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ReFlections

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LETTER FROM THE EDITOR

Dear Readers:

This entire edition of *ReFlections* is devoted to the topic of underwriting coronary artery revascularization procedures. Its author, Dr. Oscar Cartaya, examines the challenges faced in underwriting complex medical cases in which information about coronary artery revascularization has been provided. He helps underwriters understand the clinical information that is available on attending physician's reports and correlates it to the science of risk selection.

I hope you enjoy reading this article as much as I did!

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UNDERWRITING CORONARY ARTERY REVASCULARIZATION PROCEDURES

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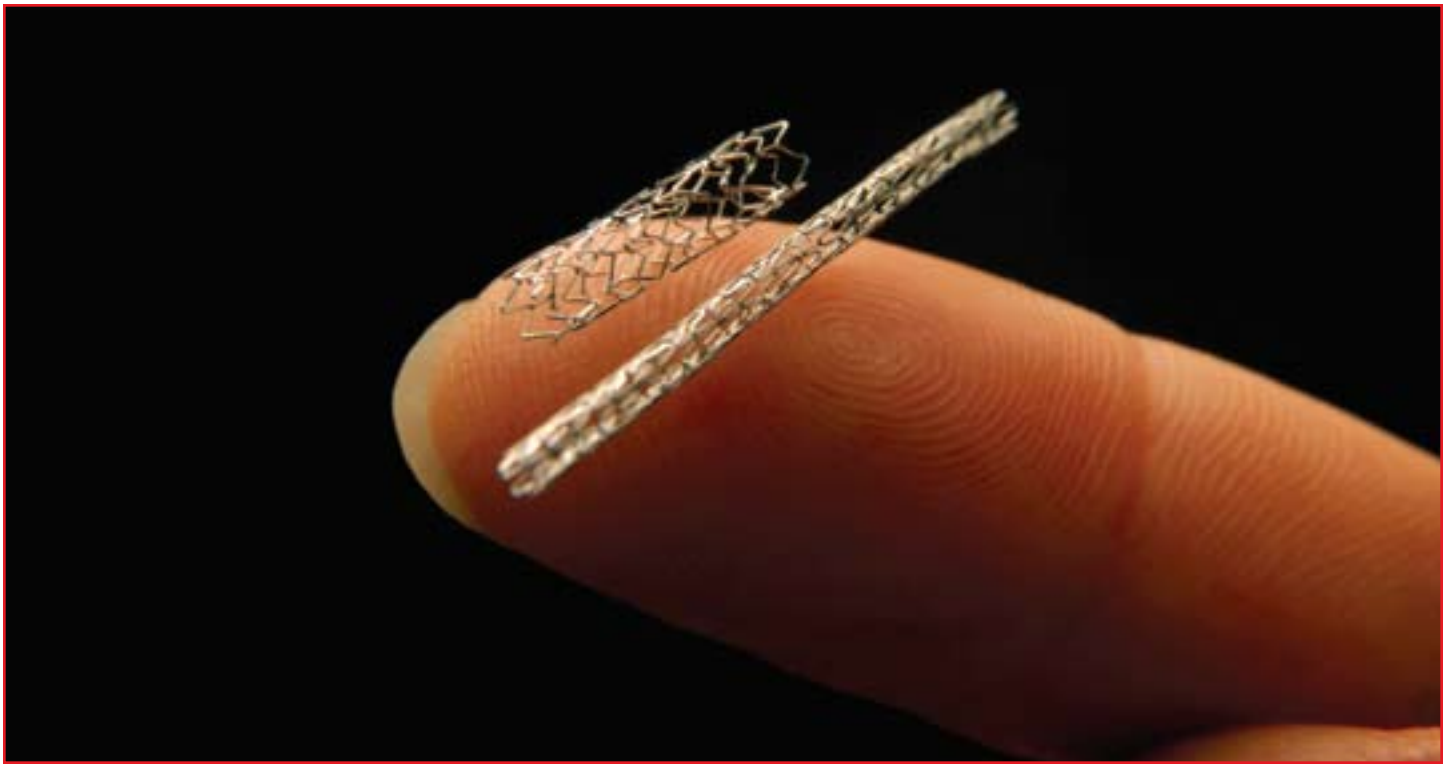
The treatment of Coronary Artery Disease (CAD) has improved significantly in the last few decades, resulting in a marked decrease in the mortality associated with this disorder. A significant portion of the improved success in the treatment of CAD has been due to the development of increasingly effective coronary artery revascularization procedures. These procedures are now bundled together under the name Percutaneous Coronary Intervention (PCI). They have achieved widespread acceptance and are used worldwide, with the increase in the use of revascularization treatments paralleling the decrease in CAD mortality.

