Stents or Surgery:
Coronary Revascularization in the Drug-Eluting Stent Era

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This is to acknowledge that Dr. Warner has disclosed relationships with commercial concerns related directly or indirectly to this program. Dr. Warner will be discussing off label uses in his presentation.

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Introduction

Since its inception in 1977, percutaneous coronary transluminal angioplasty (PTCA) has evolved into an effective therapy for relief of angina pectoris and/or ischemia in patents who fail to respond to medical therapy (1-3). Improvements in operator technique and advances in angioplasty equipment have made percutaneous coronary intervention (PCI) successful in a variety of clinical and anatomic scenarios, including interventions in native coronary arteries, in arterial and saphenous vein coronary artery bypass grafts, and in the setting of acute myocardial infarction (4-7).

From the beginning, the Achilles heel of PCI has been restenosis. Initially seen in over one-half of patients with balloon angioplasty, this rate has been cut by approximately 50% with the development of the coronary stent (8-12) . However, in selected patients with complex lesions, small vessels and/or diabetes mellitus, the angiographic restenosis rates still approach 40%, with over one-half of those patients requiring symptom-driven repeat percutaneous revascularization or coronary artery bypass surgery (9,13). Failures on many fronts to affect these results with adjunctive plaque removal techniques (14) and locally-delivered or oral drugs (15) has led to the strategy of placing drugs with anti-proliferative properties on coronary stents. This discussion will focus on the development and rationale for these drug-eluting coronary stents and examine their clinical applicability in the evolving landscape of coronary revascularization.

Mechanisms of Restenosis

The first decade of percutaneous coronary intervention was performed with balloon angioplasty, which failed to provide a durable result in over 50% of patients. Balloon angioplasty works by producing a series of controlled coronary artery dissections, producing deep fissures in intraluminal atherosclerotic plaque (16,17). These fractures extend into the intima, or even the media, creating channels for blood flow. While many people assume that compression of the atherosclerotic plaque plays a dominant role in increasing lumen size, this is not the case. While minor compression of atherosclerotic plaque is seen, the other main mechanism in successful balloon angioplasty is stretching of the arterial wall. This primarily occurs at sites with no or minimal atherosclerosis.

Figure 1 depicts the typical scenario seen in balloon angioplasty patients who develop restenosis (17-19). Immediately after the procedure, a combination of arterial wall stretching and compression of a fractured eccentric atherosclerotic plaque produces an acute gain in the lumen diameter. Within a period of hours, there is recoil of the stretched arterial wall with return to its pre-procedure diameter. In patients who develop restenosis, over the next 1-6 months, a phenomenon known as negative remodeling occurs. Patients who have successful balloon angioplasty have an enlargement in artery diameter to accommodate the displaced atherosclerotic plaque. Angioplasty failure patients develop constriction of the arterial wall, with morphologic similarity to shrinkage of a scar. Multiple trauma or inflammation-mediated mechanisms for this phenomenon have been proposed, including collagen deposition in the extracellular matrix and thickening of the surrounding adventitia (20). Finally, within the same 1-6 month time-frame, vascular smooth muscle cells undergo a phenotypic modulation from a contractile to a synthetic phenotype and proliferate into the media (20). There these

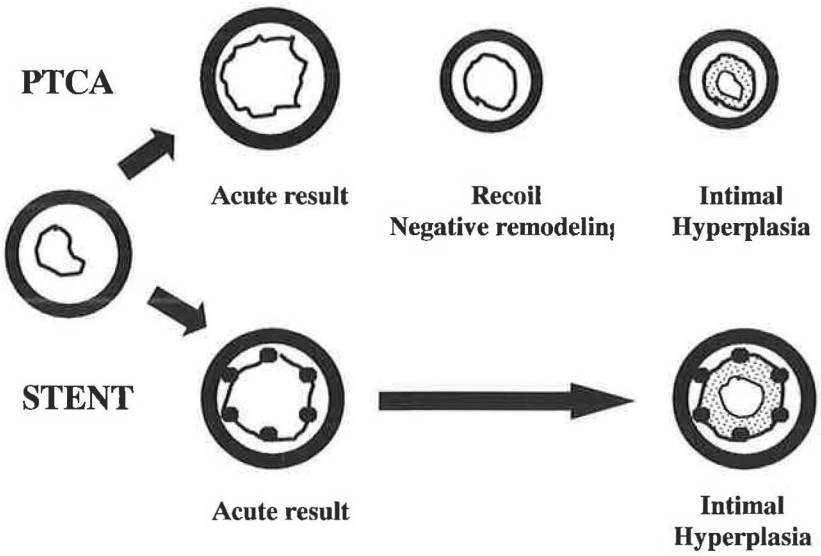
"dedifferentiated" vascular smooth muscle cells migrate into the intima, proliferate and form the final component of the restenotic process, the neointimal layer referred to as intimal hyperplasia.

The failure of balloon angioplasty to provide relief of angina in up to 60% of patients led to a second decade of strategies designed to impact the restenotic process (21). Most innovations focused on removal of atherosclerotic plaque, either through cutting it out with directional atherectomy (DCA) or a transluminal extraction catheter (TEC)) or ablating it with rotational atherectomy (Rotablator) or eximer laser angioplasty. These strategies were aimed at reducing the volume of atherosclerotic plaque and inflammatory scar formation which contributed to negative remodeling (14). While these devices found applicability in specific anatomic niches, all failed to lower restenosis rates and each were associated with longer procedure times and higher rates of procedural complications, mainly peri-procedural myocardial infarctions.

Why Coronary Artery Stents Work

The exception to this long series of coronary device failures to prevent restenosis has been the development of the intracoronary stent. Modern coronary artery stents are slotted tubes of stainless steel, cobalt chromium, or nitinol pre-mounted on angioplasty balloons. They are inflated in a coronary artery stenosis to a diameter to match the non-diseased adjacent segment. Stents are successful in reducing restenosis because they prevent the immediate artery recoil and negative remodeling which defines unsuccessful balloon angioplasty (22).

Figure 1. Mechanisms of restenosis in balloon angioplasty and coronary artery stenting



The landmark trials which established coronary artery stents were the BENESTENT and STRESS trials (12,23,24), both of which used the Palmatz-Schatz coronary stent

(Table 1). Each of these studies established coronary stents as an improvement to balloon angioplasty, lowering restenosis rates by approximately one-third.

Table 1. Clinical Results of the BENESTENT and STRESS Trials

	BENESTENT Study			STRESS Study		
	Balloon n=257	Stent n=259	p	Balloon n=202	Stent n=205	p
Restenosis (%)	32	22	<0.05	42	31	<0.05
1 year-event free survival (%)	70.4	79.9	<0.05	71.5	80.3	NS
Acute closure/stent thrombosis	2.7	3.5	NS	1.5	3.4	NS

Since these landmark studies, improvements in stent delivery system design, deployment techniques, and refinement of anti-thrombotic and anti-platelet therapy during and following coronary intervention have increased procedural success rates in coronary stenting to greater than 95% while reducing stent thrombosis rates to <1%. These improvements have also impacted restenosis, as the rates of angiographic restenosis in the types of lesions enrolled in the BENESTENT and STRESS trials (discrete lesions <15 mm in length in relatively large 3.0 mm vessels) now average around 15%, and approach single digits in non-diabetic patients.

