Coronary Stenting: A Breakthrough Technology or Just Another Step to Improve the Luminal Appearance ? – The Need for an Improved Late Response

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Coronary revascularization, either by CABG or by PTCA, improves survival in selected patients (triple vessel disease, depressed left ventricular function, left main disease), and also improves symptoms compared to medical therapy [1]. The revascularization strategy has changed substantially at both the lesion and the patient level. The techniques and technologies in use have improved success rates and enlarged the range of indications. Cardiac surgery has developed less invasive procedures without cardiopulmonary bypass, and also minimally invasive approaches [2,3]. Innovative, catheter-based technologies and improved adjunctive medical therapy have enormously expanded the spectrum and success of PTCA in the therapy of focal lesions in coronary artery disease [4,5]. Altogether, these advances have led to an increase in health care costs and resulted in an ongoing and controversial discussion between health care managers and physicians in general, and in particular considering the increased rate of coronary stenting ("over-use") [6]. To prove hypotheses and assumptions about superiority and health benefits using scientific-based methods in clinics needs years. Related practice guidelines are sometimes far behind the actual clinical knowledge and should not be used to enforce medical decisions. On the other hand, a new method, a new design, a new technology is not a certificate for success.

On of the most dramatic developments in coronary therapeutics that has lead to such rapid expansion of indications and, subsequently, costs, has been coronary stenting. Stents are already being used in more than 70 % of coronary interventional procedures, which doubtlessly makes them the centerpiece of the so-called new devices. While stents were introduced primarily to limit the bailout situations, unsatisfactory results after "conventional" ballooning, and proximal one-vessel disease during surgical backup [7], the spectrum of indications has been expanded now to include protected left main, multivessel disease, long lesions, recanalized vessels, acute thrombotic situations in unstable angina, and myocardial infarction without the necessity of direct surgical backup. Technically, nearly any relevant region or lesion can be accessed and stented in the cathlab. However, some fundamental considerations must be made. Is the improved luminal appearance identical to a relevant clinical success? Can we assume that a clearly improved angiographic result is identical to an analogously improved short- and long-term outcome of the patient, ultimately improving health benefits for the individual and the society? Is the permanently increasing rate of coronary stenting caused by being the "procedure in vogue" or by scientific-based medicine? What are the real shortcomings at the present time, and how can we improve our methods?

It is generally agreed that stenting is a safe procedure with a success-rate of 98 %. However, one of the drawbacks of stenting using uncoated stents is their surface thrombogenicity. Advances in stent design technology (smooth surface, thin stent struts, decreased turbulence, assimilated stenting), changes in deployment techniques (high-pressure or IVUS-controlled placement), combined with the use of aspirin and ticlopidine or clopidogrel, have resulted in lower thrombosis rates (from 4 – 8 % to < 1 % in pooled patient populations) [8]. Considering such data, is it necessary to improve the stent surface characteristics further with regard to thrombogenicity? Yes, we should do it!

- Conclusions drawn from preselected or pooled clinical trials may not be generalized to the broader population treated in daily practice. In many clinical sit-

uations (unstable angina, myocardial infarction, identifiable thrombus at the lesion site, after recanalization) the risk of stent thrombosis is increased [9-11].

- The clinical consequences of stent thrombosis are deleterious, especially in an almost "out-patient type" of intervention. In the majority of such cases, acute stent thrombosis leads to myocardial infarction.
- The use of additional adjunctive medical treatment such as IIb/IIIa-platelet inhibitors in case of patients/lesions having primary higher risk for stent thrombosis is increasing the cost of the procedure extensively [12].
- There is a clear evidence that brachytherapy has been clinically documented as an effective way to reduce the neointimal proliferative response. However, the price for that benefit is the inhibition of neo-endothelial cell seeding onto the stent struts over months, resulting in "late stent thrombosis" in 4 – 8 % of patients [13,14]. In case of a permanent hypothrombogenic stent surface, this clinically dire situation might be alleviated even without long-term platelet inhibitory therapy.
- Some assumptions have been made concerning the direct relationship between early local thrombogenicity and the degree of the late neointimal response (local release of PDGF, TGF-beta, b-FGF and other mitogenic cytokines). Less local thrombosis might lead to a reduction in the local release of growth factors and other cell- and vasoactive substances/cytokines.

