Two Decades of Coronary Artery Stents:
Lessons Learned and What's Next

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Purpose

This presentation will provide the participant with a perspective on the current role of percutaneous coronary revascularization using coronary stents in treating symptomatic coronary artery disease. Emphasis will be placed on selecting the appropriate patients for revascularization with drug-eluting stents and optimal management of the required anti-platelet therapy following coronary stenting procedures.

Objectives

After viewing this presentation, the participant will be able to:

- Describe the role of drug-eluting stents in managing patients with advanced coronary artery disease
- Understand which patients benefit most from a strategy of percutaneous coronary revascularization with coronary stenting or from coronary artery bypass grafting
- Identify the risk factors for stent thrombosis following percutaneous coronary revascularization
- Recommend the appropriate best practice for antiplatelet therapy following drug-eluting stent implantation

Introduction

Percutaneous coronary transluminal angioplasty (PTCA), first introduced in 1977, quickly evolved into an effective therapy for relief of angina pectoris and ischemia in patents who fail to respond to medical therapy and as a superior reperfusion strategy in patients suffering an acute myocardial infarction.[1-4] From the beginning, balloon angioplasty success was limited by the development of two complications — abrupt closure and restenosis. Abrupt artery closure during the procedure usually results in a myocardial infarction and in the early days of angioplasty resulted in emergency surgical revascularization in up to 4% of patients. The other Achilles heel of PTCA was restenosis, initially seen in up to 50% of patients. Initial strategies to address this problem were focused removal of atherosclerotic plaque, either through cutting it out (atherectomy) or ablating it (rotational atherectomy or laser angioplasty).[5,6] 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.

The game-changer in interventional cardiology has been the development of the coronary artery stent, which addressed the two major limitations of balloon angioplasty – propping open coronary arteries compromised by balloon angioplasty and markedly lowering rates of restenosis. Initial results of coronary stent procedures reduced rates of restenosis by approximately 50%, though for many 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.[7-10] Failures on many fronts to affect these results with adjunctive plaque removal techniques and locally-delivered or oral drugs led to the next big advance in coronary stenting, placing drugs with anti-proliferative properties on coronary stents.

Drug-eluting stents (DES) have provided dramatic decreases in restenosis rates over 1st generation stent (now referred to as "bare-metal" stents), and in doing so made percutaneous coronary intervention (PCI) more attractive as an initial revascularization strategy for patients with multi-vessel coronary artery disease and lesion subsets previously treated with coronary artery bypass surgery (CABG). The initial enthusiasm for the widespread use of PCI in patients with advanced coronary artery disease (CAD) has been tempered by the recognition of an increased risk for stent thrombosis in DES patents, necessitating a longer duration of aggressive anti-platelet therapy. This requirement for prolonged antiplatelet therapy has complicated both clinical and revascularization decision making in CAD patients with medical and surgical comorbidities. This discussion will focus on the advances in the care achieved through the use of coronary artery stents, and strategies for achieving the best results in the constantly evolving landscape of coronary revascularization.

Mechanisms of Restenosis

The first decade of percutaneous coronary intervention was performed with balloon angioplasty. Balloon angioplasty works by producing a series of controlled coronary artery dissections, producing deep fissures in intraluminal atherosclerotic plaque.[11,12] These fractures extend into the intima, or even the media, creating channels for blood flow and in combination with stretching of the arterial wall, produce an increase in the lumen of a

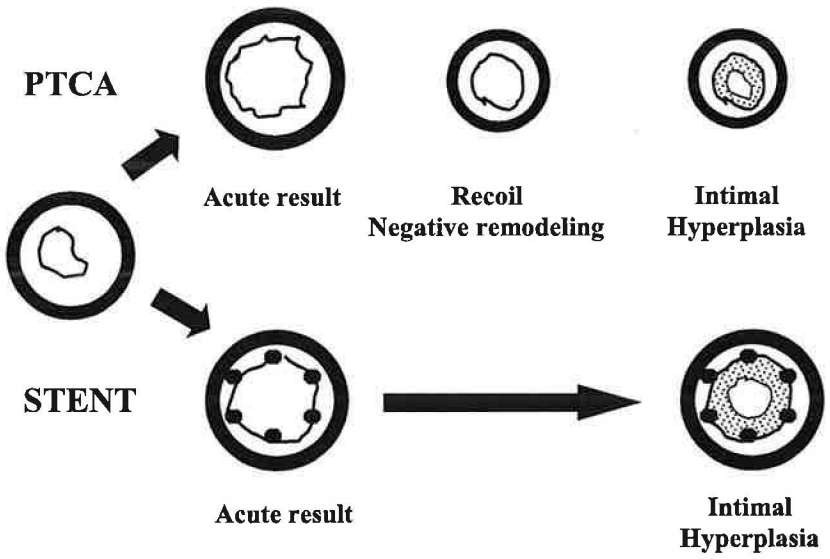
stenosed artery. Unfortunately, this series of events fail to produce a durable result in over 50% of patients, and the artery develops restenosis.

Figure 1 depicts the typical scenario seen in balloon angioplasty patients who develop restenosis.[12-14] 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. 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.[15] 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.