However, most of the patients who undergo coronary intervention do not have discrete disease, have reference artery sizes that are much smaller, and have clinical characteristics (Table 2) that place them at higher risk for restenosis ((25-32).

Table 2. Predictors of Restenosis

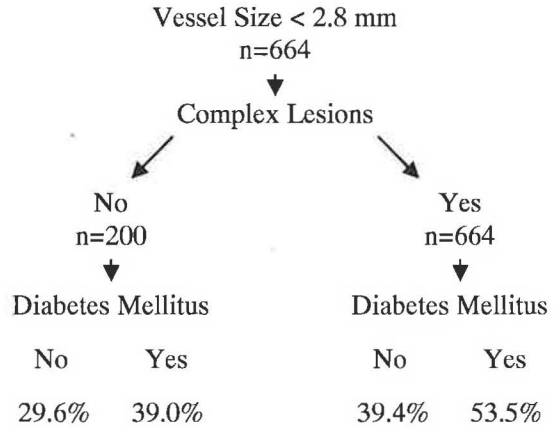
Patient	Angiogram
Diabetes	Lesion length
Unstable angina	Stent length
Hypertension	Smaller vessel diameter
	Restenotic lesion
	LAD location
	Ostial location
	Saphenous vein grafts
	Chronic total occlusion

As a result, while most non-diabetic patients have a restenosis risk of around 20%, patients with diabetes mellitus in combination with longer, more complex lesions and smaller vessel size can easily approach restenosis rates of 50%. These points are emphasized in Figure 3 and Table 3, taken from a study by Elezi et al. (33) of 2,602 patients with successful stent placement, 80% of whom had routine angiographic follow-up at 6 months.

Table 3. Results of follow-up angiography stratified by vessel size
(Elezi et al. Circulation. 1998;98:1875-80)

	< 2.8 mm n=664	2.8 – 3.2 mm n=676	>3.2 mm n=677	p
Vessel diameter	2.59±0.33	3.02±0.31	3.52±0.46	<0.001
Restenosis rate	38.6%	28.4%	20.4%	<0.001

Figure 3. Risk of restenosis in patients with complex lesions and diabetes mellitus



Therefore, while coronary artery stents are clearly the success story of the past decade in interventional cardiology, most patients seen in everyday practice continue to have restenosis rates that are unacceptably high. Restenosis in stented patients is caused by neointimal hyperplasia, induced by the migration and proliferation of vascular smooth muscle cells in the intimal lining of the stented coronary segment. Debulking strategies, such as atherectomy or eximer laser-assisted angioplasty, used in conjunction with coronary stents have failed to impact this process and in some cases have been shown to lead to higher rates of restenosis (14). Trials of pharmacologic agents with potential to impact this process, including lipid-lowering agents, beta-blockers, calcium channel blockers, ACE inhibitors, anti-oxidants, anticoagulants and oral anti-proliferative agents have been uniformly unsuccessful. These failures, along with unsuccessful attempts to deliver locally drugs with anti-inflammatory or anti-proliferative properties during or immediately after the coronary intervention, led to the strategy of placing drugs with anti-proliferative properties directly onto a coronary stent (34).

Anatomy of a Drug-Eluting Stent

Drug-eluting stent delivery systems have three components. The stent must provide significant metal-artery contact and be fairly uniform in structure in order to predictably deliver the drug to the vessel wall. Attempts to place drugs directly on coronary stents

have been met with mixed results, therefore most current efforts center around using a polymer, containing the drug, which can more easily be attached to a bare-metal stent. These polymers must be durable to prevent being detached from the stent as it is navigated across calcium-containing atherosclerotic plaque. These polymers must also provide predictable, even elution of the drug throughout the stented segment of the artery so allow for correct dosing of the drug.

Finally, the drug itself must be lipophilic in order to be rapidly taken up by vascular smooth muscle cells and exert an anti-proliferative effect throughout the time-window that neointimal hyperplasia occurs, typically in the first 1-3 months after intervention (11,35). These drugs must exert an anti-proliferative effect without causing cell death, as extensive cell death within the intimal layer will lead to separation of the stent from the vessel wall. When such malaposition occurs, thrombosis of the stented segment occurs, a process which leads to death or a Q-wave myocardial infarction in up to two-thirds of patients (36). Ideally, one would prefer a moderate effect of the anti-proliferative drug, allowing enough neointima formation to cover the surface of the coronary stent, but inhibiting the aggressive neointima formation that defines in-stent restenosis.

The Drugs

Sirolimus

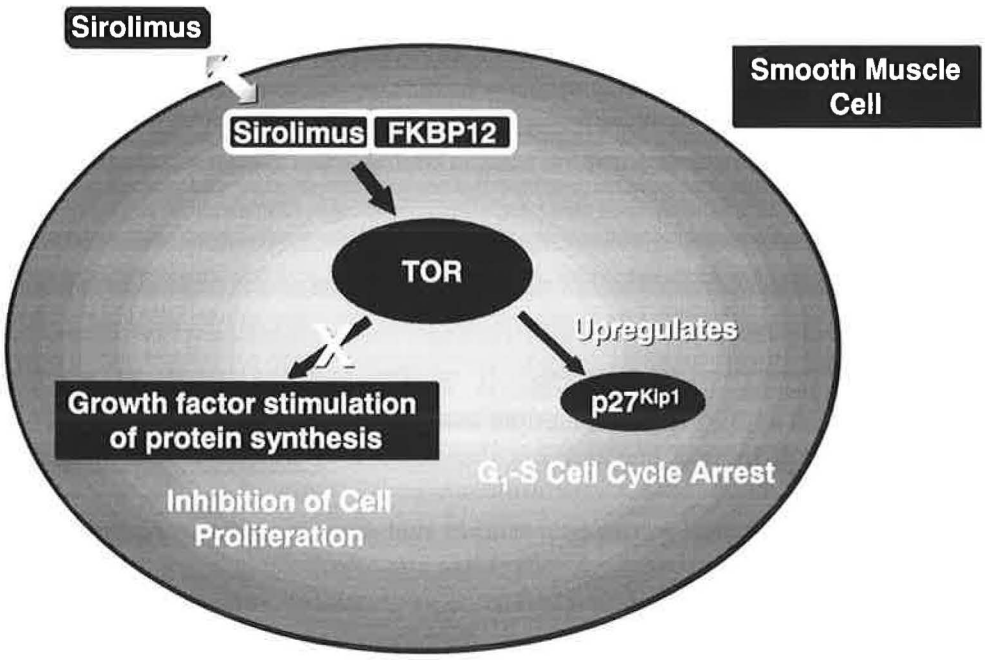
Sirolimus (35,37,38), or rapamycin, is a fermentation product of *Streptomyces hygroscopicus* discovered in a soil sample from Easter Island.(Rapa Nui). It was initially developed as an anti-fungal product, but this indication was largely abandoned when the drug was noted to have potent immunosuppressive properties. In the early 1990's, a series of investigations led to the observation that sirolimus was a potent inhibitor of the proliferation of vascular smooth muscle cells (39). A study in a pig model of angioplasty showed that systemic sirolimus therapy could inhibit restenosis (40). While this observation did not hold true in human investigations of oral sirolimus (41), the use sirolimus as a component of a drug-eluting stent has provided extraordinary results.