Thus, clinicians and stent developers should continue seeking the best means to lower the thrombotic risk after coronary stenting permanently. Different concepts are being developed to improve the surface characteristics with respect to thrombogenicity (e.g., coating of stent surfaces with drugs like heparine, coating with cell-surface-like membrans or autologeous vein materials, coating with gold, carbon). Considering the well known electronic theory on interactions between metallic implants and the human blood [15], it is not surprising that gold coated stents elicit greater restenosis than uncoated stainless steel stents [16]. A completely different approach is to provide a biologically inert barrier between the stent surface and the circulating blood. Based on biophysical principles concerning surface electrochemistry and their rule in biocompatibility [17], a carefully adapted semiconducting material (amorphous, hydrogen-rich, phosphorous-doped silicon carbide) was used to preclude permanently the contact-activation of fibrinogen, thus inhibiting the fibrin-polymerisation and the coagulation cascade [18]. This metal-semiconductor hybrid concept as a physical model has been proven extensively by cell culture techniques and in vitro analysis of the host tissue response [19,20]. Also some clinical results from open registries [21,22] and an international multicenter randomized trial (TRUST-investigators, personal communication) in patient populations with higher risk for stent thrombosis are promising since they indicate very low rates of stent thrombosis without the use of IIb/IIIa-adjunctive therapy.

However, what about the second "achilles heel" of coronary stenting, the in-stent stenosis or stent-restenosis? Different mechanisms are responsible for some exaggerated neointimal proliferative response and matrix formation after stent implantation. Besides of the degree of arterial injury during the implantation itself, the type and degree of local inflammation, as well as cell migration and thrombus formation influence the local vessel response. Are we correct in assuming that a relationship exists between the biocompatibility of the stent surface and the stent-restenosis rate? Does stent thrombosis and stent restenosis arise from the same source? Can enhancing the release of cytokines and growth factors make smooth muscle cells proliferate and provoke the formation of an extracellular matrix [23]?

Using conventional stents the incidence of stent restenosis remains unacceptable high. The extent of plaque burden determines the prognosis just in primary high risk lesions. Undoubtedly, stents reduce the clinically relevant lumen re-stenosis, but, not as the result of a reduced neointimal response. The primary lumen enlargment (sometimes oversizing) and the prevention of vessel recoil are the dominating factors. The chronic injury induced by mechanical forces, the permanent mismatch in local vessel compliance between the stented and unstented regions, the unspecific permanent inflammation process [24] and the corrosion properties of the alloys used [25], are all contributing to an exaggerated in-stent neointimal response at the long term follow-up which offsets the excellent early results of coronary stenting. A good example is

described previously by Serruys et al [4] concerning the cost-effectiveness relationship of coronary stenting in multivessel disease compared to CABG. One year after the procedures, coronary stenting was less expensive than bypass surgery by offering the same degree of protection against death, stroke, and myocardial infarction. However, stenting was associated with a greater need for repeated revascularization as the result of in-stent restenosis (16.8 % in the stented group versus 3.5 % in the surgery group). The rate of event-free survival at one year was 73.8 % among the patients who received stents and 87.8 % among those who underwent CABG. Obviously, the need for revascularization was the dominant event! Concerning the cost-effectiveness, the clear difference of the costs for the initial procedure in favour of stents was clearly reduced after a one year follow-up period, because of the additional need for repeated revascularization (Re-PTCA or CABG). These differences might be further pronounced in patients experiencing primary complicated thrombotic lesions and diabetes. This is of great significance especially at a time of dramatic expansion of the therapeutic window of PTCA and stenting in the palliative treatment of focal lesions.

