Stents, Surgery or Statins:
Medical Therapy or Revascularization for Stable Coronary Artery Disease?

John J. Warner, MD
Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center

June 29, 2007

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.

Introduction

Patients with stable coronary artery disease are typically defined as those with evidence of myocardial ischemia and obstructive coronary artery disease (stenosis ≥70%) in at least one major epicardial coronary artery, who are either asymptomatic or are able to be stabilized with medical therapy. In general, this term is not applied to patients presenting with an acute coronary syndrome, although some include patients with an acute myocardial infarction who stabilize on initial medical therapy in this definition. In this era, most stable coronary artery disease patients fall into two categories, those with chronic angina pectoris and patients without symptoms who have coronary artery disease diagnosed on a screening stress or imaging test.

Chronic stable angina is the initial symptom of coronary artery disease in approximately one-half of patients with ischemic heart disease.(1,2) In 2004, the American Heart Association estimated that almost 9 million people in the U.S. suffer from angina, or approximately 4.1% of the population.(3) Through educational efforts, the public has learned to associate angina with myocardial infarction (MI), and many patients with chronic angina are fearful of suffering a MI and equate relief of angina to a lower risk of MI or cardiac death. Over the past 30 years, this perceived benefit has made the use of revascularization, surgical and percutaneous, common as an initial treatment strategy in stable coronary artery disease patients.

This has occurred even as treatment guidelines have recommended an initial approach of optimal medical therapy, defined as a combination of intensive medical therapy, risk factor reduction and lifestyle modifications. In the United States, an estimated 70-85,000 coronary stent procedures are performed each month (4), with some registry data suggesting that as many of 85% of these procedures are performed electively for stable coronary disease.(5) This observation is also true for coronary artery bypass grafting (CABG) operations, where similar registry data also suggests that a significant percentage of patients referred for CABG do not have the high risk features associated with improvements in mortality and morbidity.(6-9)

Where stable coronary disease once was synonymous with chronic stable angina, a new patient subset in this category has grown in increasing numbers. Improvements in imaging technology and more aggressive screening tests in patients at risk for coronary disease have generated a larger group of patients with newly diagnosed obstructive coronary disease, but no symptoms. The widespread use of screening coronary CT angiography in asymptomatic patients has magnified this issue at a time when we have controversial clinical data as to what constitutes a high risk finding in these patients.

This discussion will focus on the treatment of patients with stable coronary artery disease, and will attempt to delineate which patients can safely be treated with optimal medical therapy and which patients may need to be referred for revascularization as an initial strategy. More than one-third of patients will fail optimal medical therapy, usually due to limiting angina. This discussion will highlight the appropriateness and benefits of both percutaneous coronary intervention and coronary artery bypass grafting in these patients.

Why Preventive Revascularization in Stable Patients Does Not Always Work

It makes intuitive sense that relieving a stenosis in a coronary artery might prevent a myocardial infarction, hospitalization for an acute coronary syndrome and even death. This has been true for patients preventing with an acute coronary syndrome in which an unstable coronary plaque causes a myocardial infarction or unstable angina.(10-14) In these patients, particularly those presenting with non-ST segment elevation myocardial infarctions or unstable angina, routine cardiac angiography followed by appropriate revascularization when indicated has been shown to reduce the incidence of myocardial infarction, death and repeat hospitalizations for acute coronary syndromes. A similar benefit of routine angiography and revascularization in patients with stable coronary artery disease does not exist.

Atherosclerotic plaque differences in acute coronary syndromes versus chronic angina

These differences may be explained by differences in atherosclerotic plaque characteristics in patients with acute, rather than chronic coronary syndromes. Atherosclerotic plaques which lead to acute coronary syndromes have large lipid cores and a thin fibrous cap, the edges of which are prone to rupture. Histologically, these plaques have fewer smooth muscle cells, more macrophages, and less collagen.(15) These plaques are often associated with outward (positive) remodeling of the coronary vessel wall, meaning the artery expands to accommodate the plaque, producing less stenosis of the coronary lumen. Typically these plaques do not obstruct the lumen enough to cause angina, and are clinically silent until the fibrous cap ruptures, exposing the lipid core to circulating blood and forming a thrombus which either completely or partially obstructs the coronary lumen.

Stable plaques are very different. They have more smooth muscle cells, less lipid content, and thicker fibrous caps. They have fewer macrophages and more collagen. These "harder" plaques are not accommodated into the vessel wall, but rather are associated with constructive remodeling of the arterial wall, a phenomenon not unlike that of routine scar formation. This so-called "negative" remodeling process constricts the vessel lumen and limits flow, clinically producing lesions which produce angina, lead to abnormal stress test results, are easily identifiable by cardiac catheterization and CT angiography. These lesions are much less likely to result in an acute coronary syndrome. Figure 1 shows two intravascular ultrasound photographs which represent the extremes of these two processes.

Stenotic plaques are not necessarily unstable

The differences in these two processes underpin the difficulty in predicting which coronary stenoses are likely to produce a myocardial infarction. Patients with chronic angina are not immune to suffering a myocardial infarction. In two longitudinal studies of patients with chronic angina (Olmsted County, Minnesota, and Framingham, Massachusetts), the incidence of myocardial infarction was 3.0-3.5% per year.(1,2,16)

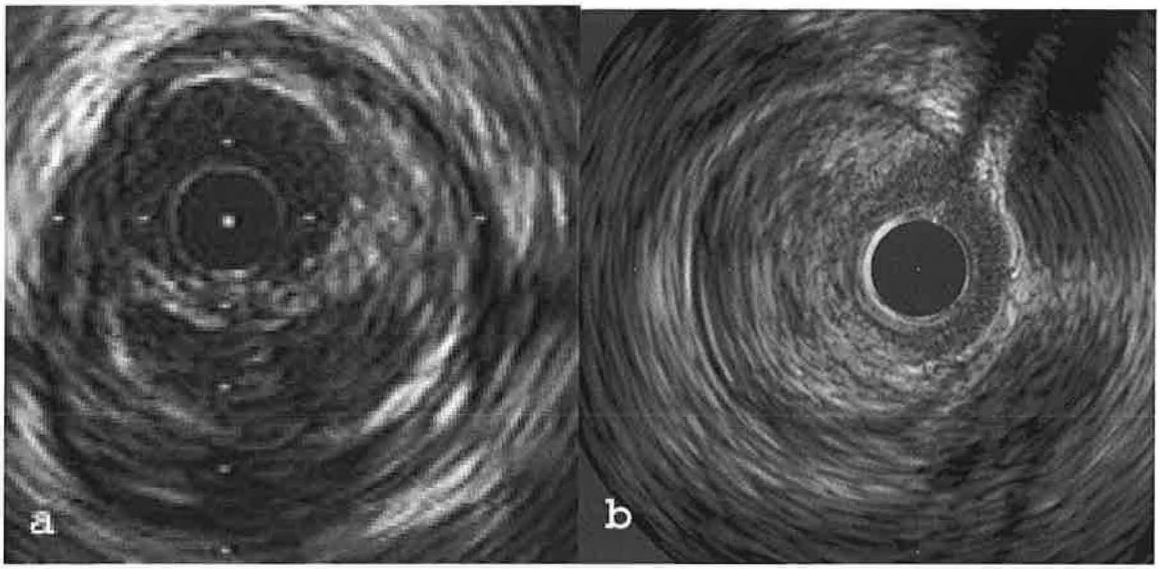
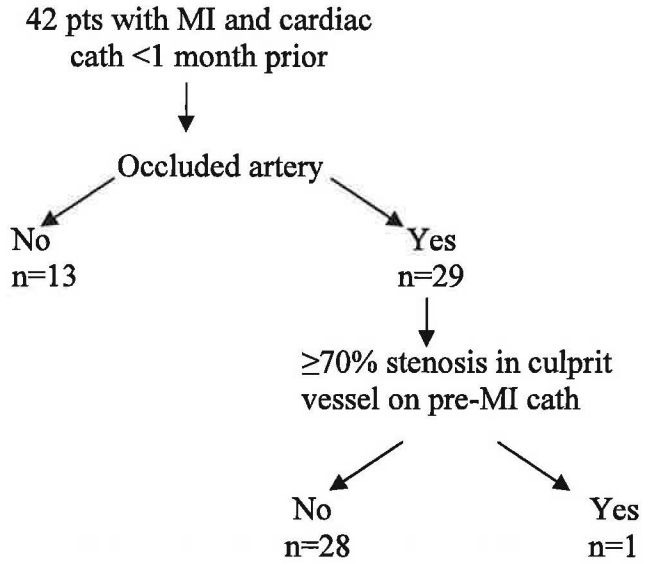