In the U.S. alone more than half a million revascularization procedures are performed each year, and the use of these procedures is also increasing rapidly in the rest of the world. The initial limitations and problems associated with these procedures have been minimized by newer procedures and techniques. The standard percutaneous coronary angioplasty (PTCA) procedure is currently performed in less than 30% of all cases; while about 70% of the cases receive stents in the U.S., with the rest of the world following these trends closely.

Although these trends are generally positive, there are problems associated with the proliferation of the newer revascularization techniques. Many of these techniques have been developed for special situations, like total occlusion of a coronary artery, but are being used in a widespread fashion. Drug eluting stents elute a large variety of different therapeutic agents, but there is a lack of valid medical research and general information about outcomes produced by the substances being eluted. Particularly problematic is the lack of long-term mortality statistics, which are unavailable for many of these newer revascularization techniques.

This article does not in any way attempt to minimize the advances in the medical treatment of CAD. A number of new medical interventions have gained widespread usage over this period of time. Some of these have been preventative in nature, for example the widespread use of statins to lower the rate of progression of CAD; others have been targeted to the early identification of individuals with a greater risk of developing early CAD, like the coronary calcium scores produced by specialized scans; and yet others have been focused on better control and treatment of arrhythmias. All of these medical therapeutic approaches have produced positive outcomes and contributed to the overall reduction of CAD mortality. However these medical therapeutic approaches will not be discussed further in this article.

This article is an attempt to review specific aspects of the PCI procedures, particularly in relation to their effect



upon the overall reduction in mortality from CAD. It is not intended to be a comprehensive review of the PCI field. I intend to focus on the difficulties associated with underwriting CAD cases treated with PCI. Underwriting is not an exact science that can be applied based upon strict rules; much of the underwriting process is determined by the availability of information at the time a decision is made. I intend to document the difficulties in underwriting these cases properly when the information available is less than complete, and provide valid data to evaluate the multiple complications found with PCI procedures.

To start this process, I will present an actual case without any identifying information about the applicant or company sending this case:

CASE #1

Male, 59 years of age, smoker, 5 feet 7 inches, 180 lbs., who drinks one beer daily, and is collecting disability for chronic back pain treated with hydrocodone. This man has a very significant family history of early CAD. His mother had died of a myocardial infarction (MI) before age 60; both of his brothers had received multiple coronary bypass grafts at an early age, one at age 48. He had no personal prior cardiac history until a hospitalization in 2004 for persistent chest pain.

Because of his family history, an extensive work-up was done which showed very little: He had an EKG with a Q wave in III, and sinus bradycardia. A treadmill exercise test (TM) was done which was stopped after 9 minutes of exercise and read as negative for ischemia by the treating physicians. A nuclear perfusion scan was done at that time which showed no redistribution but did show mild hypokinesis of the septum and an ejection fraction of 54%.

Summarizing this case up to this point, this man had essentially a significant family history of CAD with a 2004 history of persistent chest pain and a cardiac work-up that included a TM and a perfusion test which were not diagnostic, although they had some minor changes. Assuming this was all the information available for underwriting purposes, a low rating might have been a correct way to assess the risk involved in this case.

However, in this case the treating doctor was highly concerned about this man's family history, so a cardiac catheterization was done with full coronary angiography. The angiogram was highly abnormal; it documented a very long obstructing lesion of the right coronary artery, with a variable degree of obstruction between 75% and 90%. The other vessels were free of disease or had minor (not hemodynamically significant) amounts of plaque.

Therefore, the case's underwriting assessment changed with the cardiac catheterization results. This man not only

has a significant family history of CAD, and symptoms compatible with CAD, but has documented single vessel disease of the right coronary artery. Of course the size of the single vessel obstruction should raise questions about the actual severity of this man's disease among the reviewing underwriters. Is a long single vessel obstruction worse, in terms of mortality risk, than a well-defined discrete obstruction? Yes, indeed it is, because the procedure to relieve the obstruction is much harder to perform and requires a longer duration for the balloon inflation to reduce the obstruction in a long lesion. Cases with long high-grade obstructions are much more prone to complications during the revascularization procedure.

