Editorials
Is the end of restenosis the beginning of a new era?

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On the occasion of a symposium in commemoration of the 25th anniversary of the first coronary angioplasty performed in the United States at Lenox Hill Hospital, we had the opportunity to review the challenges of percutaneous intervention over the course of the last quarter century; from its initial difficulties achieving a safe acute result due to the frustrating problems of dissection, abrupt closure, and the intolerably high necessity for emergency bypass surgery[1].

We then reviewed the qualitative leap in safety introduced by the advent and predominance of coronary stenting[1], and the subsequent frustration with the problems of in-stent restenosis[2]. The capstone of this evolution was the advent of localized therapy for the prevention of in-stent restenosis, a technology that holds the prospect of eliminating this issue as a barrier to the treatment of even the most complex patients with percutaneous coronary intervention. Thus, we are on the threshold of realizing the dream of Andreas Gruentzig; a safe, durable revascularization procedure that can be performed on an awake patient that will ultimately replace coronary bypass surgery.

The modern era of coronary intervention was inaugurated by the pioneering work of Antonio Colombo and Marie Claude Morice[3,4] which led to the nearly universal adoption of intracoronary stenting without anticoagulants. The product of this revolution was a remarkable enhancement of safety with the near elimination of the need for emergency bypass for abrupt closure, and an additional 30-50% decrease in the incidence of angiographic and clinical restenosis[5,6]. A new barrier emerged because of the enhancement of intimal hyperplasia by stenting. With the elimination of geometric causes of restenosis, there was a 400% increase in tissue growth compared to balloon angioplasty[7]. This process led to diffuse stenoses in approximately 50% of patients with stent restenosis[2].

The one positive aspect of this phenomenon was the fact that restenosis was now due to a single biologic process: wound healing. Thus, an ability to inhibit this proliferative response could lead to an "ideal device" for percutaneous intervention – a stent without restenosis.

By confining drug delivery to the specific site of injury, high doses of medication could be administered, without the risks of systemic toxicity. The technology involved in achieving this is far from simple. Initial forays into designing polymer drug carrier vehicles were fraught with inherent problems of inflammation and thrombosis. This was accompanied by several false starts in the choice of pharmacologic agents and the admixture of a drug with a carrier vehicle. This was highlighted by several trials including SCORE where initial enthusiasm for this technology with a taxane-eluting polymer sleeve stent was rapidly diminished due to enhanced thrombosis rates and a late catchup phase after a short term inhibition of intimal proliferation[8,9].

Fortunately, subsequent iterations of drug-eluting stents combined sophisticated bio-neutral, bio-stable encapsulating polymers with low doses of drugs, with targeted mechanisms of actions with contemporary stent designs The outcomes of recent trials with sirolimus and paclitaxel on such platforms have been remarkably consistent[10-17]. The first report with sirolimus, a cyclic

macrolactone antibiotic used for immunosuppressive therapy for inhibition of transplant rejection, was a small pilot study performed in Sao Paulo and Rotterdam. The initial outcomes of this study revealed a 90% inhibition of neointimal hyperplasia within the stent at 4 months; a result sustained for at least 2 years[10]. The subsequent randomized trial, RAVEL, compared bare metal to sirolimus-eluting stents in 238 patients. There was virtually no restenosis in the treatment arm with 26% in the bare metal arm[11]. These results have also been sustained up to 2 years.

The recently reported SIRIUS trials – the US SIRIUS, the E-SIRIUS and C-SIRIUS – have reinforced the robustness of this therapy by incorporating more challenging lesion subsets into the study design[12-14]. These three trials were predominantly directed toward the longer lesion and smaller vessel subsets. Nonetheless, they resulted in a reduction in in-stent restenosis of over 90%, and in-segment restenosis of over 75%. Importantly, the degree of the inhibition of neointimal hyperplasia was the same 90% as seen in preliminary trials with simpler lesion subsets. Subgroup analysis extending to a wide variety of clinical and anatomic groups revealed a profound reduction of clinical events in all categories. These marked benefits were extended to the usually quite vexing subsets including diabetes, small vessels and long lesions.

Further supporting evidence has emerged from TAXUS trials in *de novo* lesions including TAXUS I, TAXUS II, and TAXUS IV[15-17]. Using a paclitaxel-eluting stent, they revealed a profound reduction in restenosis and in the clinical necessity of target vessel revascularization across a broad range of patients.

