Safety and Efficacy of Drug-Eluting Stents

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This review characterizes the relative effectiveness and safety of drug-eluting stents (DES) compared to bare metal stents. The data evaluated will include clinical and angiographic outcomes from randomized clinical trials as well as observational databases and registries including RESEARCH, e-CYPHER, and DYNAMIC, which typically include a much broader spectrum of patients. In addition, specific patient subsets, including those patients with multivessel coronary disease, will be evaluated.
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Since its initial development, the sirolimus-eluting stent has been the prototype for all comparisons of drug-eluting stents (DES) versus bare metal stents. A robust database exists for sirolimus and, specifically, the CYPHER® stent (Cordis Cardiology, Miami Lakes, FL) in broad patient populations as well as specific subsets. It is also noteworthy that an evolutionary process has occurred in DES trials, beginning with randomized investigations of small cohorts of very

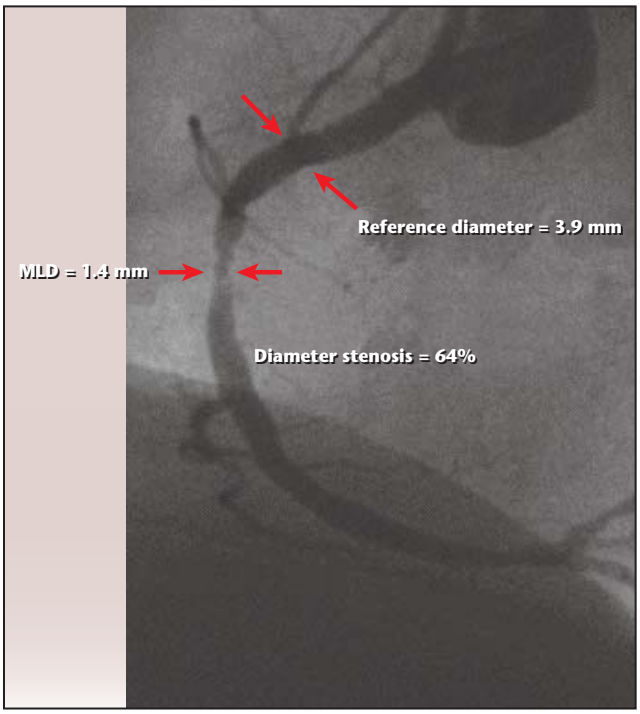


Figure 1. *Right coronary artery cine angiogram demonstrating proximal coronary stenosis (see text). MLD, median lumen diameter.*

highly selected patients from few centers and subsequently expanding into larger patient cohorts with more complex coronary anatomy in multicenter trials. Furthermore, as the sirolimus-eluting stent was the first DES to be investigated, more longer-term follow-up data are available than for any other DES. This fact is important not only for investigating efficacy, but also in determining the long-term safety of the technology.

When we evaluate angiographic outcomes of patients enrolled into randomized trials, it is important that we understand the specific terms or variables that are used to measure the effectiveness of DES. The term angiographic restenosis is most commonly defined as narrowing within the stent itself or in the vessel segment immediately adjacent to the stent (stent margins) of ≥ 50%, at the time of follow-up.[1] Conversely, clinical restenosis is typically defined as the clinical need to perform repeat target lesion revascularization by either bypass surgery or repeat percutaneous coronary intervention (PCI). A broader definition of clinical restenosis includes target vessel revascularization (any revascularization procedure performed in follow-up that involved any part of the original target artery) in addition to target lesion revascularization alone.[2] Other important angiographic measures include minimum lumen diameter and late lumen loss. These 2 terms are derived from quantitative coronary angiographic (QCA) analyses. Minimal lumen diameter is the size of the lumen measured in millimeters at the narrowest point of stenosis in whatever view shows the lesion to be most severe. Late loss is the difference, measured in millimeters, in luminal diameter between the immediate post-PCI assessment and that measured at late follow-up. Figure 1 shows a right coronary cine angiogram with a stenosis in the proximal portion. By QCA, the reference vessel diameter proximal to the stenotic lesion is 3.9 mm with a minimal lumen diameter at the point of stenosis of 1.4 mm. The degree of arterial narrowing is the difference between 3.9 and 1.4 (2.5 mm). That number, over the reference diameter (2.5 / 3.9 mm) x 100 = 64%, the percent diameter stenosis.

