Coronary artery stenting has changed the face of interventional cardiology. In the USA what started as a niche device in the form of the Gianturco-Roubin® stent (Cook, Inc., Bloomington, Indiana) for acute and threatened closure in the late 1980s evolved into an approved anti-restenosis device in the form of the Palmaz-Schatz® stent (Cordis, Miami Lakes, Florida) which was approved by the FDA in August 1994. Early reports from STRESS¹ and BENESTENT² proved beyond a shadow of a doubt that better initial minimum lumen diameters (MLD), achieved with the Palmaz-Schatz stent, correlated with less restenosis 6 months later compared to balloon angioplasty, in accordance with the theories of Kuntz and Baim.³ BENESTENT quoted a 13.5% rate of bleeding complications and a 3.5% rate of subacute stent thrombosis. Bleeding complications of 7.3% and subacute stent thrombosis rates of 3.4% in STRESS did not hamper the explosive growth of coronary stenting. Interventionists were reluctantly content to accept these complications in order to achieve the long-term benefit of reduced restenosis. Restenosis rates and complications have improved since these early stent experiences, and in order for these to be further reduced or eliminated, efforts must continue in three directions: 1) better stent technique; 2) refined stent design; and 3) improved pharmacologic regimens and agents.

Stent technique. If the Achilles’ heel of early coronary angioplasty was restenosis, then the Achilles’ heel of early coronary stenting was subacute stent thrombosis and bleeding complications. Subacute stent thrombosis rates were reported to be 15.8% by Sigwart with the Medinvent® stent in 1987,⁴ 16% with the Palmaz-Schatz stent by Schatz in 1989,⁵ 7.6% with the Gianturco-Roubin stent by Roubin in 1992,⁶ and 10% with the Wiktor® stent by de Jaegere in 1992.⁷ An editorial in 1989 by Serruys criticized these complications and questioned “…are we the sorcerer’s apprentice?…”

Early stent techniques usually consisted of predilatation with a balloon catheter followed by low pressure stent implantation with the stent delivery balloon only. A great contribution to stent technique was made by Colombo and his colleagues from Milan, Italy.⁹ Prior intracoronary ultrasound (ICUS) data showed that over 80% of Palmaz-Schatz coronary stents were underdeployed. Colombo theorized that stent thrombosis may be secondary to incomplete stent apposition rather than the inherent thrombogenicity of the stent, and that if adequate stent expansion was achieved the systemic anticoagulation with coumadin may not be necessary. Colombo concluded that if high pressure (> 16 atm) non-compliant balloon dilatations were used post-Palmaz-Schatz stent implantation that patients could safely be released on a combination of ASA + ticlopidine with a subacute stent thrombosis rate of 0.8%. He also concluded that stent use could be expanded to achieve the benefit of reduced restenosis.

Stone et al. studied the Palmaz-Schatz stent using serial ICUS measurements post-stent delivery at 12, 15 and 18 atm pressure to determine the ideal pressure at which the Palmaz-Schatz stent was deployed in the OSTI (Optimal Stent Implantation) trial.¹⁰ This labor
intensive study, which included both core lab QCA (quantitative coronary angiography) and core lab ICUS, provided several interesting conclusions. First, the adequacy of stent deployment was more accurately assessed by ICUS than by QCA. Secondly, incremental increases in pressure resulted in progressive increases in stent dimension. Finally, even for operators with extensive stenting experience, the angiographic difference between optimal and sub-optimal stent deployment were so subtle that angiography alone could not replace ICUS in guiding Palmaz-Schatz stent implantation.

Further insight into stent technique was gained by Baim et al. with the Multi-Link® stent (Guidant, Santa Clara, California).11 The IVUS Multi-Link trial studied 49 patients with a protocol similar to OSTI, where serial ICUS was performed at 8, 12 and 16 atm of pressure post-stent deployment. The anticoagulation protocol was ASA + coumadin. Successful deployment was accomplished in all 49 patients with no instances of subacute stent thrombosis or other major complications. Stent expansion to 16 atm led to significant increases in intrastent dimension by both QCA and ICUS.