The efficacy of sirolimus (11,20,35,38,39,42) revolves around arresting vascular smooth muscle cell migration and proliferation at a point in the cell cycle which does not cause cell death. Vascular smooth muscle cells within the media of the artery are normally quiescent and exist in the G_0 phase of the cell cycle. When stimulated by growth factors and/or mechanical trauma, these cells exit the G_0 stage and proceed through the G_1 and G_1/S transition of the cell cycle. Progression through the G1 phase of the cell cycle is regulated by the assembly and phosphorylation of G1 cyclin/cyclin dependent kinase (CDK) complexes.

When placed in contact with vascular smooth muscle cells, sirolimus is rapidly taken up and interacts with its principal intracellular receptor, a protein called FK506-binding protein (FKBP12), a member of the immunophilin family of cytosolic binding proteins. This sirolimus-FKBP12 complex interacts with a member of the lipid kinase family of proteins called TOR (the target of rapamycin) which is potent in the inhibition of signaling to downstream targets... Acting through TOR, production of the cyclin-dependent kinase inhibitor $p27^{Kip1}$ is upregulated. Increased $p27^{Kip1}$ blocks the kinase

activity of certain cyclin/CDK complexes responsible for progression into the G1 phase of the cell cycle and thus arrests the cell cycle in G_0. Sirolimus has also been shown to inhibit growth factor stimulation of synthesis of proteins necessary for smooth muscle cell proliferation. The end-result of the interaction of sirolimus with a smooth muscle cell is the inhibition of both migration and proliferation of these cells through halting of the cell cycle at the G1-S transition. .

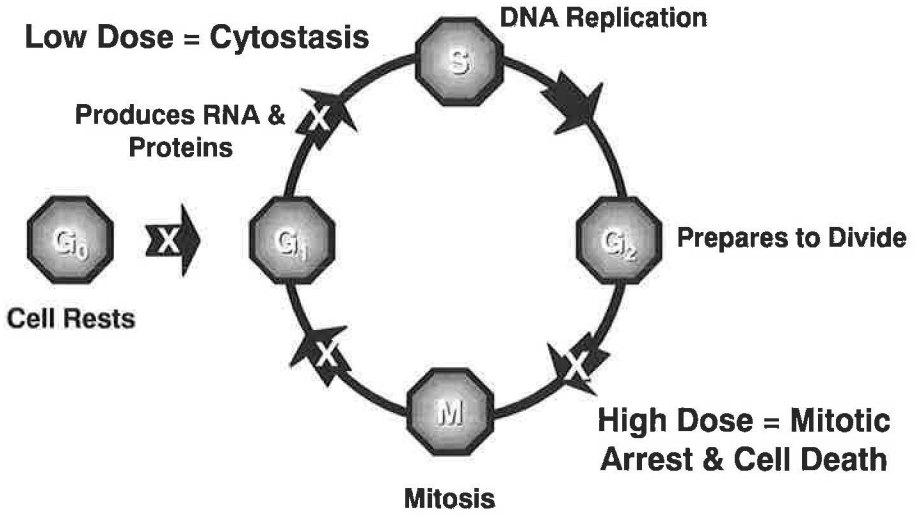
Figure 4. Sirolimus Cell Cycle Effects



Paclitaxel

Paclitaxel (20,43,44) was discovered in 1963 through a National Institute of Cancer initiative in which thousands of plant extracts were screened for anti-neoplastic activity. Paclitaxel is an extract derived from the Pacific yew tree *Taxus brevifolia,* a scarce evergreen which grows in the Pacific Northwest, particularly in the area near the base of Mount St. Helens. Like sirolimus, paclitaxel is very lipophilic and is rapidly taken up by smooth muscle cells. At low doses, paclitaxel enhances the assembly of stable but dysfunctional polymerized microtubules, primarily through bundling and formation of asters of mitotic spindles. These stable microtubules contribute to the inhibition of cell division and migration, intracellular signaling, and protein secretion, all of which are dependent on efficient depolymerization of microtubules. At doses used in the coronary circulation, formation of these dysfunctional microtubules inhibits cell replication (45-47), predominantly at the G_0/G_1 phase of the cell cycle. Higher doses of paclitaxel act at the G2/M phase of cell division and lead to complete mitotic arrest and cell death.

Figure 5. Paclitaxel Cell Cycle Effects



Everolimus

Everolimus is a macrolide with a stable 2-hydroxy-ethyl substitution at position 40 on the sirolimus structure, making it more polar. It was developed in an attempt to increase oral bioavailability over sirolimus. Its mechanism of action is similar to that of sirolimus. Clinical trials of everolimus as a component of drug-eluting stents (48) are still in early stages.

Clinical Trials of Drug-Eluting Stents

We now have in hand several large randomized, double-blinded trials of both sirolimus and paclitaxel-eluting stents in comparison with bare-metal stents of identical design mounted on identical balloon delivery systems. Similar to the history of bare-metal stents, these trials of drug-eluting stents have first been applied to patients at relatively low risk for restenosis to assess safety, and then are gradually applied to patients with clinical and angiographic characteristics which place them at higher risk of restenosis.

There are four clinical endpoints used in these trials which merit definition. **Binary restenosis** is the percentage of patients who exhibit greater than a 50% angiographic stenosis (as measured by quantitative coronary angiography) within the stented segment of the artery. **Target lesion revascularization (TLR)** is the percentage of patients who receive, in the 9 months following the procedure, revascularization for ischemia in the presence of a stenosis of at least 50% within the stent or within 5 mm borders proximal or distal to the stent. **Target vessel revascularization (TVR)** is clinically driven CABG or

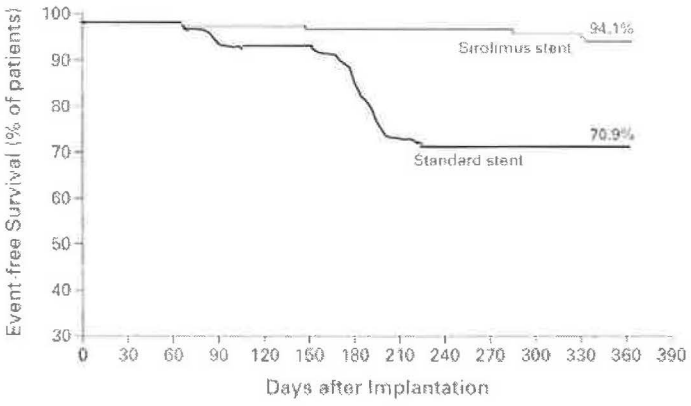
PCI of the target vessel within 9 months of the index procedure. **Target vessel failure (TVF)** is defined as the occurrence of any of the following in the interval following the index procedure: death from cardiac causes, Q-wave or non–Q-wave myocardial infarction, or revascularization of the target vessel by CABG or PCI. It is worth noting that rates of target lesion and vessel revascularization in trials including angiographic follow-up are typically higher than those seen in clinical trials without angiographic follow-up, due in part to the subjectivity of the investigator in determining ischemia and angiographic severity of restenosis at the time of the procedure ('the oculostenotic reflex").