How Coronary Artery Stents Work

The first device used during PCI to have a significant effect was the intracoronary stent. Modern coronary artery stents are slotted tubes of stainless steel or cobalt chromium 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.[16]

Figure 1. Mechanisms of Restenosis in Balloon Angioplasty and Coronary Stenting



The landmark trials which established coronary artery stents were the BENESTENT and STRESS trials, both of which used the Palmatz-Schatz coronary stent (Table 1).[9,17,18] 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 acute stent thrombosis rates to <1%. These improvements have also impacted restenosis, as the rates of angiographic restenosis in patients receiving bare-metal stents for the types of coronary 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.[19-22]

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%.

Therefore, while the 1st generation of coronary artery stents was clearly the biggest advance in interventional cardiology since balloon angioplasty, most patients treated in everyday practice with "bare-metal stents" continue to have restenosis rates that are unacceptably high. Debulking strategies like atherectomy or 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.[5] 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.[23]

Anatomy of a Drug-Eluting Stent

Drug-eluting stents have three components. The stent itself 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, or in cavities in, 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 elution of the drug throughout the stented segment of the artery to 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.[24,25] 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 can occurs, a process which leads to death or a Q-wave myocardial infarction in up to two-thirds of patients.[26] 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 and Sirolimus Analogs

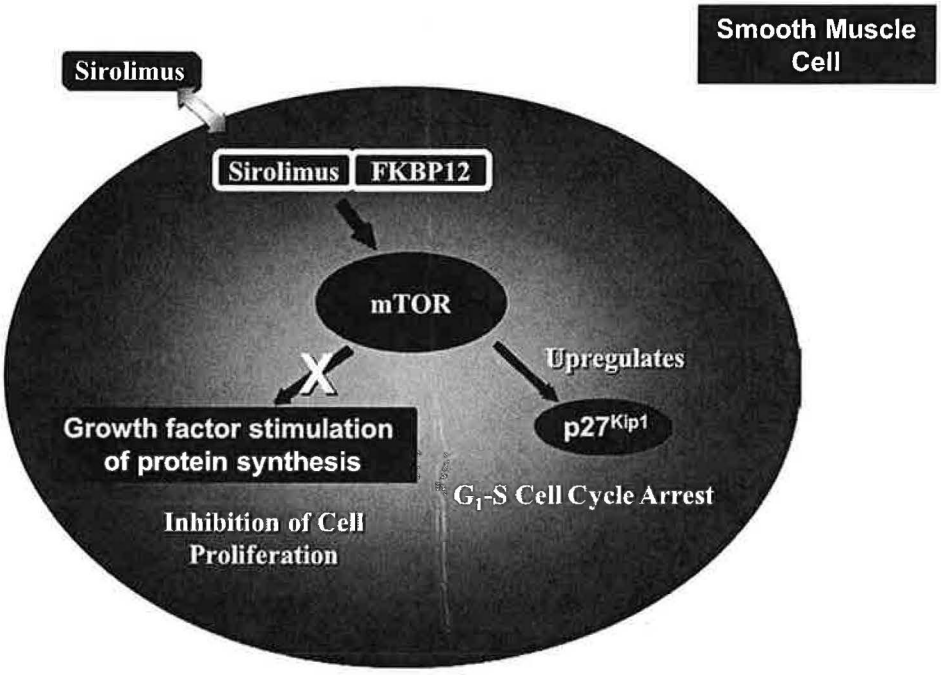
Sirolimus, or rapamycin, is a fermentation product of *Streptomyces hygroscopicus* discovered in a soil sample from Easter Island. (Rapa Nui).[24,27,28] It was initially developed as an anti-fungal product, but this indication was largely abandoned when the drug was noted to have potent immunosuppressive 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.[29] Shortly thereafter, initial study in a pig model of angioplasty showed that systemic sirolimus therapy could inhibit restenosis. While this observation did not hold true in human investigations of oral sirolimus, the use of sirolimus as a component of a drug-eluting stent has provided extraordinary results.

The efficacy of sirolimus revolves around arresting vascular smooth muscle cell migration and proliferation at a point in the cell cycle which does not cause cell death.[24,28-30] 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 mTOR (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 2. Sirolimus Cell Cycle Effects



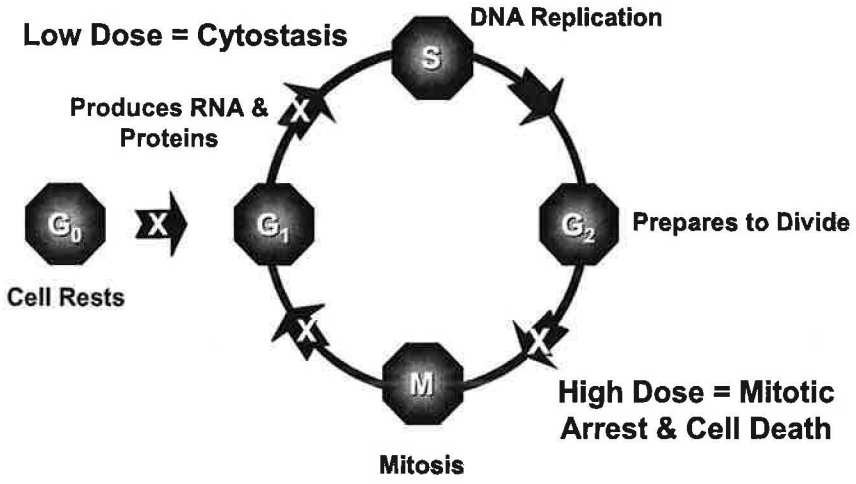
As sirolimus was deployed on the first coronary stent, and initial results were positive, other companies quickly ramped up their efforts to deliver a polymer-deliver analog of sirolimus on an existing coronary stent platform. Two of these analogs – everolimus and zotarolimus – are FDA approved for coronary use. Everolimus was initially developed in an attempt to increase oral bioavailability over sirolimus. Its primary mechanism of action is similar to that of sirolimus, but everolimus has been shown to have less of an effect on the vascular smooth muscle cell migratory component of restenosis.[31]