A schematic illustration of late loss is shown in Figure 2. Immediately following stent deployment, the minimum lumen diameter is illustrated. In follow-up, significant neointimal hyperplasia has developed and has resulted in considerable narrowing of the arterial lumen. Subtracting the lumen diameter measured at follow-up from the lumen diameter immediately following the procedure gives the measure of late loss and reflects the degree of neointimal hyperplasia that has occurred over time. For DES, late loss should be less than

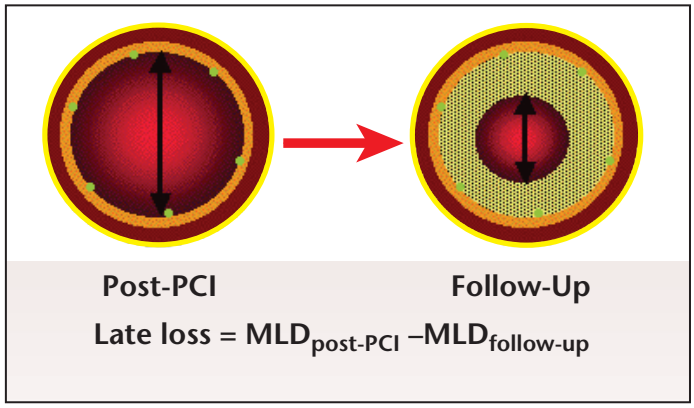


Figure 2. *Graphic representation of late coronary lumen loss occurring within the stented arterial segment (see text). The magnitude of late loss reflects the degree of neointimal hyperplasia that has occurred over time. PCI, percutaneous coronary intervention; MLD, median lumen diameter.*

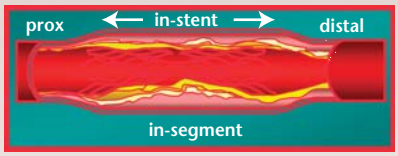
that observed with bare metal stents. In addition, the magnitude of late loss allows a quantitative comparison of the relative potency of 2 different DES. If each stent utilizes a different drug and the intent of both drugs is to prevent neointimal hyperplasia, the drug that exhibits the lowest degree of late lumen loss would be the more potent drug in the sense of its intended effect.

Sirolimus-Eluting Stent Trials

In the Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL),[3] 238 patients undergoing single-vessel, single-lesion stenting were randomly assigned to treatment with either a sirolimus-eluting stent (CYPHER) or bare metal stent (Bx Velocity,™ Cordis Cardiology). Despite the limited complexity of lesions in the patients enrolled into this trial, no CYPHER-treated patient exhibited clinical angiographic restenosis, and late lumen loss was virtually zero (no difference between immediate post-PCI and follow-up lumen diameters). Importantly, safety endpoints (death, myocardial infarction, urgent revascularization, or stent thrombosis) were similar in frequency for both stent treatment groups. Of note, in this initial study of DES, the duration of antiplatelet therapy with combination ticlopidine and aspirin was only 8 weeks and no stent thromboses were observed.

Following RAVEL, the US Multicenter, Randomized, Double-Blind Study of the Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) trial[4] was performed in the United States. This pivotal trial, which led to US Food and Drug Administration approval of the CYPHER stent, randomly assigned patients with reference vessel diameters of 2.5 mm to 3.5 mm and target lesion lengths of 15 mm to 30 mm, involving a single coronary vessel, to therapy with either the CYPHER sirolimus-eluting stent or the bare metal Bx Velocity stent. More than one quarter of patients enrolled had diabetes mellitus. In SIRIUS, the duration of combined antiplatelet therapy (aspirin and clopidogrel) was 3 months. The SIRIUS trial confirmed that both angiographic and clinical restenosis rates were substantially reduced by the CYPHER stent. The angiographic follow-up data for the SIRIUS trial are shown in Figure 3.