Trials of Sirolimus-Eluting Stents

RAVEL

The first trial of the currently available sirolimus-eluting stent platform (CYPHER® stent, Cordis Corporation) was the RAVEL trial (49). This trial enrolled a group of patients at relatively low risk for restenosis, as evidenced by the average lesion length of ≈ 9.5 mm and low percentage of diabetics (16% in sirolimus, 21% in control). Despite the fact that these were low risk patients, the results were spectacular, with a 6 month restenosis rate of 0% in the patients receiving the sirolimus stent as compared with 26.6 % in the control stent group. Even more impressive was the clinical outcome of target vessel failure in the sirolimus-treated group with 94.1% of patients free from myocardial infarction or revascularization at one year (Figure 6). These results have proved to be durable with 90% of sirolimus-treated patients free from death, myocardial infarction or revascularization at 2 years (50).

Figure 6. Kaplan-Meier Estimates of Survival Free of Myocardial Infarction and Repeated Revascularization among Patients Who Received Sirolimus-Eluting Stents and Those Who Received Standard Stents in the RAVEL trial



Morice, M.-C. et al. N Engl J Med 2002;346:1773-1780

The SIRIUS Trial

The SIRIUS trial (51) was the first trial to examine the effect of a sirolimus-eluting stent in patients as high risk for restenosis. This trial was designed to mirror clinical practice (Table 4) and included typical numbers of diabetics and excluded patients with short

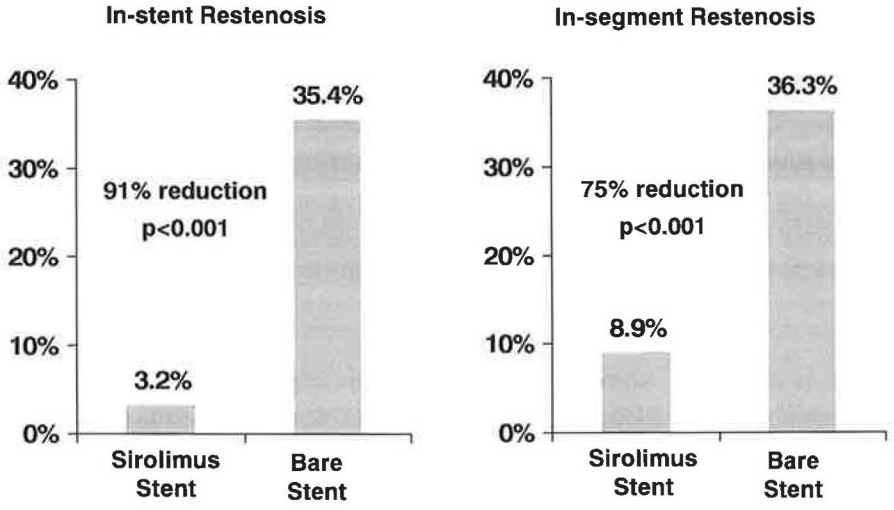
lesions and large diameter vessels. The primary endpoint of the trial was target vessel failure defined as cardiac death, MI or target vessel revascularization at 9 months.

Table 4. Sirius Trial Baseline Clinical Characteristics

Characteristic	Sirolimus (N = 533)	Control (N = 525)
Diabetes	25 %	28 %
Unstable angina	53 %	54 %
LAD lesion	44 %	43 %
Ref. vessel diameter (mm)	2.79 ± 0.45	2.81 ± 0.49
Lesion length (mm)	14.4 ± 5.7	14.4 ± 5.8
Stent length (mm)	21.5 ± 6.7	21.2 ± 6.8

While SIRIUS did not show the spectacular 0% restenosis rate seen in the RAVEL trial, the results were none-the-less impressive. The primary endpoint of target vessel failure occurred in 21.0% of the patients treated with a bare-metal stent compared to only 8.8% of patients receiving a sirolimus-eluting stent. Restenosis at 8 months was also markedly reduced in the sirolimus-treated patients (Figure 7). These marked improvements in clinical outcomes were the basis for approval of the sirolimus-eluting Cypher stent by the FDA in April 2003.

Figure 7. SIRIUS: 8 Month Angiographic Restenosis Rates

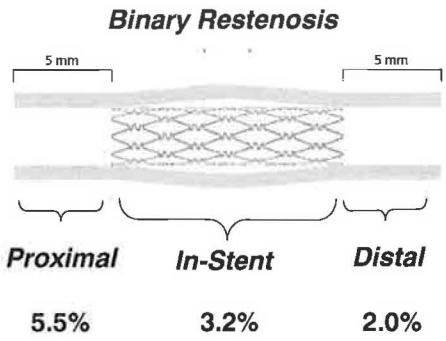


Lessons from the SIRIUS trials

While the decrease in angiographic restenosis in the SIRIUS trial was pronounced, few investigators expected such a pronounced difference in in-stent restenosis rates compared with a segment including the stented area ± 5 mm on both the proximal and distal ends.

This analysis was included in the trial out of concern that downstream elution of sirolimus might have a deleterious effect on the adjacent vessel. The opposite of what many expected was seen, with more restenosis noted on the proximal edge of the vessel (Figure 8).

Figure 8. Distribution of In-Segment Restenosis in the SIRIUS Trial



The reason for this observation is now clear. At the time the trial was performed, interventional cardiologists were performing most interventions using a technique known as "spot-stenting". Aware that increased stent length is an independent predictor of restenosis when using bare-metal stents, cardiologists would often just stent the most severe portion of the lesion, often dilating but not stenting mild atherosclerotic disease adjacent to the obstructive lesion. Another common practice was to "flare" the proximal end of a stent, matching its diameter to the usually larger proximal vessel. The net result of these practices was that minor atherosclerosis on the perimeter of obstructive lesions was often dilated but not stented.