Zotarolimus, an analog of sirolimus with a markedly shorter half-life, has been shown to act in a very similar manner to sirolimus, although most studies have suggested slightly less potent effects.[32] Clinically this is observed as less neointimal suppression seen in trials using intracoronary ultrasound or optimal coherence tomography, a finding proposed as advantageous in patients at risk for delayed stent endothelialization or premature discontinuation of aggressive antiplatelet therapy.[33]

Paclitaxel

Paclitaxel, a plant extract of the Pacific Yew tree, was discovered in 1963 through a National Institute of Cancer initiative in which thousands of plant extracts were screened for anti-neoplastic activity.[15,34,35] 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, predominantly at the G_0/G_1 phase of the cell cycle.[36-38] Higher doses of paclitaxel act at the G2/M phase of cell division and lead to complete mitotic arrest and cell death.

Figure 3. Paclitaxel Cell Cycle Effects



Clinical Trials of Drug-Eluting Stents

We now have extended follow-up of large randomized, double-blinded trials of all currently available platforms of stents eluting sirolimus, its analogs and paclitaxel in comparison with bare-metal stents of identical design. Intermediate follow-up exists of head-to-head studies of one drug-eluting stent versus another. Similar to the history of bare-metal stents, these trials of drug-eluting stents were first 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. It is very difficult to compare

trials performed in different time periods, as advances in overall stenting technology and anti-platelet therapy can greatly influence results.

Clinical Endpoints in Stent Trials

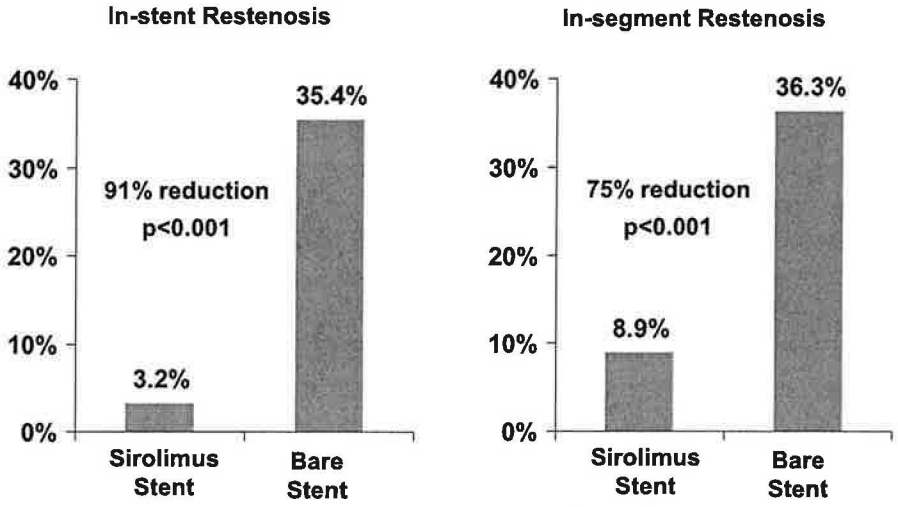
There are four clinical endpoints used in these trials which merit definition. **Binary restenosis** is the percentage of patients who exhibit greater than a 50% angiographic stenosis (as measured by quantitative coronary angiography) within the stented segment of the artery. **Target lesion revascularization (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 in the specified time period after 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

The first trial of a sirolimus-eluting stent platform (CYPHER® stent, Cordis Corporation) was the RAVEL trial. 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.[39] The SIRIUS trial 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 and included typical numbers of diabetics (≈25%) 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.

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.[40] Restenosis at 8 months was also markedly reduced in the sirolimus-treated patients (Figure 4). These marked improvements in clinical outcomes were the basis for approval of the sirolimus-eluting Cypher® stent by the FDA in April 2003.

Figure 4. SIRIUS Trial: 8-Month Angiographic Restenosis Rates



Recently, a FDA-mandated 5-year follow-up of 1,748 patients enrolled in the SIRIUS trials performed in the U.S. and abroad was completed and showed a durable advantage of sirolimus-eluting stents over bare-metal stents.[41] Target lesion revascularization in the sirolimus-treated group was 9.6% compared with 27.7% in the control group (P<0.0001). Rates of death, MI and stent thrombosis were not different between groups. These types of durable results have been seen across the broad spectrum of coronary disease presentations including patients treated with acute myocardial infarction, saphenous vein graft disease and restenotic lesions following prior bare-metal stent procedures.

Trials of Paclitaxel-Eluting Stents

The second drug to show efficacy when coupled with a coronary stent was paclitaxel, initially available as the TAXUS® stent platform (Boston Scientific Corp.). The clinical results in the TAXUS IV trial were overwhelmingly positive (Fig. 10). Angiographic restenosis in the paclitaxel group was reduced by 70% (7.9% VS. 26.6%) 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. As in the sirolimus trials, stent thrombosis was low (0.6%), at the time 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.