At this time, numerous systemic pharmacological approaches to reduce restenosis have failed, possibly due to insufficient local drug concentrations and/or unfavorable release kinetics [26]. A stent-based local drug delivery using sirolimus or paclitaxel shows promising results, however, the number of stented patients is small, the follow-up period relatively short, and some pitfalls (e.g., late stent thrombosis) have just been reported [27,28]. An effective and also clinically documented way to reduce the neointimal proliferative response is brachytherapy. However, the effect of local radiation has some late adverse effects (edge stenosis, late thrombosis) [29,30]. From my personal point of view, the duration of the clinical performance and the future of this principle will be determined by the availability of alternatives.

What about the potential and realistic rule of inorganic stent-hybrids, what about coating with silicon carbide (a-SiC:H) with respect to this exaggerated neointimal late response?
The comprehensive in vitro analysis of the molecular and cellular mechanisms of the SiC-coating revealed more than just the described mechanisms with respect to hypothrombogenicity of the coated surface. In addition, platelet and granulocyte binding, as well as granulocyte release and platelet activation were inhibited by this type of coating [31] (additional data reported by van Oeveren are included in this issue). Furthermore, ions can act as haptens (metal ion). Previously, Köster et al. [25] reported that coronary in-stent stenosis might be triggered by contact allergies to nickel or molybdenum ions slowly released from the stainless steel material. This was clinically observed in patients with orthopaedic, dental, and other stainless steel implants, who experienced formation of new matrix-rich tissue around the implanted metal. The authors assumed there was a similar association between inflammatory reactions around the stent struts. The amorphous modification of silicon carbide used for SiC-stent coating is well known as an inert material in different chemical environments with an excellent corrosion resistance at neutral pH and body temperature. The dissolution rate is well below 30 nm per year [32]. However (and probably even more important), this closed coating also acts as a diffusion barrier. The ions that are released from the underlying 316L substrate must diffuse through the coating before they can get into the vessel wall and act as a hapten. As a result of the internal structure of amorphous SiC, such diffusion is so slow that the ion release is negligible.

This is the biophysical background. The in-vitro data are convincing. Thus, from the basics we have to expect improved clinical results concerning the late response, too. Open registries have shown some favorable long-term clinical follow-up data [22,33,34] and stimulated an international randomized multicenter trial in the arena of acute coronary syndroms (Tenax for the prevention of Restenosis and acute thrombotic complications; a Useful Stent Trial – TRUST). The database was just completed in March 2001. The investigators will give their first comprehensive and detailed report at a hotline session during the 2001 European Society of Cardiology meeting in Stockholm. To the best of my knowledge, preliminary data coming from this database verifies the findings described above for the first time. Especially in the subgroup of unstable angina pectoris with primarily higher thrombotic risk and subsequently expected higher restenosis rate after stent implantation (Braunwald classification IIIb), the MACE (TVR/-TLR) rates were significantly reduced in the group of

patients stented with SiC-coated stents (Tenax, Biotronik,Germany) compared with uncoated stainless steel stents (preliminary data, personal communication, TRUST- investigators) 6 months after implantation, and this was achieved without the use of cost-expensive IIb/IIIa-platelet inhibitors!

Altogether, stent surface coating with long-term hypothrombogenic surface characteristics and improved biocompatibility as well as reduced cell adhesion/activation and local inflammatory response (by providing a diffusion barrier for ions potentially acting as haptens) plays an important role especially in the therapy of patients with higher risk for developing stent thrombosis and in-stent restenosis. Such concepts, based on the principles of surface biophysics, were comprehensively proven in vitro. Also, clinical studies in selected patient groups have demonstrated superiority with respect to both the cost-effectiveness of the therapeutic procedure and the improved outcome in the palliative therapy of focal stenosis in coronary artery disease.

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