEARCH to Clinical Practice" (16). We documented a systematic treatment effect in reducing reintervention from 60% to 80% in the global population, which also holds true in specific subsets of patients, such as those with acute MI, renal failure, previous bypass surgery, chronic total occlusions, very long lesions, in those undergoing bifurcation stenting, or in those receiving undersized stents, to treat in-stent restenosis, mild stenosis, very small vessels, main-stem stenting, or multivessel stenting.

I would like to draw your attention to the main-stem subgroup with a restenosis rate of 8% (17) and the multivessel stented subgroup with a major adverse cardiac event (MACE) rate of 14%, which is not far away from the MACE rate of 11% observed in ARTS-I after surgery (8). We have published a meta-analysis of Stent or Surgery (SoS), Argentine Randomized Trial of Coronary Stents versus Bypass Surgery in Multivessel Disease (ERACI), and ARTS, which indicates that the cumulative incidence of death, nonfatal myocardial infarction (MI), stroke, and repeat revascularization (18) is 13% in the bypass group: I cannot resist the temptation to compare our current MACE rare in multivessel eluting stenting (i.e., 14%) with the cumulative event rate observed in the surgical arm of the meta-analysis (i.e., 13%).

Recently, we reported the results of ARTS-II as compared with the surgical and PCI arm of ARTS-I (19,20). Despite the fact that we had a majority of three-vessel disease and despite the fact that an average of 3.2 lesions were stented using 3.7 stents, with a total average stent length of 73 mm (compared with 48 mm in ARTS-I), freedom from death, stroke, MI, coronary artery bypass grafting, and re-percutaneous transluminal coronary angioplasty curve was 89.5%. Figure 1 shows the Kaplan-Meier curve of ARTS-II: it is well above the surgical arm of ARTS-I and the PCI arm of ARTS-I. Therefore, the rosy prophecy has come true.

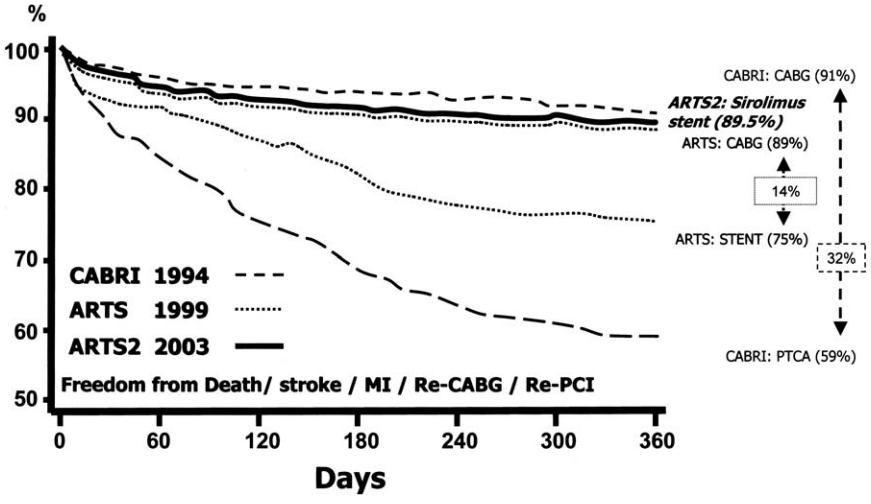

Figure 1. The rosy prophecy. ARTS = Arterial Revascularization Therapies Study; CABG = coronary artery bypass graft; CABRI = Coronary Angioplasty versus Bypass Revascularization Investigation; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.