Stent design. Stent technique should not be a surrogate for good stent design. Four basic coronary stent designs are in clinical use today. The coil stent is composed of a single strand of wire, which though flexible has a tendency to recoil. The slotted tube stent is cut from a continuous metal tube and provides radial strength though is less flexible. The mesh stent is self-expanding and is available in large sizes, but by design shortens significantly. The ring design stent consists of repeating modules of short coils and provides excellent flexibility with modest radial strength.

An elegant animal study of stent design was published by Rogers and Edelman in 1995.12 The vascular response to denuded rabbit iliac arteries was examined at 14 days in slotted tube versus corrugated right stent designs. Virtually all factors were held constant in this study except 1) stent geometry and 2) a proprietary polymer coating. The study concluded that the corrugated ring design, though having exactly the same amount of metal, surface area and implantation technique, consisted of 29% fewer strut-to-strut intersections which translated into 1) a 42% lower vessel injury score; (p < 0.0001); 2) a 38% reduction in neo-intimal hyperplasia at 14 days (p < 0.0001); 3) a marked reduction in monocyte adherence at 14 days (p < 0.001); and 4) a marked reduction of thrombosis at 14 days (p < 0.01). The polymeric coating virtually eliminated thrombosis in the corrugated ring stent design (15% vs. 0% in the non-coated vs. coated; p < 0.04) and reduced thrombosis from 42% to 8% in the slotted tube stent design (p < 0.01). The authors concluded that the geometry of the corrugated ring stent alone compared to the slotted tube stent design was responsible for the reduction in injury, thrombosis, and neointimal hyperplasia in this animal study.

Goy et al. reported in 1995 that the slotted tube stent had a lower restenosis rate than a coil design stent.13 In a porcine model in 1997 Carter reported that stent design does indeed matter.14 A multicellular geometric matrix stent design reported less neointimal hyperplasia and less restenosis at a mean follow-up of 56 days compared to a slotted tube stent design.

The ASCENT randomized human clinical trial reported in 1997 by Baim et al. showed that the Multi-Link (corrugated ring design) stent had a lower 30-day major adverse clinical event (MACE) rate, a lower rate of device delivery failure, a lower 30 day mortality, and a better final percent diameter stenosis, than the Palmaz-Schatz (slotted tube design) coronary stent.15

Stent pharmacology. Equally important to coronary stent technique and coronary stent design are the pharmacological agents and pharmacological regimens used in conjunction with coronary stenting. The studies quoting high incidences of subacute stent thrombosis and bleeding complications of the Medinvent®, Palmaz-Schatz, Gianturco-Roubin, and Wiktor (Medtronic, Inc., Minneapolis, Minnesota) stents were in the era of intense anti-coagulation regimens.4-7 Most early studies with coronary stenting required anticoagulation with ASA, dipyridamole, low molecular weight dextran, heparin and coumadin. The focus of attention was the inherent thrombogenicity of the stent and on anticoagulant regimens rather than antiplatelet regimens. These anticoagulant concerns likewise overshadowed the inherent flow characteristics, i.e. the rheology of the vessel.

Subsequent authors have noted that the majority of the patients in Colombo’s series were on ASA + ticlopidine, and that the antiplatelet activities of ticlopidine might be an additional or even alternative explanation as to the low, 0.8% incidence of subacute stent thrombosis. Schomig randomized 517 patients after Palmaz-Schatz stent implantation to an anticoagulation regimen of ASA, heparin and phenprocumon (260) or ASA and ticlopidine (257) in the ISAR (Intracoronary Stenting and Antithrombotic Regimen) trial.16 The primary cardiac endpoint of death, MI, CABG or repeat PTCA occurred in only 1.6% in the antiplatelet therapy group vs. 6.2% in the anticoagulant group (p = 0.01). In addition, the primary non-cardiac endpoint of death from non-cardiac causes, CVA, severe hemorrhage and peripheral vascular events occurred in 1.2% in the antiplatelet therapy group vs. 12.3% in the anticoagulant group (p < 0.001). With antiplatelet therapy there was an 82% lower risk of myocardial infarction and a 78% lower chance of repeated interventions. This study
clearly favored altering the pharmacologic regimen after Palmaz-Schatz coronary stenting from ASA + coumadin to ASA + ticlopidine.