Restenosis Rates in the SIRIUS Trial



	Sirolimus, % (n = 533)	Control, % (n = 525)	*P* value
In-stent	3.2	35.4	< .001
Proximal margin	5.8	8.1	.285
Distal margin	2.0	7.2	.002
In-segment	8.9	36.3	< .001

Figure 3. *Quantitative coronary angiographic analysis in the SIRIUS trial. Values shown represent binary (> 50%) lumen diameter stenosis by segment analyzed.*

Within the stented segment, the control (Bx Velocity) patients demonstrated restenosis (≥50% narrowing) in more than 30% of cases, whereas only 3.2% of the sirolimus- (CYPHER) treated patients were observed to have in-stent restenosis. Of note, some evidence of luminal narrowing was observed at the proximal and distal margins of the stent itself. This "in-segment" or "segment of interest" (versus stented segment only) included 5 mm vessel margins both proximal and distal to the stent and represents the entire potential zone of vessel injury. In the distal margin, the degree of stenosis in the sirolimus-treated group was statistically less than that in the control group. In the proximal margin, although the degree of stenosis was less in the sirolimus-treated group, this difference was not statistically significant. For the entire segments of interest, any restenosis was observed in 36% of the control (Bx Velocity) group versus observation in 9% of the CYPHER stent group. This dramatic reduction in restenosis was consistent across multiple patient subgroups (Figure 4). The magnitude of late lumen loss observed in the control Bx Velocity stent was approximately 1.0 mm, similar to that observed in prior QCA evaluations of bare metal stents (see Figure 4 of Dr. Emerson Perin's article in this issue). In the CYPHER-treated patients, late loss was substantially reduced to only 0.17 mm in-stent.[4]

Clinical events were also improved following CYPHER stent (vs Bx Velocity) deployment. Indeed, the relative benefit of the CYPHER stent in reducing the requirement for target vessel revascularization or the occurrence of major adverse cardiovascular events (MACE) including death, myocardial infarction, or repeat tar-

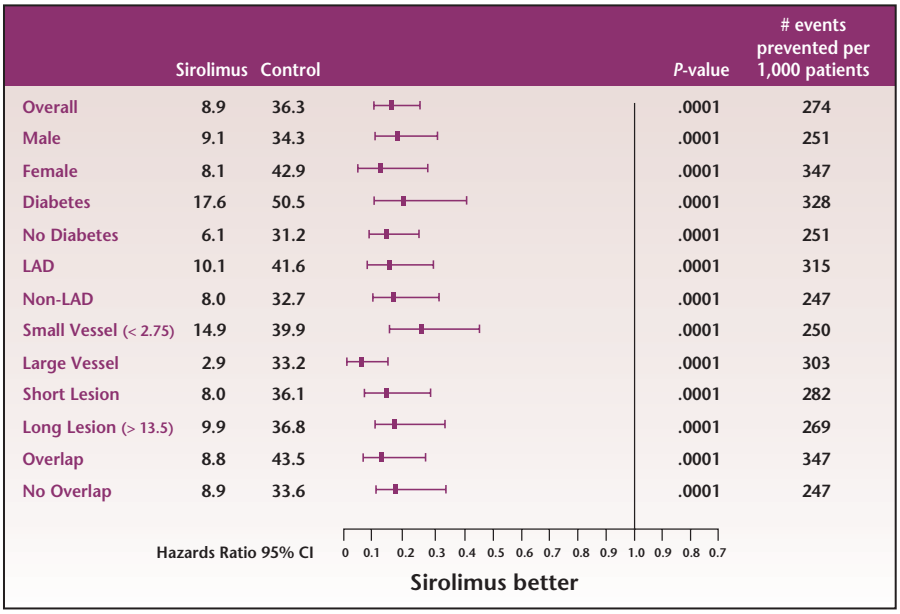


Figure 4. *Relative benefit of the CYPHER sirolimus-eluting stent (vs. bare metal Bx Velocity stent) for reduction in in-segment restenosis overall and by specific patient cohorts. Reduction in in-segment restenosis approximates 80% across all subgroups. The number of events presented for 1000 patients treated is shown in the far right column. LAD, left anterior descending artery.*