Figure 1. Coronary intravascular ultrasound pictures from left anterior descending coronary arteries showing a) a vulnerable plaque in an acute coronary syndrome patient with a large lipid core and a thin fibrous cap and b) a dense, more fibrotic plaque in a patient with longstanding angina

Overall estimates are that 18% of patients suffering a myocardial infarction have had preceding, long standing angina. Certainly, patients with chronic angina are at risk at risk for myocardial infarction, but the difficulty lies in predicting which atherosclerotic plaque will be the culprit. Two classic and similar studies by Ambrose(17) and Little(18) illustrate the difficulties in predicting the long and short term behavior of coronary artery plaques. In the latter study (Figure 2), 42 consecutive patients who had undergone coronary angiography within one month prior to sustaining an acute myocardial infarction underwent a subsequent coronary angiogram. Twenty-nine patients had a newly occluded coronary artery. All of the patients had visible coronary artery disease, however in 28 of 29 patients, the culprit stenosis leading to the coronary occlusion was <70% in severity. In 19 patients, the subsequently occluded artery had less than a 50% stenosis. In the similar study by Ambrose et al.(17), only 22% of patients presenting with a Q-wave infarction had an initial stenosis of >70% in the infarct artery. That group also studied a subset of patients that presented with an occluded artery without sustaining a MI, finding that 61% of lesions which progressed to total occlusion were >70% stenosed when studied during the initial catheterization. These studies reinforce that the point that the most of the lesions which go on to precipitate myocardial infarctions are not the lesions that are addressed during revascularization procedures, particularly percutaneous coronary interventions.

Figure 2. **Can coronary angiography predict site of subsequent myocardial infarction. (Adapted from Little et al. *Circulation* 1988;78:1157-66.)**



Some would argue that these observations are no longer applicable in an era where the modification of cardiovascular risk factors has reduced the incidence of myocardial infarction and death by approximately 30%. While this progress is undeniable, predicting plaques with a tendency towards instability remains difficult. This difficulty is highlighted in a modern study of 3747 PCI patients at 17 centers reporting to the National Heart, Lung and Blood Institute Dynamic Registry.(19) Of these 3747 patients undergoing PCI, 5.8% required a subsequent PCI at one year for progression of atherosclerotic plaque outside the original target stenosis. Clinical presentations of these patients were not just angina, as 59% presented with new unstable angina and 9.3% presented with a non-fatal myocardial infarction. Only 24% of patients had stable angina as their presenting symptom for the subsequent presentation. Just as in previous studies two decades prior, the majority of the lesions (86.9%) requiring subsequent PCI were ≤60% in severity.

Overall plaque burden plays a large role in the probability of progression of atherosclerosis. Simply said, the more plaques in the coronary vascular tree, the more opportunity exists for one of these plaques to progress and contribute to a clinical event. This is illustrated well in Figure 3 which shows the rates of subsequent PCI at one year in the NHLBI Dynamic Registry by the amount of coronary atherosclerosis noted on the initial angiogram.(19) Patients with angiographically visible disease in only one vessel had a rate of repeat non-target PCI of 4.4%, while those with visible non-obstructive disease in all three vessels had a rate of subsequent PCI of 12.8%.

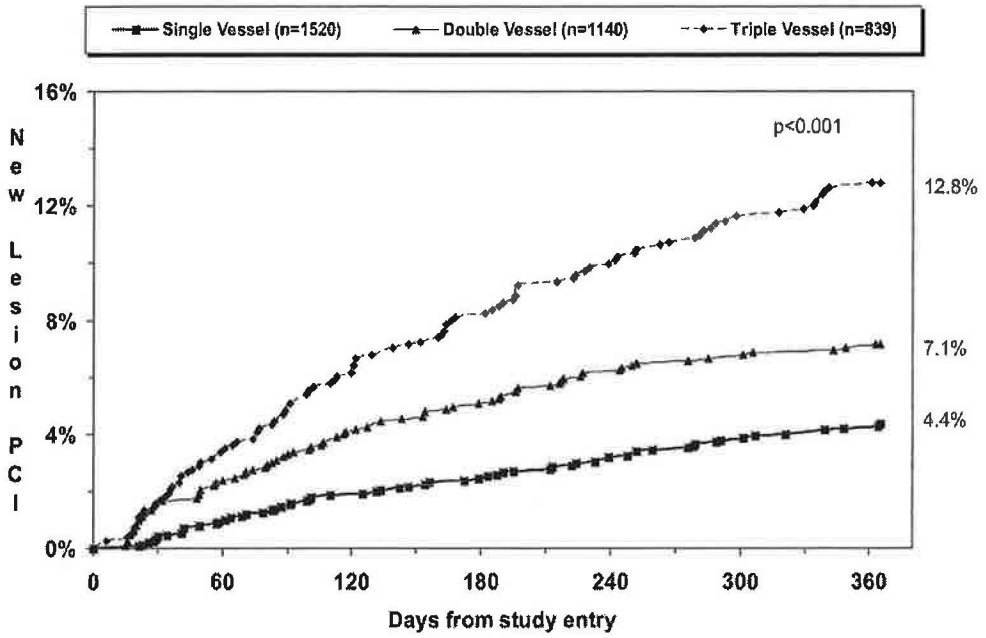


Figure 3. **Non-target lesion PCI at 1 year according to initial degree of coronary artery disease. Data from NHLBI Dynamic Data Registry (*Circulation* 2005;111:143-149)**

These observations, consistent over twenty years, reinforce the point that the risk of coronary occlusion is not proportional to the previous severity of stenosis. Severe stenoses, while responsible for angina, are at best a signal that many more non-obstructive plaques exist, most of them the angiographically subtle, lipid-filled lesions more likely to initiate an acute coronary syndrome and sudden cardiac death.

Percutaneous Coronary Intervention for Stable Coronary Disease

In the modern era, management of patients diagnosed with stable coronary artery disease frequently begins with percutaneous coronary intervention (PCI), even though guidelines support a trial of intensive medical therapy. Each year in the United States, over 1 million coronary stent procedures are performed, with the majority being elective patients in patients who are presumably stable. While the use of PCI in patients with acute coronary syndromes has been shown to reduce the subsequent incidence of myocardial infarction and death, these same benefits have not been shown to accrue in patients who receive PCI for stable coronary disease. Successful PCI of obstructive stenoses decreases the frequency of angina and has been shown to improve exercise tolerance, particularly in the immediate period following PCI.(20-22) Many patients and physicians have interpreted the improved results with PCI in a variety of clinical settings to mean that patients with stable coronary artery disease may have decreased rates of death, myocardial infarction and hospitalizations for acute coronary syndromes. Contributing to this widespread belief is that fact that the comparisons of PCI versus medical therapy are few and contain small numbers of patients, most of who were treated

before the widespread use of coronary artery stents and the adjunctive pharmacotherapy which has contributed to the safety of PCI.

COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) Trial

The first modern trial of PCI versus intensive medical therapy in the era of coronary stent-based percutaneous revascularization is the COURAGE trial.(23) Rather than testing medical therapy versus PCI, COURAGE was designed to examine whether adding PCI to optimal medical therapy reduces cardiovascular events, specifically death and non-fatal myocardial infarction. The trial included patients with stable coronary artery disease and patients with Canadian Class IV angina who stabilized on initial medical therapy. Patients had to have a stenosis of >70% on a coronary angiogram accompanied by either ischemic resting ECG changes or an abnormal stress test, or a stenosis of >80% accompanied by classic angina.

Importantly, patients were excluded if they had high risk variables including persistent CCS IV angina, a markedly positive exercise test (hypotension or positive during stage 1), refractory heart failure or shock, LVEF <30%, prior revascularization within 6 months, or anatomy unsuitable for PCI. Patients meeting these criteria were randomized to receive either PCI and optimal medical therapy or optimal medical therapy alone. The definition of optimal medical therapy was an aggressive one and included recommendations of all pertinent guidelines at the time the trial was initiated. The optimal medical treatment goals are described in Table 1.

Table 1. COURAGE Trial Optimal Medical Treatment Goals

Variable	Goal
Smoking	Cessation
Total Dietary Fat / Saturated Fat	<30% calories / <7% calories
Dietary Cholesterol	<200 mg/day
LDL cholesterol (primary goal)	60-85 mg/dL
HDL cholesterol (secondary goal)	>40 mg/dL
Triglyceride (secondary goal)	<150 mg/dL
Physical Activity	30-45 min. moderate intensity 5X/week
Body Weight by Body Mass index	Initial BMI — Weight Loss Goal 25-27.5 — BMI <25 >27.5 — 10% relative weight loss
Blood Pressure	<130/85 mmHg
Diabetes	HbAlc <7.0%

Table 2. COURAGE Pharmacologic Therapy

Medication Class	Protocol Drug(s)
Anti-platelet therapy	Aspirin; clopidogrel according to established practice standards
Lipid-lowering therapy	Simvastatin ± ezetimibe or ER niacin
ACE inhibitor or ARB	Lisinopril or losartan
Beta-blocker	Long-acting metoprolol
Calcium channel blocker	Amlodipine
Nitrate	5-mononitrate

The COURAGE trial was performed between 1999 and 2004. Males compromised 85% of the randomized patients. The average duration of angina prior to enrollment was 5 months. Most patients (95%) had objective evidence of myocardial ischemia with only 5% enrolled on the basis of angina and obstructive CAD alone. Two thirds of the patients had multi-vessel coronary artery disease. Prior myocardial infarction was present in 38% of patients with 15% of patients having prior PCI, and 11% having previous CABG. Diabetes was present in 33% of patients and was slightly more common in the optimal medical treatment group (p=0.12).

In the PCI group, PCI was successful 89% of the time, with success defined as all lesions dilated with no in-hospital complications. PCI was attempted for 1688 lesions in 1077 patients, with 94% of patients receiving at least one stent. Successful treatment by angiography was seen 1576 of 1688 lesions. In the stented patients, 41% received more than one stent. Drug-eluting stents were used in only 31 patients

COURAGE Results

At a median follow-up of 4.6 years, the primary outcome of freedom from death and myocardial infarction was not different between patients treated with medical therapy alone and those patients receiving PCI in addition to medical therapy (Figure 3). Nine percent of the patients were lost to follow-up, a finding not exclusive to either group. The rates of hospitalization for acute coronary syndromes were 12.4% in the PCI group and 11.8% in the medical-therapy group (p=0.56). No significant differences were noted in rates of myocardial infarction or stroke. The PCI group had higher rates of MI initially, due primarily to the 2.8% incidence of peri-procedural MI in PCI patients, a rate higher than expected in stable PCI patients. When these peri-procedural MIs were excluded, the MI rates were 16.2% in the PCI group compared with 17.9% in the medical therapy group (p=0.29). No particular subgroup benefited from either strategy, including women, diabetics, and patients with either single or multi-vessel coronary artery disease.

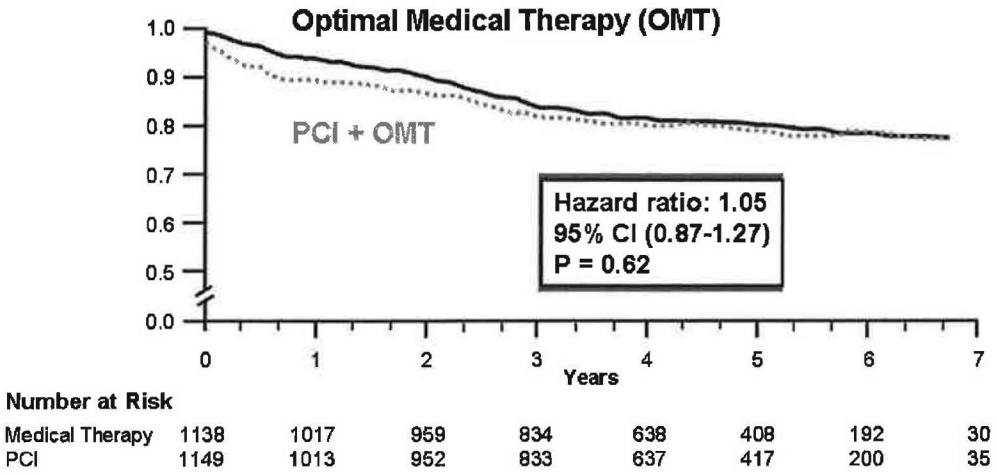


Figure 3. Survival Free from Death and Myocardial Infarction in COURAGE Trial (Reproduced with permission from Boden W et al. *NEJM* 2007;356:1512)

Significant reductions in angina were seen in both groups throughout the follow-up period. There was a small, but significant reduction in angina in favor of the PCI group throughout the majority of the follow-up period, however the difference at 5 years was not statistically significant (Table 4). At the median follow-up of 4.6 years, 32.6% of the patients in the optimal medical therapy group had undergone revascularization for angina refractory to medical therapy or worsening ischemia on non-invasive imaging (at the discretion of the patient's physician). The median time to revascularization in medically treated patients was 10.8 months. In the PCI group, 21.1% of patients required repeat revascularization at a median interval of 10 months. Approximately 7% of patients in both groups went on to eventual CABG during the follow-up period, a rate virtually identical in both groups.

Table 3. Freedom from Angina in COURAGE Trial Follow-up

Percent of Patients Free of Angina	PCI + OMT	OMT	P value
Baseline	**12%**	**13%**	
1 Yr	**66%**	**58%**	**P<0.001**
3 Yr	**72%**	**67%**	**P=0.02**
5 Yr	**74%**	**72%**	**P=0.35**

** PCI = percutaneous coronary intervention, OMT = optimal medical therapy

Efforts to modify risk factors in patients enrolled in the COURAGE trial were successful in regards to both lipid levels and blood pressure (Table 4). Efforts at improvement in weight loss, smoking cessation, and increased exercise were less successful.