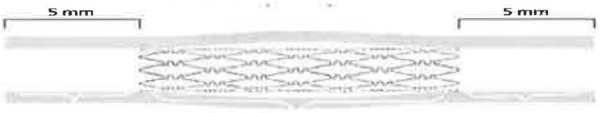
One hypothesis generated from the SIRIUS trial restenosis data was that lower concentrations of anti-proliferative agents present just outside the edges of a drug-eluting stent might actually accelerate atherosclerosis, particularly in injured segments dilated with a balloon. This phenomenon has been observed with other immunosuppressive drugs in animal models of balloon injury and was a prominent finding early on in trials of brachytherapy for in-stent coronary restenosis (52,53). The second series of investigations with sirolimus-eluting stents, the Canadian-SIRIUS and European-SIRIUS (C-SIRIUS and E-SIRIUS) trials (54,55) were helpful in providing an answer to this hypothesis.

Both of these trials were similar in design, and enrolled patients at high risk for restenosis. Twenty percent of patients were diabetic, and the lesions were longer and the vessels smaller than in the initial SIRIUS trial. The operators in the trial were asked to avoid pre-dilatation whenever possible (so-called direct stenting), and if they dilated either before or after the stent was placed, to confine the dilatation to the stented segment of the artery. Operators, in general, placed longer stents and were careful not to leave any injured segment of the artery unstented.

Despite longer lesions in smaller vessels, both C-SIRIUS and E-SIRIUS reported improvements in angiographic restenosis, predominantly due to a loss of the excess restenosis seen on the proximal and distal edges seen in the SIRIUS trial (Figure 9). Operators in these trials used longer stents and took great care to cover completely any diseased segment or area injured by balloon dilatation. The clinical benefits continued to accrue, with only 4% of sirolimus-treated patients in these trials requiring ischemia-driven revascularization compared with 20.9% of patients in E-SIRIUS and 18% of patients in C-SIRIUS treated with bare-metal stents. These trials clearly showed that the best outcomes with drug-eluting stents are operator-dependent and careful, meticulous technique by an informed interventionalist is required for optimal results (56).

Figure 9. Improvements in Edge Restenosis in SIRIUS Trials

Angiographic Restenosis



	Proximal	*In-Stent*	*Distal*
SIRIUS (N=533)	**5.5%**	**3.2%**	**2.0%**
E-SIRIUS (N=175)	**2.1%**	**3.9%**	**1.3%**
C-SIRIUS (N=44)	**2.3%**	**0.0%**	**0.0%**

Pivotal Trials of Paclitaxel-Eluting Stents

TAXUS II

The second drug to show efficacy when coupled with a coronary stent is paclitaxel, available as the TAXUS® stent platform (Boston Scientific Corp.). Similar to the sirolimus clinical trial experience, a series of TAXUS trials began first with a trial of patients at relatively low risk for restenosis, the TAXUS II trial (44). TAXUS II contained very similar patients to the RAVEL sirolimus trial, with 14% diabetics, an average vessel diameter of 2.8 mm, and an average lesion length of 10.6 mm. After a series of promising pilot trials with paclitaxel, much of the effort in this trial was devoted to establishing whether or not a slow-release form of paclitaxel or a formulation with an 8-fold quicker-release would provide a superior result. The slow-release form prevailed, and reduced restenosis from 17.9% in the control group to 2.3% in the slow-release paclitaxel group. Although not powered for clinical endpoints, 6-month target vessel revascularization in the paclitaxel group was 7.7% as compared with 14.3% of control patients.

TAXUS IV

The landmark trial to date with paclitaxel-eluting stents is TAXUS IV (57), which used the slow-release formulation of paclitaxel established as efficacious in TAXUS II.

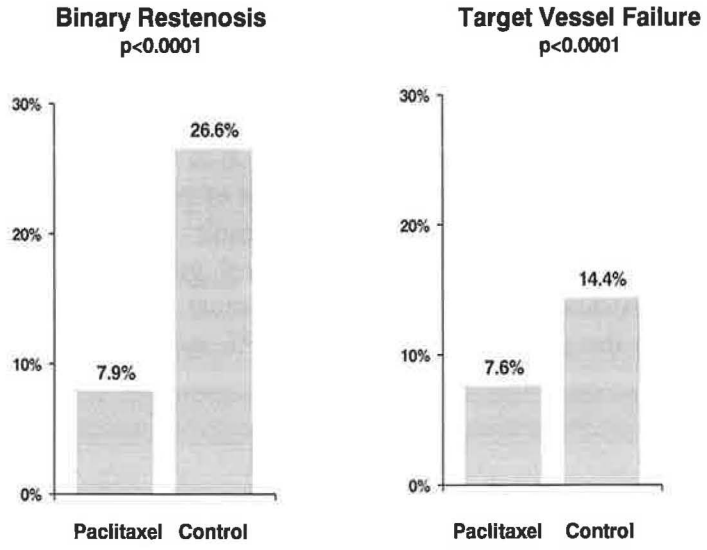
TAXUS IV enrolled patients at high risk for restenosis with patient and lesion demographics (Table 5), similar to the SIRIUS trials with sirolimus.

Table 5. TAXUS IV Baseline Characteristics

	Paclitaxel N=662	Control N=652
Diabetes	23.4%	25.0%
Unstable angina	35.8%	32.7%
LAD location	40.0%	41.4%
Lesion length (mm)	13.4±6.3	13.4±6.2
Vessel size (mm)	2.75±0.47	2.75±0.49
Stent Length (mm)	21.9±8.1	21.7±8.8

The clinical results in the TAXUS IV trial were overwhelmingly positive (Fig. 10). Angiographic restenosis in the paclitaxel group was reduced by 70% as compared to control, and target vessel failure occurred in only 7.6% of the paclitaxel group as compared with 14.4% of control patients. No "edge effect" restenosis was seen in this trial. This observation was most likely a refection of operator knowledge of the importance of using long stents and avoiding balloon trauma to unstented areas of the target coronary coronary artery. However, another plausible explanation may be that paclitaxel at doses on the TAXUS stent platform does not promote acceleration of intimal hyperplasia in injured or atherosclerotic tissue adjacent to deployed stents.

Figure 10. Nine Month Results: TAXUS IV Trial



As in the sirolimus trials, stent thrombosis was low (0.6%), a very reassuring observation given the potential by all drug-eluting stents for delayed endothelialization. This combination of safety and markedly improved clinical outcomes in the TAXUS 4 trials won approval by the FDA of the TAXUS stent platform in March 2004.

Paclitaxel and Sirolimus Drug-Eluting Stents- Is There a Difference?

Now that there are two competing products with excellent clinical results in the marketplace, there is much discussion about potential differences in outcome. Most of this has been generated by the vendors, as competition for market share is fierce. Drug-eluting stents are expensive, originally priced at $3200 and now costing $2500-$2700 per stent. Current U.S. utilization is approximately 1.5 stents per case, with around 70% of stent-eligible patient receiving drug-eluting stents in the United States.