The 5-year extended follow-up of patients enrolled in the relatively diverse series of Taxus trials (2,797 patients) has also been published.[42] Like the SIRIUS trials, paclitaxel-eluting stents had a markedly lower rate of ischemia-driven target lesion revascularization (12.3% vs. 21.0%, P<0.0001) with no differences in the 5-year rates of death or myocardial infarction. Unexpectedly, cardiac death or MI was increased significantly between years 1 and 5 (6.7% vs. 4.5%, p=0.01) as was protocol defined stent thrombosis (0.9% vs. 0.2%, p=0.007). Extended follow-up of other patients in high-risk groups treated with paclitaxel-eluting stents have not shown this same late difference in mortality and stent thrombosis,

though patients in more modern trials tend to be treated with longer durations of dual-antiplatelet therapy.

Trials of Newer Sirolimus Analogs

The initial success of drug-eluting stents led to large shifts in the coronary stent marketplace, and companies moved quickly to hasten the development a similar product. Given sirolimus was the first to market, and demonstrated compelling early results most companies accelerated the development of their own sirolimus analog delivered with their own proprietary polymer. As these stents platforms readied for clinical trial testing, it made little sense to test them versus bare-metal stents as efficacy had been established, and comparisons against a similar drug like sirolimus seemed unlikely to provide a competitive advantage. Instead, most chose to test the "sirolimus-like" drug-eluting stent platforms against the paclitaxel-eluting stent.

The SPIRIT trials tested the XIENCE everolimus-eluting stent platforms (Abbot Vascular) against the 1st generation paclitaxel-eluting stent. The trial most similar to the original DES approval trials was SPIRIT III, which showed a 32% reduction at 2-years in target vessel failure in patients treated with the everolimus stent compared with a paclitaxel stent.[43] Target lesion revascularization was significantly lower in the everolimus group (6.1% vs. 11.3%, p=0.006). Interesting at the time was the fact there were markedly fewer thrombotic events in the everolimus group which discontinued clopidogrel early, an observation which framed a new line of investigation over the next several years.

The zotarolimus-eluting stent development program (Medtronic) took a different clinical trial tact when readying its platform for entrance into the market, choosing to compare the zotarolimus-eluting platform against the established Cypher® sirolimus-eluting stent in a trial known as ENDEAVOR III.[44] At 8-months, the zotarolimus-eluting stent was noted to have significantly more angiographically defined endothelialization – a term known as late loss – and a much higher binary restenosis rate of 11.7% vs. 4.3% in the zotarolimus group. Clinically-driven revascularizations were not different between the groups nor were rates of target vessel failure significantly different. This observation led to a proposed new line of thought that perhaps markedly inhibiting most neointimal endothelial growth might be detrimental, and perhaps a more modest decrease in neointimal growth might be advantageous – preventing clinical restenosis but allowing enough endothelialization to decrease the risk of stent thrombosis — and could decrease the duration of required anti-platelet therapy. At 5 years of ENDEAVOR III trial follow-up, this hypothesis has gained some credibility with statistically lower rates of mortality and myocardial infarction, and similar rates of clinically-driven target lesion and target vessel revascularization in patients treated with a zotarolimus stent.[45] Arguing against this protective effect of more endothelialization in the zotarolimus group were low rates of stent thrombosis in both groups (0.7% vs. 0.9%).

As the clinical trials data evolved, for the most part, trials of everolimus stents versus sirolimus stents showed equivalence in terms of restenosis, with perhaps a slight decreased risk of stent thrombosis in patients treated with an everolimus-eluting stent.[46] During the same time interval, advances in technology by stent competitors and failure of a non-polymer-based sirolimus delivery platform led Johnson & Johnson to withdraw the

sirolimus-eluting stent from the market in 2011. With accumulating evidence for higher stent thrombosis events in the paxciltaxel-eluting stent platforms, the discussion has turned to which drug, everolimus or zotarolimus, might be most effective going forward. Early head-to-head data suggests similar results with a large multicenter trial showing a target vessel failure rate of just over 8% in both groups with no differences in revascularization requirements or stent thrombosis.[47]

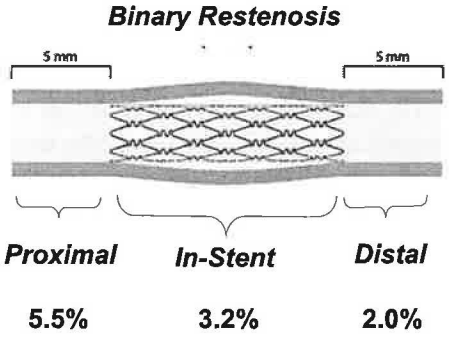
At this point in time, the safety profile of everolimus, sirolimus and zotarolimus drug-eluting stents appears to be slightly superior to paclitaxel-eluting stents, with differences in restenosis and revascularization requirements being less clear between groups.

Lessons from Drug-Eluting Stent Trials

Cover the Plaque, Not Just the Stenosis

One unexpected finding in the SIRIUS trial was the pronounced difference in in-stent restenosis rates compared with a segment including the stented area ± 5 mm on both the proximal and distal ends.[40] 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 5).

Figure 5. Distribution of In-Segment Restenosis in the SIRUS 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. 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.[48,49]

When subsequent trials were performed and operators were encouraged to use longer stents to cover every region that was dilated, these "edge restenosis" findings were markedly decreased and were similar in occurrence to patterns seen with bare-metal stents.[50,51] The change in clinical practice resulting from this finding was a requirement that cardiologists place longer stents and treat all injured areas of a vessel. This practice led to an overall increase in the numbers and length of stents placed, and in theory, an increased risk of stent thrombosis.