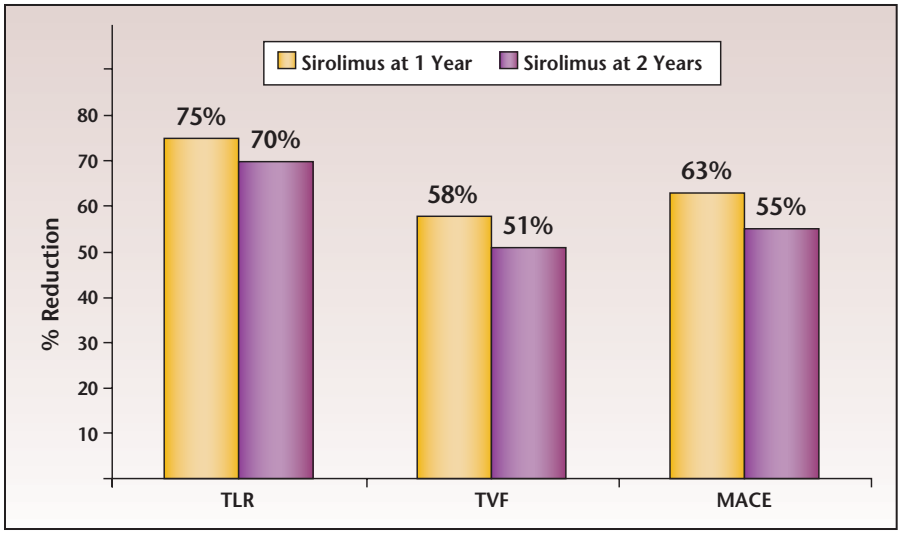
get lesion revascularization was durable and maintained at both 1- and 2-years follow-up[5,6] (Figure 5). Furthermore, this benefit was accrued without any excess of adverse events, specifically death, myocardial infarction, or stent thrombosis, in patients who received the CYPHER stent.

Following the SIRIUS trial, 2 other randomized clinical trials with similar design were performed in Europe (E-SIRIUS)[7] and Canada (C-SIRIUS).[8] The aggregate results from these 2 studies have been termed the "new SIRIUS" trial.[9] One potentially significant difference between new SIRIUS and SIRIUS, with regard to procedural technique, was the allowance for direct stenting (no predilatation requirement) in new SIRIUS. Direct stenting may serve to limit the zone of vessel injury outside the stented segment. This difference in stenting technique may be responsible, in part, for results of new SIRIUS that were superior to those observed in SIRIUS. Quantitative coronary angiography (QCA) results at 8-months follow-up in SIRIUS demonstrated an 8.9% in-segment restenosis rate in CYPHER-treated patients.[4] In E-SIRIUS, this rate was reduced to 5.9%.[7] Similarly, the in-stent restenosis rates were 3.2% (SIRIUS), 3.9% (E-SIRIUS), and 0% (C-SIRIUS).[8] Thus, in SIRIUS, an appreciable portion of in-segment restenosis was due to restenosis at the margins. Differences in technique for stent deployment are important in achieving the lowest values for angiographic restenosis. In new SIRIUS,[9] restenosis at the proximal margin was reduced to 2.1% and at the distal margin to 1.5%. These numbers contribute to the relative benefit observed in new SIRIUS when compared to SIRIUS. The modification of stent deployment technique also reduced the need for repeat revascularization (clinical restenosis).

Paclitaxel-Eluting Stent Trials

More recently, another DES has become available for use in the United States. Polymer-based paclitaxel elution from the Express 2™ metal platform (TAXUS™, Boston Scientific, Natick, MA) has also demonstrated effectiveness in randomized clinical trials. In the TAXUS IV trial,[10] patients undergoing stenting for single-vessel (reference diameter 2.5-3.75 mm), single-lesion (length 10-28 mm) disease were randomly assigned to treatment with

Figure 5. *Relative percent reduction in endpoints of target lesion revascularization (TLR), target vessel failure (TVF), and major adverse cardiovascular events (MACE) in the CYPHER sirolimus-eluting stent compared with the bare metal Bx Velocity stent in the SIRIUS Trial. The relative benefit observed at 1-year follow-up was maintained at 2-years follow-up.*