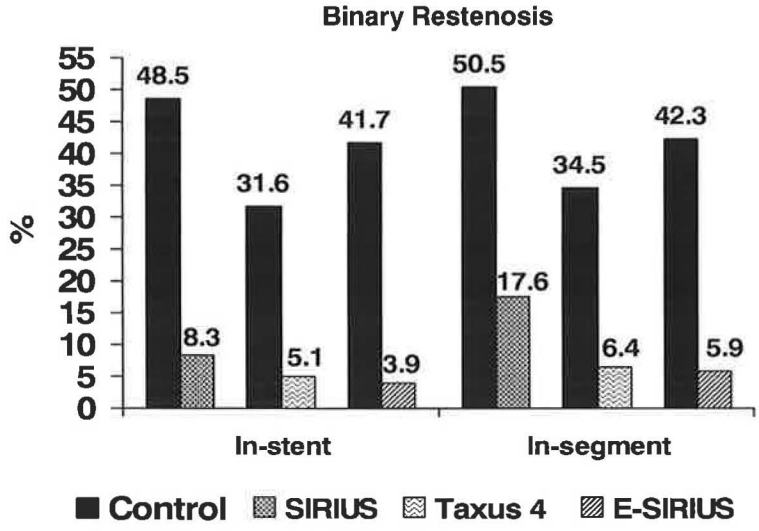
There are, however, some interesting observations in the initial trials with drug-eluting stents. One prominent issue is the topic of diabetes mellitus. In all drug-eluting stents trials to date, diabetics have received an attenuated benefit when compared to non-diabetic patients (58,59). In the SIRIUS trial, angiographic restenosis was reduced by 65% (from 50.5% to 17.6%) in diabetic patients as compared to an 80% reduction (30.7% to 6.1%) in non-diabetics. Target vessel failure was reduced from 27.0% to 12.2% in diabetics and from 18.6% to 7.7% in non-diabetics. Insulin-requiring diabetics fared worse across the board, with 35% in-segment angiographic restenosis rates, despite an in-stent restenosis rate of only 10.5%. While provocative, caution should be exercised in reaching any conclusions, as only 82 of 1,057 analyzed patients in SIRIUS were insulin-requiring diabetics. This degree of separation in outcomes in oral versus insulin-requiring diabetics has not been observed in other sirolimus-eluting stent trials.

TAXUS IV (57), the largest paclitaxel-eluting stent trial thus far, reported angiographic restenosis rate reductions of 24.4% to 8.5% in non-diabetic patients, 29.7% to 5.8% in orally-treated diabetics, and 42.9% to 7.7% in insulin-requiring diabetics. Numbers of insulin-requiring diabetics in TAXUS-4 were low as well, 47 out of 136 total diabetic patients.

While much has been made of discrepancies in diabetic outcomes in SIRIUS and TAXUS 4, subgroup analyses of such small numbers of patients are unlikely to provide conclusive answers to whether or not one drug-eluting stent is more effective than another. As illustrated by Figure 11, control group diabetic group restenosis rates vary widely across trials, making it unlikely that questions of superiority will be answered with anything other than a dedicated clinical trial of diabetic patients.

What is clear is that drug-eluting stents have had a major impact on restenosis in diabetic patients. Across all trials, >65% reductions in restenosis have observed along with a 55% or greater reduction in need for revascularization or an adverse clinical outcome. This represents real progress in the group of patients that have significantly trailed others in benefiting from percutaneous revascularization (9,13,30,33)

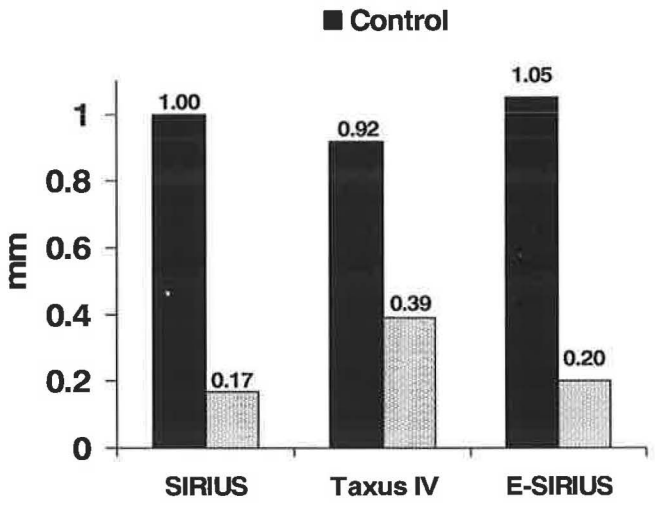
Figure 11. Angiographic restenosis rates in diabetic patients versus control in SIRIUS, TAXUS 4, and E-SIRIUS trials



Differences in Late Loss

Another area where differences in stent trials with sirolimus and paclitaxel exist is angiographic late loss. Late loss is defined as the difference between minimal lumen diameter immediately after stent placement and the minimal lumen diameter measured at follow-up. Late loss has been a consistent predictor of the risk of both angiographic and clinical restenosis during the first two decades of angioplasty. The higher the late loss, the less effective the therapy is and the worse the outcomes. In patients receiving a coronary stent, late loss represents the amount of neointimal hyperplasia. Average late loss in most bare-metal stent trials is around 1.0 mm. Drug-eluting stents have significantly less late loss than bare-metal stents. There do, however, appear to be differences in the amounts of late loss in patients treated with sirolimus or paclitaxel-eluting stents (Figure 12). While late-loss is very low across all clinical trials of drug-eluting stents, late loss is lower in patients receiving sirolimus (51,54,55,57,60) At this point, there is no indication that there is a threshold at which the amount of late loss is important. Theoretically, less late loss equals less intimal hyperplasia, and lowers the risk of restenosis. An argument can be made, however, that eliminating too much intimal hyperplasia may leave stent struts uncovered and increase the risk of stent thrombosis. At this point, it remains to be seen whether the lower late loss seen with sirolimus is beneficial, deleterious or inconsequential.

Figure 12. In-Stent Late Loss in DES Trials



Sub-Acute Stent Thrombosis

The excitement over the introduction of drug-eluting stents into clinical practice following FDA approval in April 2003 was muted by reports of stent thrombosis in the initial 30 days after coronary intervention (www.fda.gov). These reports caught interventional cardiologists off guard, as rates of stent thrombosis in the clinical trials of drug-eluting stents had been comparable to bare-metal stents (approximately 0.6-0.8%). Stent thrombosis historically leads to Q-wave myocardial infarction and/or death in two-thirds of patients (36). In October 2004, after receiving more than 290 reports of stent thrombosis involving the CYPHER sirolimus-eluting stent (including 60 patient deaths) from physicians, the FDA issued a public health notification. Investigations into the discrepancies between rates of stent thrombosis have failed to yield definitive conclusions, but the etiology is likely multi-factorial.