Different Drug-Eluting Stents for Diabetics?

One of the more provocative areas of investigation is interpreting the extensive amount of data in diabetic patients who have received drug-eluting stents. As with bare metal-stents, diabetic patients receiving drug-eluting stents have higher rates of both angiographic and clinical restenosis than patients without diabetes mellitus. In almost all drug-eluting stents trials to date, diabetics have received a greater absolute reduction in target vessel revascularization than non-diabetics. Unfortunately trials of drug-eluting stents have for the most part been underpowered to detect meaningful differences in outcomes in subgroups of patients receiving different drug-eluting stents.

Many have hypothesized that a difference might exist between sirolimus and its analogs and paclitaxel, based on their different mechanisms of action. As paclitaxel works by disrupting micro tubular function, theoretically it may interfere with more pathways of restenosis and make its effects more independent or resistant to the concurrent effects of diabetes. Some have theorized that the cell cycle effects of sirolimus may be more affected by a potential dependence on glycosylation-dependent enzymes in cellular mitosis.

Clinical trials involving head-to-head comparisons of drug-eluting stents in clinical trials have not provided conclusive evidence. While results in early trials were variable, most comparisons of sirolimus-eluting stents with paclitaxel-eluting stents favored sirolimus. A recent meta-analysis of 6 randomized trials performed exclusively in diabetic patients showed significant differences in sustained reduction of risk of target lesion revascularization in sirolimus-treated patients, with no differences between groups in mortality or rates of stent thrombosis.[52] Results from comparisons of everolimus-eluting stents with paclitaxel-eluting stents have also produced inconclusive results. Two-year follow-up of a pooled analysis of the SPIRIT trials (everolimus vs. paclitaxel) showed a definitive benefit in both requirements for revascularization and cardiac safety events in favor of everolimus in non-diabetics, but no benefit in either safety or efficacy in diabetics, either insulin-requiring or non-insulin requiring.[53]

At this moment in time, one can say conclusively that diabetics receiving drug-eluting stents have significantly lower rates of revascularization than diabetics treated with bare-metal stents. There is no convincing evidence that one drug-eluting stent is better than another in patients with diabetes. While the benefit of drug-eluting stents in diabetic patients is established, it is also likely that patients with diabetes have long-term thrombotic event rates

which may be higher than patients treated with bare-metal stents, a factor that must be taken into account when considering the duration of antiplatelet therapy.

Drug-Eluting Stent Thrombosis

While few would argue the overwhelming success of drug-eluting stents in reducing the need for recurrent percutaneous revascularization procedures, much of the enthusiasm for these results has been dampened by the lingering questions over their safety. Almost immediately following their introduction, case-reports of unusual episodes of stent thrombosis were reported by interventional cardiologists. Stent thrombosis historically leads to Q-wave myocardial infarction and/or death in two-thirds of patients, so concern over stent thrombosis quickly received the attention of the cardiology community, patients and the FDA.[54] Initially the concern was over thrombotic events in the first 30 days following stent implantation, a surprise to many interventionalists as the rates of drug-eluting stent thrombosis in clinical trials had been comparable to those seen in patients treated with bare-metal stents (approximately 0.6-0.8%).[40,55]

Most of these early events were eventually attributed to procedural and mechanical issues encountered during the "learning curve" of drug-eluting stent placement. Initially, demand for the stents by physicians was very high, as many had been delaying procedures for patients at high risk for restenosis while waiting for drug-eluting stents to become available. This led to inventory shortages in most catheterization laboratories, with many physicians doing more procedures with fewer stent sizes to choose from, increasing the potential that operators were placing inappropriately-sized stents. In addition, one clear lesson from the drug-eluting stent approval trials was, in order to optimize outcomes, that physicians should place longer stents and cover "normal vessel to normal vessel." 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. As inventories grew, physicians learned improved deployment techniques and many physicians reflexively chose a longer duration of therapy with clopidogrel, anecdotal reports of stent thrombosis decreased and analysis of registry data and ongoing clinical trials failed to identify a specific problem.

At the time drug-eluting stents were approved, dual anti-platelet therapy with aspirin and a $P2Y_{12}$ antagonist (clopidogrel for most patients) was recommended for 3 months for patients receiving a sirolimus-eluting stent or 6 months for patients receiving a paclitaxel-eluting stent. These intervals were chosen based on their use in the approval clinical trials, where rates of stent thrombosis were low and similar to those observed with bare-metal stents. As more and more patients began to receive drug-eluting stents and discontinued clopidogrel after the recommended treatment interval, cardiologists began to see cases of stent thrombosis months or even years after stent placement. Intravascular ultrasound of these patients almost always showed delayed endothelialization, with stent struts exposed to the lumen of the coronary artery and a thrombus at the site of the exposed struts. Pathologic observations suggesting a hypersensitivity reaction to either the drug or the delivering polymer were seen in many pathology specimens, as were regions of intima and media cell death adjacent to stented segments — suggesting a toxic effect of the stent delivery drug and/or platform. Another variable postulated as contributing to the stent thrombosis equation was accumulating evidence for a "rebound" effect on platelet activity following the discontinuation of clopidogrel prescribed for an acute coronary syndrome.[56]