Table 4. Improvements in Treatment Targets in COURAGE Trial

Treatment Targets	Baseline		60 Months	
	PCI +OMT	OMT	PCI +OMT	OMT
SBP	131 ± 0.77	130 ± 0.66	124 ± 0.81	122 ± 0.92
DBP	74 ± 0.33	74 ± 0.33	70 ± 0.81	70 ± 0.65
Total Cholesterol mg/dL	172 ± 1.37	177 ± 1.41	143 ± 1.74	140 ± 1.64
LDL mg/dL	100 ± 1.17	102 ± 1.22	71 ± 1.33	72 ± 1.21
HDL mg/dL	39 ± 0.39	39 ± 0.37	41 ± 0.67	41 ± 0.75
TG mg/dL	143 ± 2.96	149 ± 3.03	123 ± 4.13	131 ± 4.70
BMI kg/M²	28.7 ± 0.18	28.9 ± 0.17	29.2 ± 0.34	29.5 ± 0.31
Moderate Activity (5x/week)	25%	25%	42%	36%
Current smoker	23%	23%	19%	20%

** PCI = percutaneous coronary intervention, OMT = optimal medical therapy

The OAT (Open Artery Trial)

Additional support for the conclusions in COURAGE are provided by the OAT trial (24), which examined 2166 patients who were stable 3-28 days after sustaining a myocardial infarction and found to have total occlusions of their infarct-related artery at coronary angiography. All patients were classified as high-risk, having a left ventricular ejection fraction <50% or a proximal coronary occlusion. Patients were randomized to PCI with stenting and optimal medical therapy versus optimal medical therapy alone. Despite successful PCI in 87% of patients and infarct artery patency in 89% of patients in whom the initial PCI was successful, there was no difference in death, nonfatal myocardial infarction or NYHA Class IV heart failure in patients treated with PCI versus medical therapy (17.2% vs 15.6%, p=0.20) at a mean follow-up period of 3 years. There were significantly fewer patients with angina in the PCI group at 4 months and 1 year, but at 3 years there was no significant difference between groups (9.1% vs 10.3%, p=0.53). In patients assigned to medical therapy, 22.0% required subsequent revascularization compared with 18.4% of PCI patients (p=0.03). While one can make arguments that the routine use of drug-eluting stents would have resulted in less angina and revascularization in the PCI group, it is unlikely that their use would have impacted the primary end-points of death, MI or heart failure.

COURAGE Trial Conclusions and Implications for Clinical Practice

Like similar preceding studies, the COURAGE trial reaffirmed the strengths and limitations of percutaneous coronary intervention in the treatment of stable coronary artery disease. Skeptics of PCI will highlight the lack of benefit in terms of preventing death, myocardial infarction and hospitalizations for acute coronary syndromes. Adding to their argument is lack of long-term freedom form angina in PCI patients. Advocates for PCI will point to the fact that their was no penalty in outcomes in terms of death or myocardial infarction in patients treated with optimal medical therapy and initial PCI, highlighting the safety of PCI in the era of modern interventional cardiology. Throughout the majority of the follow-up period, PCI patients had lower rates of angina, an outcome likely to be improved in the era of markedly lower rates of restenosis seen with drug-eluting stents. Treatment with drug-eluting stents has been shown to reduce rates of target vessel revascularization by >50%, making it likely that the 21% of PCI patients requiring repeat revascularization would be markedly lower had they been treated with drug-eluting stents.

The real message of COURAGE is that optimal medical therapy should be the cornerstone of therapy in both patients treated solely with medications or with PCI. Efforts to meet guideline-mandated treatment goals are worthwhile and important to both groups of patients. It is worth noting that the medical therapy in COURAGE was very intensive and successful in relieving symptoms in two-thirds of patients. One should not extrapolate that incomplete efforts or partial guideline adherence will provide similar results. The other take-home point is that there certainly is no penalty for an initial treatment strategy of medical therapy, nor is there a penalty for up-front PCI. Individual decisions in consultation with patient preferences can be made with confidence in patients who meet the COURAGE criteria.

However, before generalizing the conclusions of COURAGE to all patients with stable cad, it is important to recognize the limitations of the study. Patients with significant left ventricular dysfunction or high risk findings on stress testing were excluded and the equivalence of these strategies is not known to be applicable to these patients. Indeed, in trials of coronary artery bypass grafting versus medical therapy, it is these patient groups who benefit most from an initial revascularization strategy.(25-29) It is also worth noting that most of the patients in COURAGE were men, and it is not know if these findings are as applicable to women. It is also worth noting that 38% of the patients in COURAGE were stable after a myocardial infarction, so those patients should not be exempt from the COURAGE and OAT conclusions. It is also notable that all patients in both COURAGE and OAT received angiography, and decisions regarding appropriateness of strategies were made after coronary artery anatomy was known. Treatment decisions made when coronary anatomy is unknown may not be appropriate in many patients.

Finally, the principal difference in both OAT and COURAGE in patients treated medically was the occurrence of angina and requirement for subsequent revascularization. It is likely that the lower rates of target vessel revascularization seen in

drug-eluting stent patients in clinical trials could tilt these variables in favor of PCI. However, in all trials of drug-eluting stents, rates of death and MI are similar in patient treated with drug-eluting stents or conventional bare-metal stents, so the repeating either the OAT trial or the COURAGE trial with drug-eluting stents is unlikely to affect the rates of death or myocardial infarction.

Revascularization Decisions in Stable Coronary Artery Disease Patients

Even when patients with stable CAD are treated with intensive medical therapy and aggressive life-style modifications, up to one-third of patients can be expected to fail medical therapy and require revascularization. The trials comparing coronary artery bypass surgery with medical therapy (25,29-32) are small and old, and conclusions are difficult to extrapolate in an era when both cardiac surgery and medical therapy are vastly improved. Performed in the 1970s, trials of CABG were shown convincingly to relieve angina and reduce the need for anti-anginal medications more effectively than medical therapy in a broad group of patients which included patients with acute coronary syndromes and stable angina. A mortality benefit was seen in patients with 1) three-vessel disease with a depressed left ventricular ejection fraction, 2) patient with multi-vessel disease and involvement of the proximal left anterior descending coronary artery and 3) patients with left main disease.

Today, most discussions in patients who require revascularization center on the options of PCI versus CABG. Recently, the introduction of drug-eluting stents (DES) has impacted this process, as dramatically lower rates of restenosis in DES patients have made their use more applicable in patients with multi-vessel disease and lesion subsets previously treated with CABG. The initial enthusiasm for the use of DES has been tempered somewhat by observations of an increase in late-stent thrombosis in DES-treated patients. While many patients and physicians strongly prefer percutaneous revascularization due to decreased short-term morbidity, the best revascularizations are made when one takes into account the strengths and weaknesses of both approaches.

Important Clinical Trials of Drug-Eluting Stents

The placement of drugs with anti-proliferative properties on coronary stents has provided a solution to the neointimal proliferation which characterized the restenosis process in patients who did not receive a durable result with a bare-metal stent. The additions of sirolimus and paclitaxel to drug-eluting coronary stents (DES) has provided dramatic decreases in angiographic and clinical restenosis, and DES implantation is now performed in approximately two-thirds of patients undergoing percutaneous coronary interventions (PCI), especially in the United States.

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. The most common primary endpoint utilized in these trials is **target vessel failure (TVF),** defined as the occurrence of any of the following in the interval following the index procedure: 1) death from cardiac causes,

2) Q-wave or non–Q-wave myocardial infarction, or 3) revascularization of the target vessel by coronary artery bypass grafting (CABG) or PCI.

The first trial of the currently available sirolimus-eluting stent platform (CYPHER® stent, Cordis Corporation) was the RAVEL trial.(33) 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. This has proved to be a durable result, with 87.9% of patients free from target vessel failure at three years, compared with 67.3% of patients receiving a bare metal stent.(34)

The SIRIUS trial was the first trial to examine the effect of a sirolimus-eluting stent in patients at high risk for restenosis.(35) This trial was designed to mirror clinical practice and included typical numbers of diabetics and excluded patients with short lesions and large diameter vessels. 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. These marked improvements in clinical outcomes were the basis for approval of the sirolimus-eluting Cypher stent by the FDA in April 2003.