In this particular case, the long lesion of the RCA was treated with stenting. The procedure to place the stent went without problems until the balloon was inflated to exert pressure on the lesion. An initial two-minute balloon inflation was done in this case. Following this initial balloon inflation, the patient went into severe bradycardia with hypokinesis which did not respond to drugs, and which progressed into full asystole, which was then treated successfully with cardiopulmonary resuscitation.

Following the resuscitation procedure, a second, again lengthy, inflation of the balloon was performed which relieved the obstruction, but which caused blood flow through the right coronary artery to cease until intravenous nitrates were administered.

This man suffered an acute MI as a result of his revascularization procedure which resulted in the obstruction of two small branches of his right coronary artery following the procedure described. He developed the typical electrocardiographic ST elevations and enzyme changes indicative of an MI after his revascularization. In the period of time immediately following this procedure, this patient developed two episodes of non-sustained ventricular tachycardia. He was discharged two days later with a normal echo. From an underwriting point of view, these complications during and following PCI appear to indicate a poor prognosis. However, these complications are not an uncommon occurrence during PCI, and will not increase the overall mortality risk after the acute peri-procedural time.

The events described occurred in mid-2004. The patient has currently applied for a large amount of insurance coverage. Review of the records since the 2004 PCI procedure reveals no cardiology follow-up since 2004. He required however additional back surgery in 2005 and had a TM (treadmill test) with Cardiolite testing done prior to the surgery. These tests were negative with the exception of a low ejection fraction in the cardiolite test. He was also seen by his doctor (a new physician) in 2007, complaining of chest pain and persistent shortness of breath. A cardiac work-up was not done in 2007.

The question, of course is whether a current offer can be made in this case and how severe is his CAD likely to be at this time, taking into account the lack of follow up in this case. The back surgery in 2005 indicates his heart condition was stable enough at that time to allow him to have a successful back surgery. The question is – how to rate this case?

I will not provide a direct answer to the question of the appropriate rating for this case, but I am using this case as an example to point out the great variability of complications and outcomes that have been documented in this specific case and which can be expected after a PCI procedure in any patient. Underwriting these cases can be difficult and requires familiarity with the procedures used, the complications that can be expected, and the overall long-term outcome expected.

Review of Progress in Surgical Coronary Revascularization Procedures

The majority of the information that follows has been developed over the last 20 years, as the ranking of PCI rose to become the dominant form of treatment for CAD that it is now. It must be understood that the only PCI procedure that has been studied in depth and for which valid long-term mortality statistics exist is the original PTCA procedure which has been largely replaced by stenting in its many forms. PCI, the percutaneous approach to coronary revascularization, has replaced the open heart Coronary Artery Bypass Graft (CABG) as the revascularization procedure of choice because of the higher cost and complexity involved in the CABG procedures. However, for certain population subgroups and certain kinds of lesions, CABG is still the treatment of choice with long-term mortality results that are better than those for PCI.

A PCI procedure should only be attempted by well trained personnel in adequately equipped labs capable of dealing with the complications that can occur with this procedure. It must be remembered that patients undergoing PCI have significant CAD and that peri-operative complications with PCI procedures are common. The mere process of inserting a catheter and inflating balloons in the heart's vasculature is risky and capable of causing damage to the vessels; the dyes used for visualization can cause allergic reactions and

nephrotoxicity; and life-threatening arrhythmias and hypotension can and do occur during these procedures and can cause any number of cerebrovascular and renal complications. A list of PCI post-operative and peri-operative complications has been published by the American College of Cardiology (ACC), as follows:

Post Operative Complications after PCI

1. Death.
2. Acute MI: diagnosed by EKG changes including new left bundle branch block (LBBB) or elevated CPK (creatinine phosphokinase) X3 times normal after the procedure.
3. Emergency CABG, usually done to salvage the patient after severe vascular disruption secondary to the PCI procedure.
4. Cerebrovascular Accident (CVA) with neurological deficits persisting over 24 hours after the procedure.
5. Local vascular complications: Bleeding which can be occult (i.e., Retroperitoneal) and cause significant loss of blood; occlusion of the vessel, usually at the site of entry of the catheters used; dissection, usually at the site of entry of the catheters used; pseudoaneurysm, usually at the site of entry of the catheters used; AV (arteriovenous) fistula formation, usually at the site of entry of the catheters used.
6. Renal failure, usually as a result of bleeding, hypotension, or an allergic reaction to the dyes used.