The initial concern over this "late stent thrombosis" (thrombosis occurring beyond the traditional 1-month timeframe seen in bare-metal stent cases) and "very late stent thrombosis" (occurring >1 year) peaked in 2006 after the presentation of two studies suggesting increased mortality in drug-eluting stent patients.[57,58] The FDA immediately convened an advisory panel to review the existing long-term follow-up data on existing trials and began requiring trials to report not only angiographically-confirmed stent thrombosis but also "probable" stent thrombosis as defined by an unexplained death in the 30 days following stent implantation or a myocardial infarction in the territory of an implanted stent in the absence of any other cause.[59] While the overall rates of stent thrombosis at 4 years were similar, the incidence of "very-late" stent thrombosis incidence was approximately 0.6-0.7% higher in the drug-eluting stent groups. What was not clear was whether this increase in late stent thrombosis translated into an increased rate of death or MI, perhaps reflecting a balance between the risk of late thrombosis and the morbidity associated with increased rates of restenosis.

The interventional cardiology community reacted to this information immediately, as did the professional societies which recommended increasing the duration of treatment with aspirin and a thienopyridine for a minimum of 1 year.[60] Many cardiologists began recommending indefinite therapy for patients at low risk for bleeding. These early findings were followed by reports of extended follow-up of both randomized trials and large registries suggesting a continuous stent thrombosis hazard of up to 0.5% per year out to as far as five years in drug-eluting stent patients.[61,62]

Table 3. Four-Year Safety Follow-up in Cypher® and Taxus® Clinical Trials

Event	Cypher® (%)	Bare-Metal	P	Event	TAXUS® (%)	Bare-Metal	P
Stent thrombosis	1.2	0.6	0.200	Stent thrombosis	1.3	0.9	0.290
Late stent thrombosis (> 1 yr)	0.6	0	0.025	Late stent thrombosis (> 1 yr)	0.7	0.2	0.033
MI	6.4	6.2	0.860	MI	7.0	6.3	0.640
Death	5.7	5.2	0.190	Death	6.1	6.6	0.700
Cardiac death	3.5	2.6	0.320	Cardiac death	2.4	3.0	0.520
Death or MI	11.6	10.3	0.390	Death or MI	12.4	11.8	0.770

Adapted from Laskey et al. Circulation 2007;115:2352-7

While the current practice of continuing clopidogrel and aspirin unless there is a reason to discontinue it is an accepted standard, there is recent evidence to suggest this conclusion may be premature. The Clopidogrel Use and Long-Term Safety after Drug-Eluting Stents Implantation (ZEST-LATE) and the Correlation of Eluting Stent Implantation and Late Correlation Arterial Thrombotic Events (REAL-LATE) trials both randomized patients who had been event-free for more than 1 year after drug-eluting stent placement to continue aspirin and clopidogrel or aspirin alone.[63] Event rates in both groups were <2% in both groups, and statistically similar with a trend favoring the group receiving aspirin alone as extended therapy.

The most recent relevant study was the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia (PRODIGY) Study, which randomized 2,013 patients to receive either a bare-metal stent, zotarolimus-eluting, paclitaxel-eluting, or everolimus-eluting stent.[64] At 30 days, during which all patients received clopidogrel and aspirin, patients were randomized to either 6 months or 24 months of treatment with clopidogrel and aspirin. A safety study, the primary endpoint was a composite of all-cause mortality, myocardial infarction or cerebrovascular accident. The results at 2 years are shown in Table 4 and were surprising, with the cumulative risk of the primary outcome measure seen in 10.1% of the 24-month therapy group and 10.0% in the 6-month group. No significant differences were observed in any of the secondary endpoints, though significant increases in bleeding were seen in the 24-month group, including a two-fold transfusion requirement during the treatment interval (2.6% vs. 1.3%, p=0.041).

Table 4. PRODIGY Trial Outcomes at 24 Months by Treatment Group

End Point	24 Month Clopidogrel (%)	6-Month Clopidogrel (%)	*P*
Primary end point	10.1	10.0	0.91
Death	8.9	9.6	0.8
Cardiovascular death	3.7	3.8	0.89
MI	4.0	4.2	0.80
CVA	2.1	1.4	0.17
Intracranial hemorrhage	1.0	0.4	0.12
Definite or probable stent thrombosis	1.3	1.5	0.70
Late	1.0	0.9	0.82
Very late	0.3	0.6	0.32

Adapted from Valgimigli et al., *Circulation* 2012;125:2015-26

Findings from these recent studies call into question the instinctive response made by most clinicians to prolong therapy with clopidogrel in drug-eluting stent patients, suggesting that prolonged therapy may not improve outcomes and that the inherent bleeding risk with prolonged therapy may not be offset with anti-thrombotic benefit. These results, while provocative, should be viewed with some caution as they were not designed to distinguish between patients with increased clinical risk for stent thrombosis (kidney disease, diabetes mellitus, acute coronary syndromes, bifurcation stents, long stents) and patients predicted to be at low risk for stent thrombosis.[65] These trials also did not address patients requiring coronary interventions for saphenous vein graft disease, chronic total occlusions or in-stent restenosis, groups which may have very different anti-platelet therapy requirements.