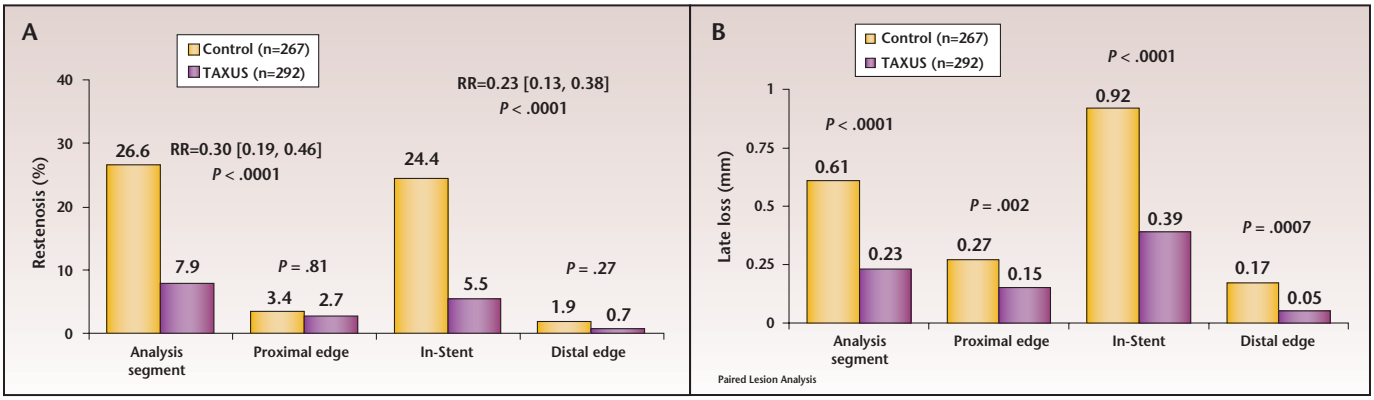


Figure 6. *Binary (> 50%) angiographic restenosis* **(A)** *and late coronary lumen loss* **(B)** *as measured by quantitative coronary angiography for each arterial segment analyzed from the TAXUS IV trial.*

either the TAXUS paclitaxel-eluting stent or a bare metal (Express 2) stent. The duration of combination antiplatelet therapy in TAXUS IV was 6 months compared with 3 months in SIRIUS. The angiographic data from TAXUS IV are shown in Figure 6. In-segment, late lumen loss in the bare metal Express stent was 0.61 mm and was reduced to 0.23 mm in TAXUS-treated patients. Of interest, however, was the observation of late loss within the Express stent, 0.92 mm, which was similar to that observed for the Bx Velocity stent, and which was reduced within the TAXUS stent to 0.39 mm. This value (0.39 mm) is considerably higher than the 0.17 in-stent late loss observed in the SIRIUS trial with the CYPHER stent and suggests that although both stents are effective in reducing late loss, sirolimus appears more potent than paclitaxel. Adverse clinical events were reduced by TAXUS (vs Express 2) in a fashion similar to that observed in the SIRIUS trial.

Drug-Eluting Stent Registries

These clinical trials were important in establishing the initial effectiveness and safety of drug-eluting stents. However, in clinical trials there is considerable selectivity involved in the types of patients enrolled, which often makes extrapolation of trial results to real-world, clinical practice difficult.

To determine the outcomes of DES procedures in the broader spectrum of patients treated in clinical practice, data must be evaluated from clinical registries such as the Rapamycin-Eluting Stent Evaluation at Rotterdam Cardiology Hospital (RESEARCH) registry,[11] conducted in the Netherlands, where patients treated with the CYPHER DES were compared to a historical cohort of patients previously treated with bare metal stents. As one might expect, registry experiences frequently involve differences in patient characteristics and in the types of stents employed. Nevertheless, the CYPHER-treated patients demonstrated a significant reduction in the requirement for repeat revascularization, when compared to the bare metal stent-treated group. A significant reduction in MACE favoring the CYPHER stent was also observed. Interestingly, analysis of RESEARCH registry statistics trend toward a reduction in death and myocardial infarction, in favor of CYPHER.

Another multi-center registry, e-CYPHER,[12] is currently on-going in Europe. e-CYPHER has targeted 15,000 patients and enrolls patients who receive at least one CYPHER stent. No restriction has been placed on the characteristics of the patients treated. The purpose of this study is to obtain more information about the safety, and to some extent the effectiveness, of sirolimus-eluting stents in routine clinical practice and to validate the results of randomized clinical trials in a real-life setting. This registry is focused on clinical events, rather than angiographic follow-up.