Two follow-up trials (36,37) in Canada (C-SIRIUS) and Europe (E-SIRIUS) reported further improvements in angiographic restenosis, predominantly due to improvements in technique which eliminated much of the "edge" restenosis seen when segments adjacent to atherosclerotic lesions were dilated but not stented. The cumulative follow-up of these three similar SIRIUS trials has been published with a specific eye towards long-term safety and efficacy.(38,39) At 2 years, clinically driven revascularization was performed in 5.6% of patients who received sirolimus stents, versus 21.3% of patients receiving bare-metal stents (Figure 5) In this analysis, rates of stent thrombosis (sirolimus 0.6%, control 0.8%) and late revascularization were not different between groups suggesting preservation of the initial benefits seen at 9 months in these trials. (38)

The second drug to show efficacy when coupled with a coronary stent is paclitaxel, available as the TAXUS® stent platform (Boston Scientific Corp.). The landmark trial to date with paclitaxel-eluting stents is TAXUS IV(40), which enrolled patients at high risk for restenosis with patient and lesion demographics similar to the SIRIUS trials with sirolimus. The clinical results in the TAXUS IV trial were overwhelmingly positive. 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. 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. Follow-up TAXUS-V and TAXUS-VI trials established similar efficacy of TAXUS stents in patients with restenotic lesions(41) and longer stenoses.(42)

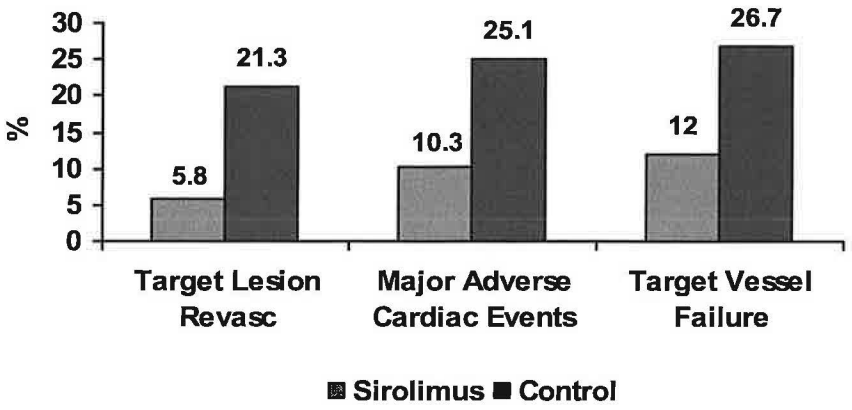


Figure 4. SIRIUS Trial Two-year Follow-up Clinical Events

Sub-Acute and Late Stent Drug-Eluting 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.(43) 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.(44) 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. 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. With improvements in techniques and better stent availability, and with many physicians choosing 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.(45)

More worrisome recently has been a series of large multi-center registry reports and recent pooled analyses of published drug-eluting stent trial data which shown increases in late drug-eluting stent thromboses.(46-49) Prior to drug-eluting stents, stent thrombosis risk was thought to be confined to the first month after stent implantation. The decreased neointima which defines the lower restenosis risk with drug-eluting stents 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. Furthermore, some patients may have delayed or impaired healing responses to drug-eluting stents and may be more prone to thrombosis, particularly when dual anti-platelet therapy with clopidogrel is discontinued. Data published in 2005 by Iakovou et al.(50) supports both of these hypotheses, with longer stents, bifurcation lesions and premature anti-platelet therapy discontinuation being anatomic predictors for stent thrombosis. Support for an attenuated healing response was seen as renal insufficiency, diabetes, and a decreased left ventricular ejection fraction were also predictors of stent thrombosis. In this "all-comers" patient population exclusive of primary angioplasty patients, the drug-eluting stent thrombosis rate was 1.3%, one-half of which occurred outside of a thirty-day window.

At this point in time, it appears that rates of drug-eluting stent thrombosis may be higher than those seen in clinical trials and may occur at later time intervals than previously thought. In October 2006, the FDA initiated an advisory panel to look specifically at this issue. Prior to this meeting, data was presented at the TCT 2006 Scientific Sessions and subsequently published showing an increase in stent thrombosis after the originally reported one-year of clinical follow-up.(51) This "very-late" stent thrombosis incidence was approximately 0.6-0.7%, bringing the overall rate of observed stent thrombosis to around 1.2-1.3%, similar to the rates reported in large registries of drug-eluting stent patients. What was not clear was whether this increase in late stent thrombosis translates into increased rates of death or MI, perhaps reflecting a balance between the risk of late thrombosis and the morbidity associated with increased rates of restenosis.(52)

Table 5. Four-Year Safety Follow-up in Cypher® and Taxus® Clinical Trials

Event	Cypher (%)	Bare-Metal (%)	p
Stent thrombosis	1.2	0.6	0.200
Late stent thrombosis (>1 yr)	0.6	0	0.025
MI	6.4	6.2	0.860
Death	6.7	5.2	0.190
Cardiac Death	3.5	2.6	0.320
Death or MI	11.6	10.3	0.390

Event	TAXUS (%)	Bare-Metal (%)	p
Stent thrombosis	1.3	0.9	0.290
Late stent thrombosis (>1 yr)	0.7	0.2	0.033
MI	7.0	6.3	0.640
Death	6.1	6.6	0.700
Cardiac Death	2.4	3.0	0.520
Death or MI	12.4	11.8	0.770

* Data presented at 2006 TCT Scientific Sessions and FDA Drug-eluting Stent Advisory Panel

At this point, there does appear be some increased risk of stent thrombosis outside the initial 3-6 month period where the majority of drug-eluting stent thrombosis was thought to occur. Preliminary data from patients followed in the Duke Cardiovascular Databank has suggested that prolonged therapy with the combination of aspirin and clopidogrel may reduce the risk of death and MI in patients receiving drug-eluting stents.(53) In the setting of this evolving information, several professional societies have come together to issue a joint guideline statement (Table 6) on the duration of dual anti-platelet therapy in drug-eluting stent patients.(54) In response to the dialogue at the FDA advisory meeting, industry has increased the follow-up of patients in DES clinical trials to 8 years and initiated large registries of drug-eluting stent patients. Careful follow-up of these patients should provide additional information about the intermediate and long-term benefits of drug-eluting stents, define the risk period for stent thrombosis, and confirm the optimal duration of dual-anti-platelet therapy.

Table 6. New Guidelines for Dual Anti-Platelet Therapy after Drug-Eluting Stents

- 1 month with Bare Metal Stent
- 12 months with Sirolimus-Eluting Stent
- 12 months with Paclitaxel-Eluting Stent
- Consider Bare Metal Stent if:
  - Upcoming surgery
  - Bleeding risk precludes long-term therapy with aspirin and clopidogrel

While the medical community remains focused on the safety issues surrounding drug-eluting stents, the overall clinical benefit in terms of reduction in restenosis and prevention of angina has more than justified their continued use. The FDA concluded that the overall clinical benefit exceeds the small risk of stent thrombosis when the stents are used for a labeled indication.(43) Concerns still exist as to the net clinical benefit when used outside the approved indications (such as in vein grafts, restenotic lesions, bifurcation disease, long lesions, etc.).(46,55) Information from ongoing trials and large registries should provide additional information on these issues in the coming two years.

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.

Trials of PCI versus CABG

There have now been 11 randomized trials (56-66) 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 (67) 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.(67) This disparity in results probably represents the extreme, as data from the BARI registry (68) and Duke Cardiovascular Disease Databank (69) 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.