In addition to defining the optimal duration of therapy with clopidogrel, the mostly widely used $P2Y_{12}$ antagonist, there is some evolving information to suggest that new $P2Y_{12}$ antagonists with increased activity against platelet aggregation may offer more protection against stent thrombosis than clopidogrel. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) l, prasugrel provided a 54% relative risk reduction in the incidence of late definite or probable stent thrombosis compared with clopidogrel in drug-eluting stent patients during a 15-month treatment interval. (0.41% vs. 0.91%, HR0.46, p=0.04).[66] Results of the Comparison of AZD6140 and Clopidogrel in Patients With Acute Coronary Syndrome (PLATO) trial using ticagrelor, a shorter-acting $P2Y_{12}$ antagonist, did not show benefit versus clopidogrel in preventing stent thrombosis in drug-eluting stent patients, though an unexplained mortality benefit was seen in ticagrelor-treated patients in this trial.[67]

While the complicated drug-eluting stent thrombosis story continues to unfold, clinicians are left in a holding pattern while further studies targeting the critical questions are completed. It is clear from long-term follow-up of drug-eluting stent trials that there is a small risk of stent thrombosis in the initial years following stent implantation. It is less clear that indefinite therapy with aspirin and a $P2Y_{12}$ antagonist like clopidogrel mitigates this risk. There is evidence from both imaging studies and histopathological studies that current generation drug-eluting stents may have improved endothelialization, and overall lower rates of stent thrombosis in trials of these newer stents suggest that perhaps the long-term risk may be lower and the duration of dual anti-platelet therapy may be able to be abbreviated. Until that time, the best practice remains to continue dual antiplatelet therapy with aspirin and a $P2Y_{12}$ antagonist for a minimum of 12 months, reserving extended therapy for patients with increased risk factors for stent thrombosis, high-risk presentations or anatomic stent locations (like left main stents) or difficult stent procedures.

The Current Place of Drug-Eluting Stents in Coronary Revascularization

While decisions about suitability for percutaneous coronary revascularization are straightforward in most patients, 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 multiple randomized trials of percutaneous coronary intervention compared with coronary artery bypass grafting (CABG) in patients with multi-vessel coronary artery disease. 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, was 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 initial information has led to many physicians basing their choice of revascularization on the feasibility of PCI and cumulative risk of restenosis.

There have been four moderate-sized randomized trials of CABG versus non-drug eluting stents in the modern era, Arterial Revascularization Therapies Study (ARTS), Argentine Randomized Trial of Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease (ERACI-II), Medicine, Angioplasty or Surgery Study for Multi-Vessel Coronary Artery Disease (MASS-II) and the Stent or Surgery (SoS) trial.[68-71] While the trials varied considerably in the extent of revascularization performed in the PCI arm, each trial generated relatively similar conclusions which are collectively summarized in a recent meta-analysis.[72] At 5 years of follow-up, the cumulative incidence of death, myocardial infarction and stroke was similar in patients randomized to stenting versus CABG (16.7% vs. 16.9%, p=0.69), with no difference noted in mortality. Repeat revascularization was required in 29% of patients receiving versus only 7.9% of CABG patients (p<0.001). Of the 29% of patients requiring revascularization, 21.5% received PCI and 10.4% required eventual CABG.

In diabetics, the cumulative incidence of death was 12.4% in PCI patients versus 7.9% in the CABG group (p=0.09) while the overall incidence of death, stroke or MI was similar (21.4% vs. 20.9%). Diabetics receiving stenting as an initial strategy were three-fold more likely to require repeat revascularization (29.7% vs. 9.2%). Rates of death, MI and stroke were similar between groups in patients with both 2-vessel and 3-vessel coronary artery disease, with PCI patients in both of those groups requiring significantly more repeat revascularization.

This meta-analysis demonstrates what has been observed in most randomized trials of bare-metal stents against CABG — the main difference in outcome is the increased revascularization requirement seen when stenting is deployed as an initial revascularization strategy. The next obvious step is to determine what effect the substitution of drug-eluting stents will have on the revascularization requirement, and if the extensive stenting required in multi-vessel disease treatment will have a negative impact on the rates of stent thrombosis.

While multiple clinical trials are in progress to address this important question, the most useful data to date has come from the SYNergy between PCI with TAXUS and Cardiac

Surgery (SYNTAX) trial. The SYNTAX trial randomized patients with 3-vessel coronary artery with or without left main disease to stenting with paclitaxel-eluting stents (TAXUS Express Stent, Boston Scientific) or CABG. In order to be enrolled, an interventional cardiologist and cardiothoracic surgeon had to be in agreement that either strategy was appropriate, a requirement that sent one-third of patients to CABG before randomization occurred. After agreement that equivalent and comparable revascularization could be achieved by either CABG or PCI, 1800 patients were randomized. In addition to the evaluation by a multidisciplinary team prior to randomization, this trial employed a novel new scoring algorithm designed to estimate the complexity of coronary disease. The SYNTAX Score awards points for characteristics such as extent of disease, high-risk locations of lesions, coronary calcification, chronic occlusions and bifurcation disease — items known to impact both the procedural success rates and long-term durability of revascularization procedures. Higher SYNTAX scores are indicative of more complex disease and patients with higher scores theoretically present a larger therapeutic challenge and carry a worse prognosis.