Another important registry, which is not industry-sponsored, is the DYNAMIC registry. This registry is derived from the initial National Heart, Lung, and Blood Institute (NHLBI) Percutaneous Transluminal Coronary Angioplasty registry[13] and originates from the University of Pittsburgh. Unlike other registries that only enroll patients who receive drug-eluting stents, the DYNAMIC registry enrolls consecutive patients undergoing PCI of any type. Enrolling centers are located in North America and multiple "waves" of patients are enrolled by specific time. These waves of enrolled patients are then followed and compared to other waves. Waves are typically defined by advances in technology. The most recent fourth wave of the DYNAMIC registry was initiated and

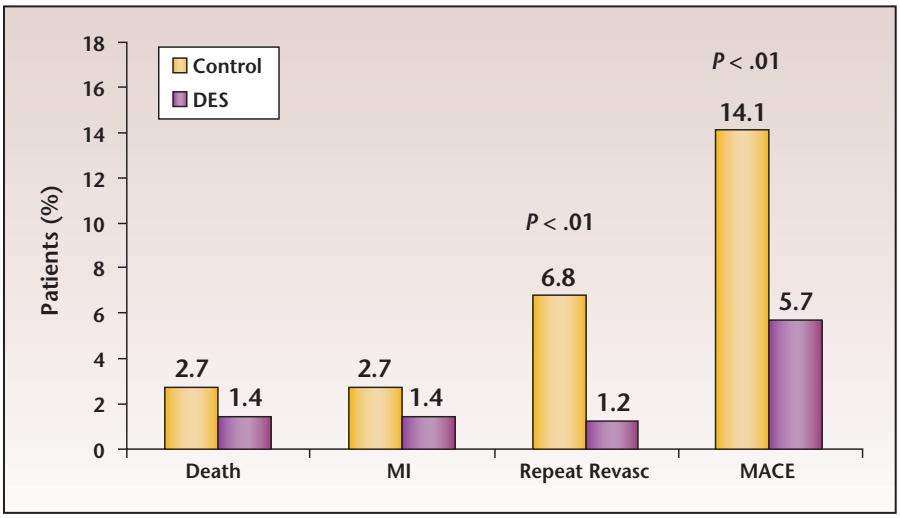


Figure 7. *Single-center, real-world experience with off-label use of drug-eluting stents. The comparator "control" group represents a historical cohort of patients treated with bare metal stents. Purple bars represent total drug-eluting stent (DES)-treated patients (78% received a CYPHER sirolimus-eluting stent vs. the TAXUS paclitaxel-eluting stent). MACE, major adverse cardiovascular events; MI, myocardial infarction.*

completed at the beginning of 2004 and involves 2690 consecutive patients. As this wave was enrolled at a time when DES were available, it should allow comparison with the prior wave of patients treated with bare metal stents.

In terms of baseline features, there appears to be a greater tendency to use DES in patients with diabetes and in those who have received a prior bare metal stent. Conversely, patients treated for acute myocardial infarction (MI), total coronary occlusion, or with angiographic evidence of thrombus were less likely to receive a DES versus a bare metal stent. Of patients who received a DES in this registry, 78% received a sirolimus-eluting stent versus a paclitaxel-eluting stent. Of particular interest is the evaluation of stent thrombosis or any other toxic effects that one might observe from DES when applied in standard clinical practice outside the rigid protocol-defined criteria of randomized trials. As shown in Figure 7, occurrences of death, death or myocardial infarction, and death/myocardial infarction and bypass surgery were less frequently observed among patients who received DES compared with bare metal stents. Of note, no excess of stent thrombosis events was observed for DES. It must be clarified that the observed differences in adverse events could be attributable to factors other than the specific stent deployed as patients had significant differences in baseline characteristics.

Yet another registry, scheduled to launch in November 2004, is the DESCOVER registry. This novel registry hopes to characterize the use of DES and outcomes of patients treated with them in a real-world setting. DESCOVER will be conducted in the United States, will include a very broad representation of hospitals and practices, and will have the potential to provide each hospital and practice with information comparing their experiences. Similar to the DYNAMIC registry, consecutive PCI patients will be enrolled regardless of treatment method.

Importantly, economic and quality-of-life data, in addition to clinical information, will be captured. The projected sample size for DESCOVER is 7500 patients at an anticipated 100-200 clinical sites. Data coordination will be provided by a centralized, experienced data coordinating center, and an organized, standardized process of adjudication of clinical events will be employed.