Coronary Stenting versus CABG for Multi-Vessel Disease

The two large PCI versus CABG trials in the stent era are the ARTS (64) trial and the SOS (Stent or Surgery) trial.(66) 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. At 1 year, 2.5% of PCI patients had died compared to 2.8% of CABG patients. At 5 years, the PCI group mortality was 8.0% versus 7.6% in CABG patients.(70) There was no difference in rates of Q wave MI , non-Q wave MI or stroke, although the combined end-point occurred less frequently in the CABG group (14.9% vs 18.2%, p=0.14). At 1 year, 21% of patients assigned to PCI had undergone repeat revascularization versus 3.8% of CABG patients. At 5 years, additional revascularization was performed more frequently after PCI than CABG (30.3% versus 8.8%). After 3 years, surgery patients had less angina (15.5% vs. 21.2%), and had a lower rate of use of anti-anginal medications.

At 1-year, diabetic patients in ARTS 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 5 years, the mortality rate in PCI patients was 13.4% vs. 8.3% (p=0.27) in CABG patients. Overall, 61.3% of diabetic patients in the surgery group were free from death, MI, stroke or repeat revascularization, as compared to 45.5% of diabetic PCI patients.

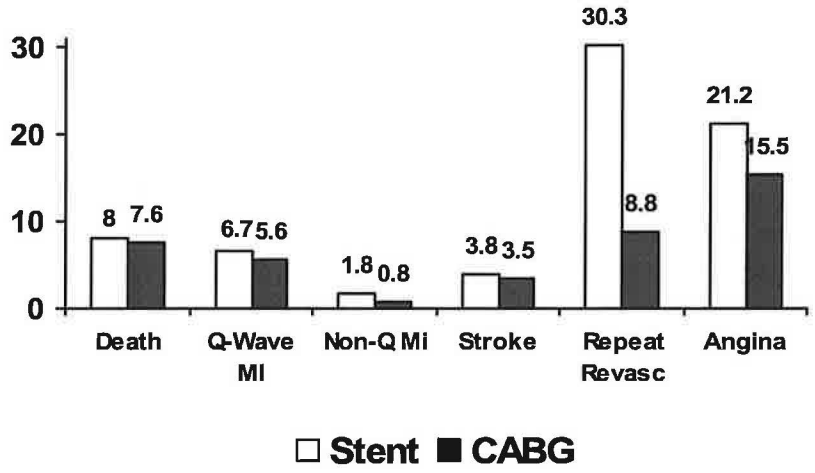


Figure 5. ARTS Five-Year Follow-up: Adverse Cardiac Events

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. This difference should be taken in context, however, as the overwhelming majority of patients are now angina-free with either revascularization

approach. Therefore, in non-diabetic patients at low risk for restenosis (discrete lesions in large vessels), a strategy of initial multi-vessel PCI seems 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. Five-year results of diabetic PCI patients in the ARTS trial are particularly sobering with 42.9% of patients requiring revascularization at 5 years compared with 10.4% 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, either alone or in combination with saphenous vein grafts.(71-73) 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.(74)

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. 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. Some of the best prospective data from the past decade comes from the VA Cooperative Study 297, in which 266 patients with 696 saphenous vein grafts underwent cardiac catheterization at 7-10 days, 1 year, and 3 years following CABG.(75) 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. The most recent trial to examine graft patency was the PREVENT-4 trial of an oligonucleotide decoy that binds to and inhibits E2F transcription factors and was thought to prevent neointimal hyperplasia and vein graft failure.(76) This strategy was negative but the control group provided a modern day look at patency rates in coronary artery bypass grafting (Figure 8). At 1 year, almost one-half of patients had at least one occluded graft, and approximately 30% of saphenous vein grafts were occluded.

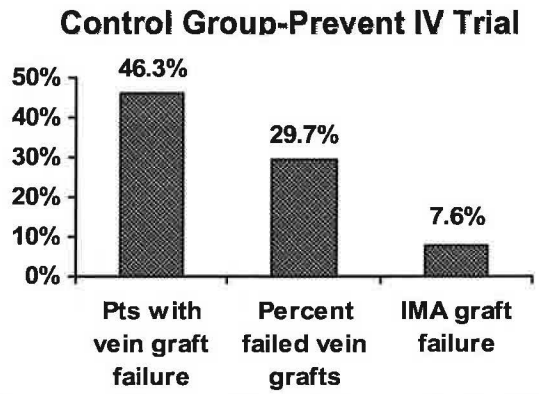


Figure 6. One Year Coronary Bypass Graft Patency in the PREVENT-IV Trial

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.

As an interim look at this question while randomized trials are ongoing, the ARTS investigators conducted ARTS II (77), a registry designed to enroll patients similar to those in ARTS I and treat them with drug-eluting stents and compare outcomes with ARTS I CABG and bare-metal stent patients. This comparison is inherently unfair as CABG and PCI techniques and post-procedure care continue to improve, a point highlighted by the low 5-year mortality (7.6%) seen in the CABG arm of the ARTS trial. However, even while taken in context, the 1-year event rates in the drug-eluting stent group are promising As shown in Table 7, despite more three vessel disease, more lesions, and more stents placed per patient, 91.5% of patients were free from repeat revascularization at one year, a number that compares favorably with the 95.9% rate seen

in the CABG group from ARTS I. Clinical MACCE rates were also similar in the drug-eluting stent and CABG groups (10.4% vs. 11.6% respectively). Similar improvements were noted in the diabetic patients.

Table 7. ARTS II Multi-vessel DES Registry vs ARTS I Trial

Event	ARTS II n-=607 (%)	ARTS I PCI n=600 (%)	ARTS I CABG n=605 (%)
Mortality	**1.0**	**2.7**	**2.7**
Stroke	**0.8**	**1.8**	**1.8**
MI	**1.2**	**5.0**	**3.5**
Repeat Revascularization			
CABG	**2.0**	**4.7**	**0.7**
PCI	**5.4**	**12.3**	**3.0**
ANY MACCE	**10.4**	**26.5**	**11.6**

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.(78-80) The protection afforded by bypass grafting in diabetic patients will need to be weighed against the increased morbidity and mortality of CABG. 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: PCI versus CABG

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. This information must be placed in context with additional forthcoming safety and efficacy long-term follow-up 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.

Conclusions: Medical Therapy or Revascularization for Stable Coronary Artery Disease

Despite two decades of consistent research findings, physicians and patients still struggle with the concept that severely obstructive stenoses in coronary arteries are not the main culprit for morbid follow-up events, namely myocardial infarctions and death. The fibrotic lesions which produce chronic angina are less likely to rupture and precipitate an acute coronary syndrome than are the subtle, non-obstructive lipid-filled plaques which more frequently populate the coronary vascular tree. For this reason, relief of severe coronary obstructions with percutaneous angioplasty and stenting is not protective against future myocardial infarction in most patients. A coronary artery bypass graft may be protective, but only if the subsequent plaque rupture is proximal to the graft insertion and the graft is patent.

The recent findings of the COURAGE and OAT clinical trials highlight the successes obtained with medical therapy over the past 20 years, showing that when patients are treated with intensive medical therapy combined with sustained lifestyle interventions, revascularization can be safely deferred. This observation is true for patients with multi-vessel disease and inducible ischemia, though this strategy has not been adequately tested in higher-risk patients. These results do not apply to those patients with markedly depressed left ventricular function and early positive exercise tests. Given less than 1 in 10 patients screened were enrolled in COURAGE and OAT, many patients with high risk anatomy were likely excluded, making conclusions as to the applicability of these data in these types of patients difficult. Most patients in COURAGE had symptoms of angina, and caution should be exercised in extending trial results to asymptomatic patients with a large burden of ischemia, a population which may be at higher risk when treated medically.(81) Finally, women and minorities are underrepresented in these trials and the conclusions may not be generalizable.