Importantly, these highly successful outcomes have been accomplished without any apparent compromise in patient safety. In none of these trials has there been an excess in coronary aneurysms or stent thrombosis. While all trials were conducted with extended dual antiplatelet therapy (from 2-6 months), this does not seem to be a burdensome price to pay, especially given the fact that there is ample evidence to suggest that continued antiplatelet therapy well beyond the traditional 1 month produces more favorable outcomes irrespective of the type of stent used[18,19].

There are several other important messages that have emerged from these trials. The first is that even the failure mode of these stents is far more benign than with bare metal stents. Whereas, previously, approximately 50% of restenoses with bare metal stents were of the diffuse variety with recurrence rates in the 30 to 60% range, over 90% of restenoses observed both with the sirolimus-eluting and paclitaxel TAXUS stent are of the benign focal variety. Additionally, the most difficult subgroups including diabetics have a greater net reduction in clinical events than even patients with "simple" lesions[12,17]. A particularly important anatomic subset, lesions in the left anterior descending artery, in both SIRIUS and TAXUS has a major adverse events rate of less than 10% at 1 year when treated with a drug-eluting stent[20]. This makes drug-eluting stents clearly competitive with the outcomes of single vessel internal mammary bypass.

Implications of current data

The triumph over restenosis must lead us to re-evaluate the status of the entire field of coronary revascularization. The obvious first implication will be that a large percentage of patients heretofore referred to bypass surgery will have percutaneous intervention. There is much work yet to be done in this area since current clinical trials did not include multivessel drug-eluting stenting, or the diffuse lesions particularly seen in the most challenging patients with multivessel disease. Preliminary data from registries in Milan[21] and Rotterdam[22] appear to be quite favorable regarding the safety and efficacy in such patients, but more formal analyses are required. Data from the ARTS II trial (which recently completed enrollment) should be quite revealing in defining the safety and efficacy of drug-eluting stenting technology in a "surgical" population. The issue of the treatment of multivessel disease in diabetics, particularly those with left anterior descending artery disease, remains controversial. In the case of diabetics, the advantage of bypass surgery over percutaneous intervention extends into a reduction of infarction and mortality, an outcome not observed in non-diabetics[23]. Therefore, trials oriented toward proving equivalence in death and myocardial infarction are necessary in this group. The currently enrolling BARI IID trial[24], as well as the FREEDOM trial will help clarify these issues in the coming years.

Finally, there are many anatomic subsets for which data are scarce including left main disease, bifurcation lesions, and diffuse disease. Nonetheless, it is hard to envision that these subgroups will not benefit markedly when compared to traditional bare metal stenting. An example of this is the preliminary data from the SIRIUS bifurcation study. While side branches had a disappointing 24% restenosis rate with drug-eluting stenting, there was only a 6% restenosis rate in the main vessels (predominantly left anterior descending)[25]. This is an undoubtedly important progress in this key anatomic group.

Ultimately, questions will be asked about the appropriateness of drug-eluting stenting interventions compared to medical therapy. If drug-eluting stents maintain their safety and deliver on their promise of a durable result, then the alternative of a single treatment with a drug-eluting stent versus a continuation of years of antianginal therapy must be proposed. Heretofore, medical therapy has been inferior to percutaneous intervention in terms of anginal relief but with a net trade-off of increased revascularization and a trend towards increased infarction[26]. Drug-eluting stents promise to

minimize both of these adverse outcomes and could potentially drastically redress the balance between medical therapy and percutaneous intervention.

Thus, one could question why this potential revolutionary technology has not been more universally adopted worldwide after more than 1.5 years since its release in Europe, Asia, and Latin America. The obvious answer is of course economics. While analyses of both the RAVEL trial and the SIRIUS trial reveal that this technology is highly cost-effective and potentially cost-saving for the healthcare system when compared to bare metal stenting[27,28], many problems remain. Limited economic resources and the lack of alignment of expenses borne by the providers and the benefits being reaped by the insurers, have to be redressed with more rational government and private sector policies. As competition increases in this field and upfront costs diminish, the potential benefit of the reduction in cost in terms of absolute dollars (or Euro) and human suffering will hopefully be reconciled and this revolutionary technology can take hold as the predominant therapy in the world at large.

Thus, drug-eluting stents are a revolutionary technology and the capstone of 25 years of work in percutaneous intervention. But as with any other advances in technology, they raise new issues and present new challenges. It is up to us in the medical community to meet them so that their full potential can be realized for our patients.

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