STRESS\textsuperscript{1} and BENESTENT\textsuperscript{2} ushered in the era of stent use for the prevention of restenosis. These studies defined angiographic restenosis rates as one third lower for stents versus PTCA and target lesion revascularization rates in BENESTENT II that were below 10\%. Additional refinements in stent implantation techniques have further improved six month angiographic and clinical outcomes. After stent deployment, an intravascular ultrasound cross-sectional lumen area greater than 9 mm\(^2\) has been associated with restenosis rates well under 10\%. Discussion of restenosis rates in the single digit range are common. Acceptance of the “bigger is better” concept is uniform.\textsuperscript{3}

It is critical to note that these excellent results have been described in highly selected patient populations. STRESS and BENESTENT were carried out in patients with reference vessels with a mean diameter of 3.0 mm. The bigger is better concept predicts excellent results in these vessels and even better restenosis rates in larger vessels such as the iliac and carotid arteries.

Despite the excellent study results, numerous clinical situations are more difficult to deal with and many problems remain unsolved. We can categorize the most problematic patient subgroups by simply reviewing the reasons for excluding patients from enrollment in recent stent trials. These reasons include smaller vessels with reference diameters less than 2.5 or 3.0 mm, long lesions, diffuse disease, highly angulated proximal segments that make stent delivery difficult, vein graft and post bypass disease, densely calcified stenoses, lesions requiring staged therapy, and those containing thrombus or filling defects. A variety of other issues remain as well.

Stents have not yet resolved a large number of clinical problems. This is reflected by the fact that our patients do not always mirror the STRESS and BENESTENT populations. A number of studies have described our “real world” experience. Among patients examined at Beaumont Hospital, 75\% of coronary patients treated with catheter therapy were not found to have STRESS type coronary artery disease.\textsuperscript{4} The target lesion revascularization rate in this group was 21\% compared to 7.5\% found in the minority of patients with STRESS lesions.

Similarly less good results for small vessels, long lesions, ostial disease, total occlusions, vein graft lesions, restenotic lesions and patients with poor ventricular function have been described.\textsuperscript{5} Higher restenosis rates in patients with smaller vessels and longer lesions have been well categorized. It has been demonstrated that as lesion length increases and vessel size decreases, target lesion revascularization rates rise sharply. This is especially true in vessels less than 2.75 mm diameter with lesion lengths greater than 15 mm.\textsuperscript{6} This experience is shown in Figure 1.

The distribution of vessel sizes in the general PTCA population has rarely been characterized. Clinical trial study populations reflect selected groups. Therefore, the mean reference vessel sizes for these patients is an artifact of the study inclusion criteria. Figure 2 shows the distribution of vessel sizes in my own practice. As

\textsuperscript{1} From the University of Chicago Hospital, Pritzker School of Medicine, Hans Hecht Hemodynamics Laboratory, Chicago, Illinois.

\textsuperscript{2} Presented at the Fifth Biennial International Andreas Gruntzig Society Meeting, Punta del Este, Uruguay.

\textsuperscript{3} Address reprint requests to: Ted Feldman, MD, University of Chicago Hospital, 5841 S. Maryland Avenue, MC 5076, Chicago, IL 60637.
seen in Figure 2A, the histogram of reference diameter demonstrates that the majority of vessels are less than 3 mm. When considering only those vessels between 2–3 mm in diameter, we find that vessels that are 2.8 to 3.0 mm are clearly stentable, between 2.6 and 2.7 mm are possibly stentable, and the large segment of vessels between 2.0 and 2.5 mm remain problematic. If the larger end of this small vessel spectrum is treated with stent therapy, the angiographic results are good but the long term clinical results are not as good as those seen in STRESS and BENESTENT. The remainder of these vessels in a 2.0–2.7 mm diameter range have even worse outcomes.

Real world lesions differ from STRESS and BENESTENT lesions primarily in terms of reference vessel size and lesion length. Both of these variables have a large impact on restenosis rates. Figure 3 shows the restenosis rates predicted by the bigger is better model for vessels 2–3 mm in diameter. It is clear that even with 0% residual stenosis after an intervention, restenosis rates of 25–40% are the best that can be achieved. Lesion length further detracts from the durability of these results.