The 3-year results of the SYNTAX trial have been recently published and the overall finding presented in Table 5.[73]

Table 5. Rates of Clinical Outcomes in SYNTAX Trial Patients

Endpoint	PCI (%)	CABG (%)	*p*
Death/Stroke/MI	14.1	12.0	0.21
Death	8.6	6.7	0.13
Cardiac death	6.0	3.6	0.02
Stroke	3.4	2.0	0.07
MI	7.1	3.6	0.002
Revascularization	21.0	11.0	<0.001
Overall adverse cardiac events	28.0	20.2	<0.001

Adapted from Kappetein et al. Eur Heart J 2011;32:2125-2134

While at first glance, one might think that the story is complete and CABG may be the preferred initial treatment strategy in patients with 3-vessel coronary artery disease with or without left main involvement. However, there are several findings in these results which suggest there is more to learn. Outcomes in patients with a low SYNTAX score (<22) were equivalent, while patients in the moderate (23-32) and high (>33) clearly benefitted from CABG, both in terms of adverse cardiac events and rates of revascularization. Diabetics again benefitted in terms of rates of revascularization (12.9% vs. 28%), but the overall end point of death, stroke or MI was similar in both groups (CABG 14.0% vs. PCI 16.3%, p=0.53). Also intriguing was the fact that outcomes in patients with left main disease with a SYNTAX score in the low or moderate category were similar between strategies, an unexpected finding which has led to further investigation in this traditionally high risk group of patients.

The safety story in this intermediate timeframe analysis of SYNTAX has been equally curious. The cumulative rate of stent thrombosis in the PCI group was 4.1% (36 patients) and 1.2% per stent. Of the nine patients who experienced a very late stent thrombosis (>1 year) in the PCI arm, 4 were receiving dual-antiplatelet therapy at the time of stent thrombosis and 2 had discontinued clopidogrel 2-4 weeks prior to the thrombosis. The rate of cumulative graft occlusion in the CABG group was 3.2% per patient and 1.2% per graft, quite similar to the rates of stent thrombosis in the PCI group. Much has been made of the difference in rates of MI between groups, though two-thirds of the MIs in the PCI group and one-half in the CABG group were peri-procedural and are explained by the differences in repeat PCI rates between the two groups.

When viewed in the context of all the trials of PCI versus CABG trials, the results of SYNTAX trial confirm many existing conclusions, and suggest more study is needed in many areas to guide decision-making in many patient groups. First, in non-diabetic patients, there is not a mortality penalty in patients receiving multi-vessel PCI with drug-eluting stents as an initial strategy, as long as the disease is not particularly extensive or complex. However, while an initial strategy of stenting may be defensible in terms of mortality, rates of revascularization are still higher, even with drug-eluting stents.

Second, outcomes among diabetics with multi-vessel disease still favor surgery, based primarily on the unacceptably high rates of revascularization high in diabetics treated with multi-vessel stenting. While the absence of increased mortality at 3-years in diabetics in the SYNTAX trial may represent an improvement over prior bare-metals stent trials, the mortality trend is still in favor of CABG as an initial strategy in most diabetics with 3-vessel or left main disease.

Third, 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 either alone or in combination with saphenous vein grafts.[74-77] 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 anastomosis. Most obstructive lesions occur in the proximal 6 cm of a coronary artery, a distance usually bypassed with a conventional coronary artery bypass graft.[78] While internal mammary artery grafts have patency rates at 10-15 years of 90-95%, 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.[79,80] 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.

So as restenosis rates with drug-eluting stents improve, 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 be similar to 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. The SYNTAX Score appears to be just such a tool, and these early results suggest that when coronary arteries with discrete obstructions without significant high risk features (low SYNTAX Scores) are treated with drug-eluting stents, one can expect results which parallel those seen with CABG, without incurring the inherent morbidity associated with bypass surgery.

The observation in SYNTAX that stent thrombosis rates are similar to graft occlusion rates — even with an average of 4.6 stents per patient as seen in SYNTAX — adds even more validity to the multi-vessel stenting argument, though the uncertainty surrounding the optimal duration of dual anti-platelet therapy complicates the decision making. In many patients with significant comorbidities, prolonged therapy with dual antiplatelet agents may be unacceptable and CABG may be a preferable initial strategy.

Finally, while SYNTAX is as relevant a trial as has been seen in the interventional cardiology literature in some time, it is just the beginning. Interventional cardiologists are quick to point out that SYNTAX was performed using only paclitaxel-eluting stents, which in intermediate and long-term follow-up show the highest incidence of both restenosis and stent thrombosis. Trials with everolimus and zotarolimus drug-eluting stents are underway and may be more representative of interventional cardiology's best practices when compared with CABG for multi-vessel coronary disease.

Conclusions

The placement on stents of anti-proliferative drugs has led striking reductions in rates of restenosis, and has dramatically altered the approach to patients with symptomatic coronary artery disease. With efficacy established, the attention has turned more towards safety as the enthusiasm for the initial results for drug-eluting stents has been muted over concern over the long-term risk of stent thrombosis — particularly following the discontinuation of dual anti-platelet therapy. While it was once thought that extending dual anti-platelet therapy with aspirin and a $P2Y_{12}$ antagonist like clopidogrel might alleviate the risk of stent thrombosis, this assumption is now in doubt. It is likely that newer drug-eluting stents which allow earlier endothelialization and more potent anti-platelet regimens will be required to mitigate this risk, and new developments in each of these categories have shown promising results.

While unlikely to surpass the longevity and efficacy of internal mammary artery grafts, the potential exists for drug-eluting stents to be proven as 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 investigations 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. This information must be placed in context with additional forthcoming

longer-term follow-up safety and efficacy information on drug-eluting stents. In an era when both coronary intervention and CABG are improving, it will likely take careful randomized trials of the best each revascularization strategy can offer to allow physicians and patients to make the correct choice between PCI and CABG.

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