PCI for Multivessel Disease

The final subject to be addressed is that of PCI for multivessel disease. Prior to assessing the impact of DES on this unique patient subset, the effect of bare metal stents alone can be evaluated by comparing data from the DYNAMIC registry with that from the Bypass Angioplasty

Table 1
Percutaneous Coronary Intervention for Multivessel Disease

	DYNAMIC-BARI†	BARI-PTCA*	*P* value
N	857	904	
Mean Age (years)	63.6	61.8	.002
Females	30%	27%	0.28
Diabetes	23%	19%	.047
3-VD	29%	39%	.001
EF < 50%	24%	19%	.014

3-VD, three-vessel disease
Figures represent baseline characteristics for patients treated in the Bypass Angioplasty Revascularization Investigation (BARI) trial PTCA cohort* compared with the Dynamic–BARI cohort of patients derived from the DYNAMIC registry,† who were treated during the stent era and who had eligibility characteristics similar to those of patients enrolled in the BARI trial (see text).
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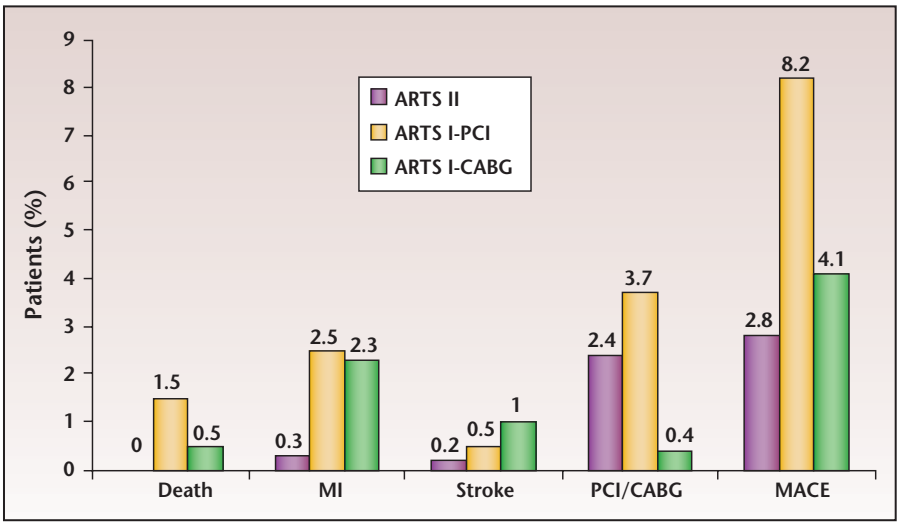

Figure 8. *A comparison of clinical events to 30 days in the ARTS II trial versus specific percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) patient cohorts enrolled in the ARTS I trial. Patients treated with the CYPHER sirolimus-eluting stent in the ARTS II trial had extremely low rates of adverse clinical events. MACE, major adverse cardiovascular events.*

Revascularization Investigation (BARI) trial.[14] As shown in Table 1, the "DYNAMIC-BARI" cohort represents patients within the DYNAMIC registry who were treated during the stent era and who had baseline eligibility characteristics similar to those of patients enrolled in the BARI trial. The BARI trial compared balloon angioplasty to surgery for the treatment of multivessel coronary artery disease. In BARI, patients with multivessel disease were treated with balloon angioplasty alone. In the DYNAMIC registry, patients with multivessel disease with characteristics similar in terms of eligibility to those enrolled in BARI were treated during the era of stent availability. As shown, there were about 900 patients in each group.

The age of patients treated for multivessel disease in the stent era was older and this group included more women, more patients with diabetes, less triple vessel disease, and more patients with impaired left ventricular function. Thus, a different population of patients with multivessel disease is now being treated in the stent era than was being treated with balloon angioplasty alone. If these patient groups are compared in terms of hospital events, dramatic differences are observed. The need for bypass surgery in the hospital has been markedly reduced in the stent era.[15,16] Similarly, the incidence of myocardial infarction has been significantly reduced.[17] No significant differences in death were observed between balloon and (bare metal) stent-treated patients. Thus, the impact of stents (vs balloon angioplasty) was primarily seen in a reduction of incidence of periprocedural MI and the need for in-hospital bypass surgery. Comparing 1-year follow-up data on both groups of patients, the primary impact of stents was a reduction in the incidence of repeat PCI or bypass surgery. The earlier difference in MI was preserved and the combined endpoint of death/MI was lower in stented patients with no significant differences observed in the single endpoint of death. No salutary effect of stents (vs balloon) was observed in either death or MI in late follow-up. This is not surprising given the context that stents prevent restenosis and restenosis does not usually present as myocardial infarction.