Instant demand for the stents by physicians, many of whom had been delaying procedures for patients at high risk for restenosis, was high, leading to inventory shortages in most catheterization laboratories. Many physicians found themselves doing more procedures with fewer stent sizes to choose from, increasing the potential that operators were placing inappropriately-sized stents. At an initial cost of $3200 apiece, many physicians were also under increased pressure to cut costs during coronary interventions. While Medicare and third-party payer reimbursements were increased for procedures utilizing drug-eluting stents, the incremental reimbursement did not cover the cost differential between bare-metal and drug-eluting stents. Many have postulated that these economics led physicians to decrease utilization of IIb/IIIa inhibitors during complicated coronary interventions and perhaps led to less routine post-dilatation of stents to decrease balloon usage. In order to optimize outcomes, physicians are also being called upon to place longer stents and cover "normal vessel to normal vessel" as mandated by the SIRIUS trial observations. Stent length is an important predictor of stent thrombosis and longer stents are more likely to be unopposed if not properly deployed with high pressure balloon inflations.

Finally, decreased neointimal hyperplasia, as evidenced by lower late loss, may magnify any mistakes made in stent deployment in ways not seen with bare-metal stents. Less intima formation may leave stent struts exposed for longer periods of time, increasing the potential for stent thrombosis. Fortunately, reports of drug-eluting stent thrombosis have decreased and careful analysis of registry data and ongoing clinical trials have failed to identify a specific problem, suggesting improved operator technique and understanding of critical issues related to drug-eluting stents (61) .

The Current Place of Drug-Eluting Stents in Coronary Revascularization

While enthusiasm for percutaneous coronary revascularization is at an all time high amongst interventional cardiologists, many physicians continue to struggle with revascularization choices in patients with multi-vessel disease and/or diabetes. The rapid adoption of percutaneous coronary intervention in the cardiology community has, at times, out-paced the evidence supporting its use in certain clinical scenarios. While few would argue against an initial strategy of PCI in patients with single-vessel coronary artery disease, conflicting messages in fairly small randomized trials of patients with multi-vessel disease and/or diabetes mellitus make decisions in these patients more difficult.

There have now been 11 randomized trials (62-72) of percutaneous coronary intervention versus coronary artery bypass grafting (CABG) in patients with multi-vessel coronary artery disease, the past six of which have included coronary artery stents in the percutaneous revascularization arm. As a whole, the results are fairly similar. While the balloon angioplasty trials collectively showed increased mortality in PCI-treated patients, when the trials are viewed collectively, the frequency of death or myocardial infarction is similar with either strategy. Freedom from repeat revascularization procedures and relief from angina, however, is superior in the surgery arms. While none of these trials was large enough to provide enough definitive answers to allow generalization of this conclusion across all patient subgroups, this information has led to many physicians basing their choice of revascularization on the feasibility of PCI and cumulative risk of restenosis.

A notable exception to this overall conclusion is patients with multi-vessel disease and diabetes mellitus. The Bypass Angioplasty Revascularization Investigation (BARI) study finding of decreased intermediate and long-term survival in diabetic patients with multi-vessel treated with PCI has remained consistent in other randomized trials of PCI versus CABG. In BARI, all-cause 5-year mortality in the diabetic angioplasty group was 34.7% compared with 19.4% in the CABG group (73) This disparity in results probably represents the extreme, as data from the BARI registry (74) and Duke Cardiovascular Disease Databank (75) has shown comparable outcomes between PCI and CABG when physicians use careful clinical criteria, including degree of atherosclerosis and presence of left ventricular dysfunction, in choosing between revascularization strategies in diabetic patients. Critics of the BARI data also point out that BARI was performed at a time when all patients in the angioplasty arm received balloon angioplasty only (no stents) and IIb/IIIa inhibitors were not routinely given, the two adjunctive therapies most

proven to improve PCI outcomes in diabetics during the past decade. Thus, many have looked primarily at outcomes of PCI versus CABG trials in the stent and IIb/IIIa inhibitor era when making an argument for or against multi-vessel angioplasty.

The two large PCI versus CABG trials in the stent era are the ARTS (Arterial Revascularization Therapy Study) trial (71)and the SOS (Stent or Surgery) trial (68). The SOS trial randomized 988 symptomatic patients with multi-vessel coronary disease to CABG or PCI. Only 14% of patients had diabetes, and only 8% received a IIB/IIIa inhibitor. At a median follow-up of two years, the rates of death and non-fatal Q-wave MI were similar in both groups, with death favoring the CABG group (2% vs. 5% out of 30 total deaths) and Q-wave MI favoring the PCI group (5% vs. 8% of 67 total MIs). Most (59%) of the CABG MIs occurred during the CABG hospitalization. Need for subsequent revascularization, the primary endpoint of the trial, was 21% in the PCI arm compared with 6% in the CABG arm. The proportion of patients free of angina at 1 year was lower in the PCI group and surgery patients were less likely to be taking anti-anginal medication.

The ARTS trial randomized 1205 patients (208 diabetics), all of which had at least two vessel disease, to CABG or PCI. Intermediate follow-up at 3 years (Figure 12) was recently reported (76). At 1 year, 2.5% of PCI patients had died compared to 2.8% of CABG patients. At 3 years, the PCI group mortality was 3.7% versus 4.6% in CABG patients. There was no difference in rates of Q wave MI (PCI 5.0%, CABG 6.0%), non-Q wave MI or stroke. At 1 year, 21% of patients assigned to PCI had undergone repeat revascularization versus 3.8% of CABG patients. Between 1 and 3 years, additional revascularization was performed more frequently after PCI than CABG (9.1% versus 3.6%). After 3 years, surgery patients had less angina (12.8% vs. 18.4%), and had a lower rate of use of anti-anginal medications.

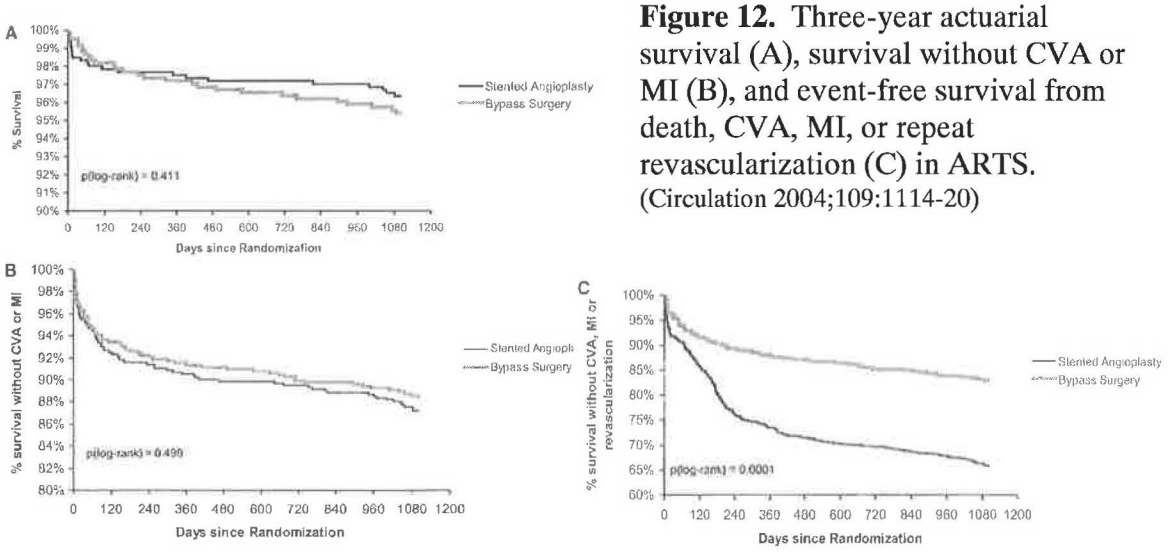


Figure 12. Three-year actuarial survival (A), survival without CVA or MI (B), and event-free survival from death, CVA, MI, or repeat revascularization (C) in ARTS. (Circulation 2004;109:1114-20)