The STARS\textsuperscript{11} (Stent Anticoagulation Regimen Study) trial randomized 1,650 patients after Palmaz-Schatz coronary stenting to one of three groups: 1) ASA + ticlopidine; 2) ASA + coumadin; and 3) ASA alone, with the primary endpoint being MACE at 30 days. These data showed the incidence of MACE to be 0.55% in the ASA + ticlopidine group, 2.6% in the ASA + coumadin group and 3.5% in the ASA alone group, again clearly favoring the antiplatelet regimen of ASA + ticlopidine as the treatment of choice after Palmaz-Schatz coronary stenting.

Barragan\textsuperscript{18} suggested that a post-stent antiplatelet regimen of ticlopidine alone, without ASA, was adequate to prevent subacute stent thrombosis. However, with data clearly supporting ASA in acute myocardial infarction and other unstable anginal syndromes the withholding ASA seemed unnecessary.\textsuperscript{18}

The EPIC,\textsuperscript{10} EPLOG,\textsuperscript{11} and CAPTURE\textsuperscript{12} trials all support the use of abciximab (ReoPro\textsuperscript{©}, Eli Lilly, Indianapolis, Indiana) for conventional PTCA and those subsets of patients that received stents as “bailouts.” The EPLOG Stent is in the study phase at present.

Clopidogrel, a new antiplatelet agent with actions similar to ticlopidine, allegedly without the neutropenia side effects of ticlopidine, has just been released in the USA, and seems worthy of further investigation in coronary stent trials.

These three avenues of coronary stent investigation, technique, design and pharmacology have lead to improved outcomes for patients over the past several years. As with any technology that is advancing, inevitably new questions arise. It is clear that low pressure (\textit{i.e.}, < 12 atm) stent implantation may enhance subacute stent thrombosis, but is 18 or 20 atm pressure necessary in all patients and with all stent designs? Does high pressure enhance edge dissections? Is ticlopidine with ASA more important than pressure? Can stent outcomes be further improved with IIb/IIIa platelet inhibitors? Will oral IIb/IIIa platelet inhibitors be more effective in preventing subacute stent thrombosis than the established regimen of ASA + ticlopidine? Will clopidogrel be as useful as ticlopidine in coronary stenting and does it reduce the incidence of neutropenia? Finally, will further refinement in stent design and polymeric coatings make stent technique and adjunctive pharmacologic agents less important? As gamma and beta irradiation studies progress, will intro- and post-procedural pharmacological regimens and technique need to be altered? This triad of improving coronary stent technique, refining stent design and improving pharmacologic agents and regimens has improved coronary stent outcomes over the past several years, and will serve as a platform from which to launch new studies and protocols that will improve outcomes further.

REFERENCES


ANTONIO COLOMBO: Many factors that control restenosis are related to lesion selection and they can only be modified by picking a different lesion. Thrombosis is more easily controlled, and this problem can be controlled most of the time with a good result and a proper antiplatelet therapy (ticlid and aspirin). I agree that clopidogrel has a better tolerance profile compared to Ticlid.

Concerning the appropriate pressure for balloon inflation, I think we have to look at this parameter in the context of balloon size and balloon to artery ratio. The other element which has to come into the equation is lesion characteristics. If the lesion is hard you need high pressure. If the lesion is soft a medium pressure is sufficient most of the time. We must recognize that an optimal result reduces restenosis, but is far from being the most important determinant of restenosis. Again, lesion selection and some patients’ characteristics are frequently more important. The best approach is to select the right patient and take the right lesion. We all know this approach is not possible. A lot of improvements have occurred in stent design in the last years. These improvements translated more to facilitate stent deliverability rather than reducing restenosis. An important new addition to our stent gallery is the covered stent. This is certainly an important device with a field of application in saphenous vein grafts and in the treatment of some emergencies like vessel rupture.

Concerning IVUS, I believe that there are no doubts that IVUS-implanted stenting gives a better immediate result compared to angiographic-guided stenting. The true impact of this approach on restenosis and, more important, on clinical restenosis still needs to be determined. We should not, however, forget that the MUSIC Trial reported an 8% angiographic restenosis rate which is the only single digit restenosis rate so far reported. This trial had stent implantation guided by IVUS.