Both reference vessel diameter and lesion length must be considered when evaluating the results of various other trials. Simply looking at the bottom line six month target lesion revascularization rate in isolation does not tell the entire story. Figure 4 shows the wide variations in reference vessel size and lesion length in a number of recent studies. Figure 4 also shows the variation in the incidence of diabetes mellitus from study to study. Diabetes is one of the most powerful predictors of restenosis and is also more prevalent in studies with smaller vessel size.

It has been suggested that the smaller vessels are less clinically important because they are primarily branch vessels such as diagonal and obtuse marginal arteries.
both the limitations imposed by the vessels and many of the limitations of both the current and older stent designs. Directional atherectomy is severely constrained by the device size. Rotational atherectomy is the most practically applicable intervention in the smaller vessels. Debulking is attractive as an adjunct therapy in vessels less than 3 mm in size. The concept of facilitated angioplasty has also been clearly demonstrated. The amount of lumen expansion for a given balloon size and pressure is significantly more favorable after debulking. Larger lumens can be achieved with smaller balloon-to-artery ratios and lower pressures.

Debulking may minimize some of the limitations of stenting in smaller vessels (Figure 6). The removal of calcifications and atheroma bulk maximizes the potential for delivery and symmetric expansion of stents in these arteries. With new stent designs, stenting has become practical in vessels that are 2.5–3.0 mm in diameter. A randomized trial comparing rotational atherectomy with PTCA prior to stenting has demonstrated a lower target lesion revascularization rate after debulking prior to stent implantation compared to simple predilation prior to stenting. The potential for stent therapy to be beneficial in vessels smaller than 2.5 mm, even with prior debulking, remains to be demonstrated.

Good late outcomes after catheter intervention have been predicted by good acute results for over a decade. Grüntzig demonstrated that post-procedure pressure gradients less than 15 mmHg were associated with STRESS-like late restenosis results, while post-procedure gradients greater than 15 mmHg were
associated with much higher late event rates. More recent reports using angiographic analysis have found similar outcomes. Post-PTCA residual stenosis of less than 30% is associated with substantially better outcome than residual stenoses that are greater than 30%.

Provisional stenting approaches in which good PTCA results are accepted when Doppler flow reserve or fractional flow reserve determined from pressure gradients are optimal have had similar success. The principle of a good acute result leading to a good late outcome has thus been reaffirmed repeatedly since the early 1980’s. It is clear that for the time being, our best approach in smaller vessels is to achieve optimal acute results. This requires the combined use of all the technologies available today. Stenting alone is clearly not the answer and may be facilitated greatly by debulking. The real solution to late durability in these smaller vessels will require the further study of intracoronary brachytherapy and the development of successful pharmacologic strategies designed to reduce restenosis.

REFERENCES


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**Figure 5.** Device use in 1997. The overall pattern of device use included 60% stenting. For vessels less than 2.5 mm, stents were used in fewer than 20% of patients while rotational atherectomy and PTCA comprised the major methods for catheter revascularization.

**Figure 6.** The left hand panel shows a chronic total occlusion in a patient with history of inferior infarction 8 years ago. After rotational atherectomy, as seen in the middle panel, there is a small caliber vessel with diffuse disease. In the right hand panel, after angioplasty and placement of multiple stents, a reconstructed artery is visible. The patient had a normal 9 month follow up stress examination. Note that the guiding catheter is a French and the caliber of the vessel, even after stent placement, is in the 2.5 mm range. Therapy for diffusely diseased vessels is not realistically possible without a multi-modality approach.
Is Bigger Always Better in Arterial Intervention?


Serruys PW, de Mario C, Piek J, et al. Prognostic value of intra-arterial nitroglycerin and/or when you do an angioplasty you find that the vessel is larger. I wonder now how many times we denied a bypass to an artery with a severe obstruction and very poor distal runoff because we considered that the distal bed was not adequate for a bypass. I would like to ask you, Dr. Feldman, how did you evaluate the small vessels?

MODERATOR: Thank you very much Ted, that was excellent. We have Dr. Feldman’s paper open for discussion. The first comment is by Mark Reisman.