At 1-year, diabetic patients in ARTS (77) assigned to PCI had worse clinical outcomes than CABG patients, with death, MI, and rates of repeat revascularization all favoring CABG, while strokes were more common in the CABG arm. At 1 year, 84.4% of diabetic patients assigned to CABG were free from death, MI, stroke or repeat revascularization compared with only 63.4% of diabetics assigned to PCI. At 3 years, 81.3% of diabetic patients in the surgery group were event free, as compared to 52.7% of diabetic PCI patients. The sample size was too small to detect significant differences in specific end-points other than revascularization rates but mortality, MI, and recurrent revascularization all favored the surgery group.

The results of these latest PCI versus CABG trials highlight several points. First, in non-diabetic patients, there is no longer a mortality penalty in patients receiving multi-vessel PCI with stents as an initial strategy. However, while an initial strategy of stenting may be defensible in terms of mortality, rates of revascularization are still approximately 20%, and patients are more likely to be angina-free with CABG. This point merits emphasis, as most revascularization procedures are performed for symptom relief and not for a mortality benefit. However in non-diabetic patients at low risk for restenosis (discrete lesions in large vessels), a strategy of initial multi-vessel PCI is reasonable.

Second, outcomes among diabetics with multi-vessel disease still favor surgery. While none of these studies are large enough to address mortality, rates of revascularization remain unacceptably high in diabetics treated with multi-vessel stenting. Three-year results of diabetic PCI patients in the ARTS trial are particularly sobering with 41% of patients requiring revascularization at 3 years compared with 8% of patients in which CABG was the initial treatment. Mortality in these studies, while underpowered, also favors CABG.

So what effect, if any, will the lower rates of restenosis seen with drug-eluting stents have on these results and will they push the outcomes of patients with multi-vessel disease in favor of PCI? The long-term benefits of CABG are dependent on graft patency, with the best outcomes seen in patients in whom one or both internal thoracic arteries are utilized (78-81), either alone or in combination with saphenous vein grafts. Unlike a coronary stent, which provides only a "spot", lesion-specific treatment for atherosclerosis, a patent bypass graft placed distally in an epicardial coronary vessel provides protection against the lesion(s) for which the bypass graft was placed and future obstructive lesions in the segments proximal to the anastamosis. Most obstructive lesions occur in the proximal 6 cm of a coronary artery, a distance usually bypassed with a conventional coronary artery bypass graft (82).

While internal mammary artery grafts have patency rates at 10-15 years of 90-95% (83), approximately 7-10% of saphenous vein grafts occlude in the first week following CABG, and another 5-10% occlude in the initial year following CABG (84,85). Vein graft occlusion within the first year is due predominantly to intimal hyperplasia with subsequent disease progression due primarily to atherosclerosis. Historically, approximately 50% of vein grafts are occluded at 10 years, although this estimate reflects

data from a period of time in which anti-platelet therapy following vein grafts was not standardized and lower-risk patients were referred for CABG than current practice. There are few prospective studies examining saphenous vein graft patency in the era of modern medical therapy. The best prospective data from the past decade comes from the VA Cooperative Study 297 (86), in which 266 patients with 696 saphenous vein grafts underwent cardiac catheterization at 7-10 days, 1 year, and 3 years following CABG. Six percent of grafts were occluded at 7-10 days and an additional 9.4% of grafts became occluded in the next year. At three years, a total of 135/696 (19.4%) of grafts were occluded.

With improved rates of restenosis with drug-eluting stents, the fundamental question now becomes: Is a drug-eluting stent better than a coronary artery graft? The high bar for patency and durability established by internal mammary artery grafts to the left anterior descending coronary artery will be difficult to surpass with any percutaneous strategy. However, in some patients with disease requiring placement of supplemental saphenous vein grafts, it is likely that intermediate- and long-term patency rates of native vessel obstructions treated with drug-eluting stents will exceed that of those treated with bypass with a saphenous vein graft. Physicians will be required to predict not only the risk of restenosis, but also which patients are at high risk for disease progression and would benefit from the protective effect of a saphenous vein graft. Similarly, physicians will need tools to identify lower-risk patients who have discrete obstructive lesions that can be treated with drug-eluting stents and aggressive risk-factor modification, with the expectation that they are unlikely to develop index-lesion restenosis or progression of atherosclerosis in the same anatomic segment.

In most patients who receive CABG rather than multi-vessel PCI, the clinical benefit is confined to angina relief and freedom from further revascularization. In non-diabetic patients, this difference is due primarily to restenosis at PCI sites. This conclusion is supported by near identical rates of target lesion and target vessel revascularization in both bare-metal and drug-eluting stent trials, reflecting low rates of disease progression. Intermediate-term results of drug-eluting stent trials have shown vessel patency rates which appear superior to those historically seen with saphenous vein grafts. These observations have set the stage for large randomized trials of drug-eluting stents versus CABG to see if this 70% reduction in restenosis rates will extrapolate to decreased long-term rates of revascularization and freedom from angina.

In diabetic patients, the questions will be more complex. While the reduction in restenosis rates in diabetics with drug-eluting stents is significant, diabetics are also more prone to progression of atherosclerosis (87-89). The protection afforded by bypass grafting in diabetic patients will need to be weighed against the increased morbidity and mortality of CABG in diabetic patients. This will require trials of large numbers of diabetics focused on intermediate and long-term clinical outcomes, rather than just native vessel and graft patency alone.

Conclusions

The placement on stents of anti-proliferative drugs designed to inhibit the migration and proliferation of vascular smooth muscle cells which defines neointimal hyperplasia has led to striking reductions in rates of restenosis. This reduction in restenosis has the potential to dramatically alter the approach to patients with symptomatic coronary artery disease. While unlikely to surpass the longevity and efficacy of internal mammary artery grafts, the potential exists for drug-eluting stents to be proven a more durable means of revascularization than CABG using saphenous vein grafts. As differences between need for further revascularization between CABG and drug-eluting stent PCI narrow, clinical investigation will need to focus on longer-term outcomes, better detailing of restenosis risks, and delineating which patients are at increased risk for accelerated progression of atherosclerosis in order to allow physicians and patients to make the correct choice between PCI or CABG

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