Approximately one-third of patients treated with an initial strategy of optimal medical therapy will require revascularization, either for symptoms or for a subsequent acute coronary syndrome. Decisions regarding revascularization should be based on the extent of coronary disease as well as the location. In patients without diabetes or left main disease, most patients can be treated with percutaneous intervention with equivalent outcomes to coronary bypass surgery. Diabetics with multi-vessel disease and patients with extensive atherosclerosis are likely to benefit from the protection that coronary artery bypass grafting provides against the progression of atherosclerosis. While coronary bypass surgery has traditionally provided better relief from angina, the lower restenosis rates seen with drug-eluting stents are likely to minimize that advantage and may tilt the scales in favor of coronary intervention for many patients. Drug-eluting stents, however, are unlikely to impact rates of death or myocardial infarction.

Above all, these trials highlight the point that patients receiving revascularization should also receive both optimal medical therapy and lifestyle modifications. While an upfront strategy of coronary intervention may not be preferable, coronary intervention performed

in "medically-optimized" patients provides symptom relief and comparable long-term outcomes. For patients with stable coronary disease, medical treatment and coronary intervention should be thought of as complementary, not mutually exclusive strategies.

References

1. Elveback LR CD. Coronary heart disease in residents of Rochester, Minnesota, V. Prognosis of patients with coronary heart disease based on initial manifestation. Mayo Clin Proc 1985;60:305-11.
2. Kannel WB FM. Natural history of angina pectoris in the Framingham study. Prognosis and survival. Am J Cardiol 1972;29:154-163.
3. Rosamond W, Flegal K, Friday G, et al. Heart Disease and Stroke Statistics--2007 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69-171.
4. Winstein K. Stent Use Declined in April. Wall Street Journal, 2007.
5. Feldman DN, Gade CL, Slotwiner AJ, et al. Comparison of outcomes of percutaneous coronary interventions in patients of three age groups (< 60, 60 to 80, and > 80 years) (from the New York State Angioplasty Registry). American Journal of Cardiology 2006;98:1334-1339.
6. Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. Propensity Analysis of Long-Term Survival After Surgical or Percutaneous Revascularization in Patients With Multivessel Coronary Artery Disease and High-Risk Features. Circulation 2004;109:2290-2295.
7. Hannan EL, Racz MJ, Walford G, et al. Long-Term Outcomes of Coronary-Artery Bypass Grafting versus Stent Implantation. N Engl J Med 2005;352:2174-2183.
8. Smith PK, Califf RM, Tuttle RH, et al. Selection of Surgical or Percutaneous Coronary Intervention Provides Differential Longevity Benefit. Ann Thorac Surg 2006;82:1420-1429.
9. van Domburg RT, Takkenberg JJM, Noordzij LJ, et al. Late Outcome After Stenting or Coronary Artery Bypass Surgery for the Treatment of Multivessel Disease: A Single-Center Matched-Propensity Controlled Cohort Study. Ann Thorac Surg 2005;79:1563-1569.
10. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction--Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004;110:588-636.
11. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of Early Invasive and Conservative Strategies in Patients with Unstable Coronary Syndromes Treated with the Glycoprotein IIb/IIIa Inhibitor Tirofiban. N Engl J Med 2001;344:1879-1887.
12. Fox KAA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Lancet 2002;360:743-751.
13. Mehta SR, Cannon CP, Fox KAA, et al. Routine vs Selective Invasive Strategies in Patients With Acute Coronary Syndromes: A Collaborative Meta-analysis of Randomized Trials. JAMA 2005;293:2908-2917.
14. Wallentin L, Swahn E, Kontny F, et al. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999;354:708-715.
15. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient - A call for new definitions and risk assessment strategies: Part I. Circulation 2003;108:1664-1672.
16. Elveback LR CD, Melton LJ III. Coronary heart disease in residents of Rochester, Minnesota 7. Incidence, 1950 through 1982. Mayo Clin Proc 1986;61:896-900.
17. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56-62.
18. Little WC, Constantinescu M, Applegate RJ, et al. Can Coronary Angiography Predict the Site of a Subsequent Myocardial-Infarction in Patients with Mild-to-Moderate Coronary-Artery Disease. Circulation 1988;78:1157-1166.

19. Glaser R, Selzer F, Faxon DP, et al. Clinical Progression of Incidental, Asymptomatic Lesions Discovered During Culprit Vessel Coronary Intervention. Circulation 2005;111:143-149.
20. Chamberlain DA, Fox KAA, Henderson RA, et al. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. Lancet 1997;350:461-468.
21. Henderson RA, Pocock SJ, Clayton TC, et al. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. J Am Coll Cardiol 2003;42:1161-1170.
22. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. N Engl J Med 1992;326:10-16.
23. Boden WE, O'Rourke RA, Teo KK, et al. Optimal Medical Therapy with or without PCI for Stable Coronary Disease. N Engl J Med 2007;356:1503-1516.
24. Hochman JS, Lamas GA, Buller CE, et al. Coronary Intervention for Persistent Occlusion after Myocardial Infarction. N Engl J Med 2006;355:2395-2407.
25. Eleven-year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina. The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. N Engl J Med 1984;311:1333-1339.
26. Alderman EL, Bourassa MG, Cohen LS, et al. Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. Circulation 1990;82:1629-1646.
27. Authors/Task Force, Fox K, Garcia MAA, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27:1341-1381.
28. Smith SC, Jr., Feldman TE, Hirshfeld JW, Jr., et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention--Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:216-235.
29. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. N Engl J Med 1988;319:332-337.
30. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. N Engl J Med 1985;312:1665-71.
31. Booth DC, Deupree RH, Hultgren HN, DeMaria AN, Scott SM, Luchi RJ. Quality of life after bypass surgery for unstable angina. 5-year follow- up results of a Veterans Affairs Cooperative Study. Circulation 1991;83:87-95.
32. Russell RO,Jr, et al. Unstable angina pectoris: National Cooperative Study Group to Compare Medical and Surgical Therapy. Am J Cardiol 1978;42:839-48.
33. Morice M-C, Serruys PW, Sousa JE, et al. A Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization. N Engl J Med 2002;346:1773-1780.
34. Fajadet J, Morice M-C, Bode C, et al. Maintenance of long-term clinical benefit with sirolimus-eluting coronary stents: three-year results of the RAVEL trial. Circulation 2005;111:1040-4.
35. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery. N Engl J Med 2003;349:1315-1323.
36. Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll of Cardiol 2004;43:1110-5.
37. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362:1093-9.
38. Schampaert E, Moses JW, Schofer J, et al. Sirolimus-Eluting Stents at Two Years: A Pooled Analysis of SIRIUS, E-SIRIUS, and C-SIRIUS With Emphasis on Late Revascularizations and Stent Thromboses. Am J Cardiol 2006;98:36-41.
39. Weisz G, Leon MB, Holmes JDR, et al. Two-Year Outcomes After Sirolimus-Eluting Stent Implantation: Results From the Sirolimus-Eluting Stent in de Novo Native Coronary Lesions (SIRIUS) Trial. J Am Coll Cardiol 2006;47:1350-1355.
40. Stone GW, Ellis SG, Cox DA, et al. A Polymer-Based, Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease. N Engl J Med 2004;350:221-231.