MARK REISMAN: I just want to compliment you on an excellent presentation — it was extremely concise. I think the issue that Ted was able to highlight, which I think is critical, is first and foremost the fact that the world seems to be broken down into particular segments: those with vessels greater than 3 millimeters and less than 3 millimeters. Although the bigger is better theory does hold to the larger vessels, it clearly appears that you need room to accommodate the intimal hyperplasia that exists after making a vessel larger. It appears that accommodation doesn’t exist, at least in the smaller vessels. I think that is very important. The second issue that Ted highlighted was the issue of whether or not debulking could be helpful in the smaller vessels. I know that Antonio Colombo is currently doing a trial looking at debulking with either directional or rotational atherectomy to provide that accommodation for intimal hyperplasia. However, it clearly appears that debulking has set the current paradigm for the bigger is better philosophy. It seems to be extremely durable. There appears to be a significant amount of room for improvement. With that I would like to open up for questions.

ANTONIO COLOMBO: I think it is very important for the future that we start to divide the population of lesions in small vessels into two groups: number one, the vessels which are small because there is a lot of plaque reducing the angiographic lumen to a small size throughout a long segment creating the angiographic appearance of a small vessel; and number two, the true small vessels where the plaque is not very large as far as mass is concerned. For example, if you see a left anterior descending that is 2 millimeters in diameter in its proximal segment, the vessel is most likely 3 mm or larger with a large plaque burden. On the other hand, a diagonal which is 2.5 mm is likely to be the true size of the vessel.

LUIS DE LA FUENTE: I think that sometimes it is very difficult to define the exact size of the coronary vessel. When you have a very severe coronary obstruction and a poor distal flow, when you give intracoronary nitroglycerin and/or when you do an angioplasty you find that the vessel is larger. I wonder now how many times we denied a bypass to an artery with a severe obstruction and very poor distal runoff because we considered that the distal bed was not adequate for a bypass. I would like to ask you, Dr. Feldman, how did you evaluate the small vessels?
teach our surgeons how to use intravascular ultrasound epicardially during their procedures.

PATRICIA THORPE: I just want to add that for many years now, the incidence of diabetes in all of the peripheral studies has been about 32–35%. I think that it is curious in the series that you quoted that it was 15%. You indicated that you believe that the percentage is going up, but for many years in the peripheral vascular disease studies it has been stable at about 30 or 35%. I’m not so sure what that means in this regard because we now know that diabetes affects medium size vessels more. Perhaps there is a correlation.

TED FELDMAN: I think it is an artifact of the patient selection criteria in coronary trials. Peripheral disease is usually diffuse disease, but the coronary trials are typically heavily weighted to include patients who have focal lesions rather than diffuse lesions.

PATRICIA THORPE: Actually, diabetic patients have very nice looking large arteries. They could almost look perfect — it is the tibial disease in many instances that is worse. No one mentions sexual difference in these small vessels versus large vessels in the coronaries and the response to intervention. I don’t know if you see a trend or if you separate your patients in female and male because there may be an overall trend in size and then the response is due to other things.

TED FELDMAN: The STRATAS Trial, which involved predominately smaller vessels, had a gender analysis. Gender did not fall out as an important factor among patients treated with rotational atherectomy.

KIRK GARRATT: A practical concern is what we should do now. I think most of us are sold on the idea that the only way to get the best durable results is to get an optimal initial result and do whatever we can to contain an intimal hyperplasia and/or contain the adverse remodeling effect. Until we have a little more experience with radiation therapies and so forth, it looks like we are left without a lot to offer in terms of intimal hyperplasia. That leaves us with the remodeling issue. As you undoubtedly know, the GRII small vessel registry showed equally grim results. I think the restenosis rate in that population was 58%. There has been a lot of discussion about errors in terms of sizing of the stent among the GRII investigators. However, it seems unlikely that this will explain those results since these were all small vessels. I think the medium size was about 2.3 millimeters and the stents are 2.5 and 3.0 millimeters. Therefore, it is unlikely that will explain the high restenosis rate. The question now is whether you see anything on the horizon with respect to new stent designs that might be of benefit. Specifically, I’m referring to the self-expanding stents. These stents may have great potential. As you know, Rob Schwartz in our laboratory has tested the Radius in vessels as small as 2.5. In his experience with animals, the stent after placement does continue to expand. You do get intimal hyperplasia, but you also get a positive remodeling effect from continued outward progression of the stent that seems to preserve lumens at least a month or two in the animal group.