Limited randomized clinical trial data are available from which to assess the impact of stenting in multivessel-disease patients. In the Arterial Revascularization Therapy Study (ARTS) trial,[18] which randomized patients with multivessel disease and compared bare metal stents to coronary bypass surgery, those patients treated with stents can be compared to those enrolled in the DYNAMIC registry. Striking similarities between these groups are apparent. For example, the requirement for either a repeat PCI or a bypass operation following the initial stenting procedure was similar between ARTS and DYNAMIC registry patients. In addition, the incidence of death or death and myocardial infarction were quite similar. Currently, the sequel to ARTS, ARTS II,[19] involves a nonrandomized comparison of consecutive multivessel patients treated with CYPHER stents, compared to the original surgical coronary artery bypass arm of ARTS. ARTS II is a registry enrolling patients with similar entry criteria, separated in time by the same clinical sites involved in ARTS I and thus, will allow a comparison of a more contemporary DES cohort to the bypass group

The need for bypass surgery in the hospital has been markedly reduced in the stent era.

from the initial trial. Similar to ARTS I, ARTS II is evaluating patients with stable angina and will analyze freedom from MACE at 1 year.

In comparing 30-day data from ARTS II (CYPHER-treated) with bare metal stent-treated patients (ARTS I), and the surgically treated cohort of patients from ARTS I, a reduction in MACE and, in particular, a reduced incidence of MI is observed (Figure 8). As certain of these findings support the safety of DES in multivessel disease, later follow-up will be needed to properly characterize their benefit. In addition, there are observational series data from single sites available. A report of 155 patients undergoing multivessel real-world CYPHER stenting observed very low rates of MACE to 30 days, and low rates of death or myocardial infarction at 6 months.[20] Interestingly, the rate of TVR was 18% in this small, complex cohort of patients.

In comparing 30-day data from ARTS II (CYPHER-treated) with bare metal stent-treated patients (ARTS I), and the surgically treated cohort of patients from ARTS I, a reduction in MACE and, in particular, a reduced incidence of MI is observed.

Obviously, the most reliable comparison of multivessel DES versus bypass surgery will require a randomized trial. The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial will be performed in the United States and will enroll patients with diabetes and multivessel disease in a head-to-head comparison of PCI with DES versus bypass surgery. FREEDOM will be an incredibly important study in a complex group of patients, which will provide data to answer the question of DES efficacy in multivessel disease. ■

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Main Points

- Since its initial development, the sirolimus-eluting stent has been the prototype for all comparisons of drug-eluting stents (DES) versus bare metal stents.
- The Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL) trial, enrolled 238 patients undergoing single-vessel, single-lesion stenting and randomly assigned to treatment with either a sirolimus-eluting stent or a bare metal stent. No sirolimus-eluting stent-treated patient exhibited clinical angiographic restenosis and late lumen loss was virtually zero (no difference between immediate post-PCI and follow-up lumen diameters).
- In the SIRIUS trial, the relative benefit of the sirolimus-eluting stent versus bare metal stents in reducing the requirement for target vessel revascularization or the occurrence of major adverse cardiovascular events including death, myocardial infarction, or repeat target lesion revascularization was durable and maintained at both 1- and 2-years follow-up.
- In the TAXUS IV trial of a paclitaxel-eluting stent versus bare metal stenting, the observation of late loss within the bare metal stent, 0.92 mm, which was similar to that observed in the SIRIUS trial, was reduced within the paclitaxel-eluting stent to 0.39 mm. This value is considerably higher than the 0.17 in-stent late loss observed in the SIRIUS trial with the sirolimus-eluting stent and suggests that although both stents are effective in reducing late loss, sirolimus appears more potent than paclitaxel.
- Registries, including RESEARCH, e-CYPHER, DYNAMIC, and DESCOVER, are currently on-going and are examining the use of DES in real-world, clinical practice to measure their effect on the outcomes of PCI procedures in general. Analysis of current findings from RESEARCH shows a trend toward reduction of death and myocardial infarction, in favor of the sirolimus-eluting stent.
- In multivessel disease, the impact of bare metal stents (vs balloon angioplasty) is primarily seen in a reduction of incidence of periprocedural myocardial infarction, the need for in-hospital bypass surgery and, at 1 year, a reduction in the incidence of repeat PCI or bypass surgery.
- The upcoming Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial will be performed in the United States and will enroll patients with diabetes and multivessel disease in a head-to-head comparison of PCI with DES versus bypass surgery.

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