41. Stone GW, Ellis SG, O'Shaughnessy CD, et al. Paclitaxel-Eluting Stents vs Vascular Brachytherapy for In-Stent Restenosis Within Bare-Metal Stents: The TAXUS V ISR Randomized Trial. JAMA 2006;295:1253-1263.
42. Dawkins KD, Grube E, Guagliumi G, et al. Clinical Efficacy of Polymer-Based Paclitaxel-Eluting Stents in the Treatment of Complex, Long Coronary Artery Lesions From a Multicenter, Randomized Trial: Support for the Use of Drug-Eluting Stents in Contemporary Clinical Practice. Circulation 2005;112:3306-3313.
43. FDA Statement on Coronary Drug-Eluting Stents
44. Cutlip DE, Baim DS, Ho KKL, et al. Stent Thrombosis in the Modern Era : A Pooled Analysis of Multicenter Coronary Stent Clinical Trials. Circulation 2001;103:1967-1971.
45. Regar E, Lemos PA, Saia F, et al. Incidence of thrombotic stent occlusion during the first three months after sirolimus-eluting stent implantation in 500 consecutive patients. Am J Cardiol 2004;93:1271-1275.
46. Beohar N, Davidson CJ, Kip KE, et al. Outcomes and Complications Associated With Off-Label and Untested Use of Drug-Eluting Stents. JAMA 2007;297:1992-2000.
47. Ellis SG, Colombo A, Grube E, et al. Incidence, Timing, and Correlates of Stent Thrombosis With the Polymeric Paclitaxel Drug-Eluting Stent: A TAXUS II, IV, V, and VI Meta-Analysis of 3,445 Patients Followed for Up to 3 Years. J Am Coll Cardiol 2007;49:1043-1051.
48. Jaffe R, Strauss BH. Late and Very Late Thrombosis of Drug-Eluting Stents: Evolving Concepts and Perspectives. J Am Coll Cardiol 2007;50:1-9.
49. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late Clinical Events After Clopidogrel Discontinuation May Limit the Benefit of Drug-Eluting Stents: An Observational Study of Drug-Eluting Versus Bare-Metal Stents. J Am Coll Cardiol 2006;48:2584-2591.
50. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, Predictors, and Outcome of Thrombosis After Successful Implantation of Drug-Eluting Stents. JAMA 2005;293:2126-2130.
51. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020-9.
52. Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. Am Heart J 2006;151:1260-1264.
53. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel Use and Long-term Clinical Outcomes After Drug-Eluting Stent Implantation. JAMA 2007;297:159-168.
54. Grines CL, Bonow RO, Casey DE, Jr., et al. Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents: A Science Advisory From the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, With Representation From the American College of Physicians. J Am Coll Cardiol 2007;49:734-739.
55. Win HK, Caldera AE, Maresh K, et al. Clinical Outcomes and Stent Thrombosis Following Off-Label Use of Drug-Eluting Stents. JAMA 2007;297:2001-2009.
56. Favarato D, Hueb W, Gersh BJ, et al. Relative Cost Comparison of Treatments for Coronary Artery Disease: The First Year Follow-Up of MASS II Study. Circulation 2003;108:II-21-23.
57. Hamm CW, Reimers J, Ischinger T, et al. A Randomized Study of Coronary Angioplasty Compared with Bypass Surgery in Patients with Symptomatic Multivessel Coronary Disease. N Engl J Med 1994;331:1037-1043.
58. King SB, Lembo NJ, Weintraub WS, et al. A Randomized Trial Comparing Coronary Angioplasty with Coronary Bypass Surgery. N Engl J Med 1994;331:1044-1050.
59. Morrison DA, Sethi G, Sacks J, et al. Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. J Am Coll Cardiol 2001;38:143-149.
60. Participants. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). Lancet 1995;346:1179-1184.
61. Participants. Coronary angioplasty versus coronary artery bypass surgery: the Randomised Intervention Treatment of Angina (RITA) trial. Lancet 1993;341:573-580.

62. Rodriguez A, Bernardi V, Navia J, et al. Argentine randomized study: coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple-vessel disease (ERACI II): 30-day and one-year follow-up results. J Am Coll Cardiol 2001;37:51-58.
63. Rodriguez A, Boullon F, Perez-Balino N, Paviotti C, Liprandi MI, Palacios IF. Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease (ERACI): in-hospital results and 1-year follow-up. ERACI Group. J Am Coll Cardiol 1993;22:1060-1067.
64. Serruys PW, Unger F, Sousa JE, et al. Comparison of Coronary-Artery Bypass Surgery and Stenting for the Treatment of Multivessel Disease. N Engl J Med 2001;344:1117-1124.
65. The Bypass Angioplasty Revascularization Investigation I. Comparison of Coronary Bypass Surgery with Angioplasty in Patients with Multivessel Disease. N Engl J Med 1996;335:217-225.
66. Zhang Z, Mahoney EM, Stables RH, et al. Disease-Specific Health Status After Stent-Assisted Percutaneous Coronary Intervention and Coronary Artery Bypass Surgery: One-Year Results From the Stent or Surgery Trial. Circulation 2003;108:1694-1700.
67. Investigators TB. Influence of Diabetes on 5-Year Mortality and Morbidity in a Randomized Trial Comparing CABG and PTCA in Patients With Multivessel Disease : The Bypass Angioplasty Revascularization Investigation (BARI). Circulation 1997;96:1761-1769.
68. Feit F, Brooks MM, Sopko G, et al. Long-Term Clinical Outcome in the Bypass Angioplasty Revascularization Investigation Registry : Comparison With the Randomized Trial. Circulation 2000;101:2795-2802.
69. Barsness GW, Peterson ED, Ohman EM, et al. Relationship Between Diabetes Mellitus and Long-term Survival After Coronary Bypass and Angioplasty. Circulation 1997;96:2551-2556.
70. Serruys PW, Ong ATL, van Herwerden LA, et al. Five-Year Outcomes After Coronary Stenting Versus Bypass Surgery for the Treatment of Multivessel Disease: The Final Analysis of the Arterial Revascularization Therapies Study (ARTS) Randomized Trial. J Am Coll Cardiol 2005;46:575-581.
71. Cameron A, Davis KB, Green G, Schaff HV. Coronary Bypass Surgery with Internal-Thoracic-Artery Grafts -- Effects on Survival over a 15-Year Period. N Engl J Med 1996;334:216-220.
72. Lytle BW, Loop FD, Cosgrove DM, Ratliff NB, Easley K, Taylor PC. Long-term (5 to 12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts. J Thorac Cardiovasc Surg 1985;89:248-258.
73. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. Lancet 2001;358:870-875.
74. Strong J ED, Oalmann M. The natural history, geographic pathology, and epidemiology of atherosclerosis In: Wissler R GJ, ed. in The Pathogenesis of Atherosclerosis. Baltimore, MD: Williams & Wilkins, 1972:20.
75. Goldman S, Zadina K, Krasnicka B, et al. Predictors of graft patency 3 years after coronary artery bypass graft surgery. Department of Veterans Affairs Cooperative Study Group No. 297. J Am Coll Cardiol 1997;29:1563-1568.
76. Investigators PI. Efficacy and Safety of Edifoligide, an E2F Transcription Factor Decoy, for Prevention of Vein Graft Failure Following Coronary Artery Bypass Graft Surgery: PREVENT IV: A Randomized Controlled Trial. JAMA 2005;294:2446-2454.
77. Serruys PW OA, Morice MT et al. Arterial Revascularisation Therapies Study part II—sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary lesions. Eurointervention 2005;1:147-156.
78. Ellis SG, Narins CR. Problem of Angioplasty in Diabetics. Circulation 1997;96:1707-1710.
79. O'Neill WW. Multivessel balloon angioplasty should be abandoned in diabetic patients! J Am Coll Cardiol 1998;31:20-22.
80. Rozenman Y, Sapoznikov D, Mosseri M, et al. Long-Term Angiographic Follow-Up of Coronary Balloon Angioplasty in Patients With Diabetes Mellitus: A Clue to the Explanation of the Results of the BARI Study. J Am Coll Cardiol 1997;30:1420-1425.
81. Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997;95:2037-43.