TED FELDMAN: I think that there are a few things that are optimistic. One is looking at our own data on debulking of smaller vessels in terms of one year clinical outcome. You can achieve good clinical outcomes without stents in vessels that are well developed. We looked at about 200 rotational atherectomy patients from 1994 before we were using elective stents in any significant numbers. At the end of one year, we had a clinical event rate of 20% in a population with a mean reference vessel size of 2.5 mm. This clinical outcome compares exactly with STRESS or BENESTENT or any of the focal lesion/large vessel trials.

Using debulking aggressively is still the best approach to smaller vessels available at the moment. We will have to wait for results from debulking/stent trials such as the trial that Antonio Colombo is looking at. The self-expanding stent concept is very attractive and not yet another avenue.

I think it is potentially important to have an appreciation for the late outcome of intimal hyperplasia. Retraction of the intimal hyperplasia tissue occurs in stents. Both Kimura and Pinkerton have demonstrated using different stents that one year MLDs are bigger than six months MLDs.

We have seen that scars retract late and that a self-expanding stent that will apply force to the vessel opposing the scar in the early phase may give you some of the tiny additional fraction of scar retraction. That is what Mark Reisman was talking about in his comment about accommodating this intimal hyperplasia. I think that this is a dynamic process. It will be very exciting if we could get negative remodeling until the scar begins to retract. We can rely on the behavior of the scar to help give us a late favorable outcome.

SOUHEIL SADDEKNI: For stents, bigger is better. When the arteries are larger than 5–6 mm, developing intimal hyperplasia (1–2 mm) is less likely to cause significant restenosis. I reported on the significance of achieving “good cosmetic” results back in 1984. Bigger balloons and over-dilating was our means to do it then. Stents can achieve results now
without overdilating. Other techniques, such as debulking and atherectomy, may be more appropriate in peripheral small arteries.

RICHARD MYLER: Bigger is apparently better with most stents due to better apposition of the struts against the arterial wall which may present a more optimal radial force (hoop strength) versus the constrictive forces of adventitial constriction (remodeling) associated with restenosis.

A controversy remains regarding “bigger is better” regarding atherectomy (or ablative) techniques. Some believe that the greater the initial gain, the more the net gain after one subtracts the late loss. However, many other investigators have noted that if one involves the media (or adventitia) to obtain a greater initial gain, then the late loss will usually exceed the initial gain and therefore result in a lower gain, i.e., restenosis.

Furthermore, atherectomy devices may leave a sizable regional plaque (> 50%). Locally, an atherectomy catheter should perform optimal atherectomy — removing as much plaque as possible or feasible without deep artery wall invasion. In this regard, IVUS-guidance may be excellent. As Patrick Serruys has said, “Mother Nature pays you back”, i.e., the greater the injury, the greater the response.

MARK REISMAN: I would just comment that I think the biggest challenge we have is to define what the arterial threshold is at which the artery starts responding in a very aggressive way. I think that is the challenge in both small and large vessels because we do see modest restenosis, and if we can somehow define that threshold I think we potentially optimize our results even further.

ANTONIO COLOMBO: I believe we still do not have a modern debulking device. We know that by placing a stent we can get away in most cases even by leaving a large amount of plaque behind. This approach is not always rewarding; we are penalized with sub-optimal follow up in 32–40% of the lesions. If we had a more friendly and contemporary debulking device, our approach would be different. I think we need the industry to focus on new developments in technology in order to give us a contemporary debulking device.

TED FELDMAN: I want to differ a little bit with you and Antonio Colombo. I think that if you look at the kind of tools we have used throughout civilization, it is not so much the tools as the way that they are used. I agree that we want to see the tools improve, but I think we have to figure out how to use them correctly to achieve optimal results.