Most of the studies noted in this article do not include the risk or mortality contributions due to renal failure or local vascular complications in their outcomes calculations. The true overall mortality is likely to be higher to some degree than the levels represented in these studies.

As we have seen in the case just presented, acute MIs during a PCI are common, even in the best centers and using the best techniques. This is only logical since PCI requires the temporary occlusion of an obstructed or partially obstructed coronary artery with a balloon while pressure is exerted to relieve the obstruction caused by plaque. Elevations of the cardiac enzymes after PCI are very common. The ACC has published guidelines indicating elevations of the CPK-MB (creatinine phosphokinase of myocardial origin) over normal levels in 10% to 15% of all PTCA procedures, 15% to 20% of all stenting procedures, 25% to 35% of all atherectomy procedures, and over 25% of all CABGs, and cases involving a long lesion in a coronary artery. Any elevations of the CPK-MB to over 3X normal is considered an acute peri-operative MI, even in the absence of Q waves. However even in cases where an acute peri-operative MI is not diagnosed; elevations of the CPK-MB to lower levels indicate some degree of myocardial damage during PCI.

Serious peri-operative complications with severe outcomes are not uncommon with PCI. ACC data indicates an expected incidence of peri-operative all cause mortality during hospitalization of 0.5% to 1.4%, a peri-operative incidence of full Q wave MIs of 1.0% to 3.0%, and peri-operative emergency CABG rates of 0.2% to 3.0%. However, the rate of peri-operative complications is made up by significant increases in life expectancy and significant decreases in the incidence of subsequent coronary events.

The early studies of the effectiveness of PCI procedures showed improved survival and a lower rate of repeat cardiac events compared with medical therapy treatment alone. For example, the ACIP (Asymptomatic Cardiac Ischemia Pilot) study determined the two-year outcomes of patients with severe CAD and ischemia diagnosed by exercise testing. The results compared survival and occurrence of further cardiac events in patients treated with PTCA or with two different types of intensive medical regimes: angina-guided therapy and ischemia-guided therapy. The results showed a much favorable outcome for the patients treated with PCI as follows:

Two-year outcomes of medical vs. PTCA treatment

	Death	Death or MI	Death or MI or Hospitalized
Angina-Guided	6.6%	12.1%	41.8%
Ischemia-Guided	1.4%	8.8%	38.5%
Revascularization	1.1%	4.7%	23.1%

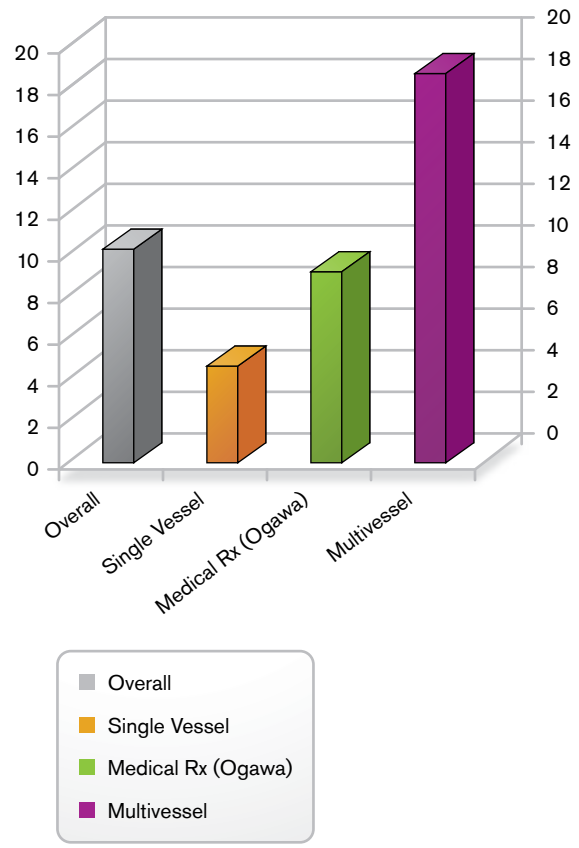
The results of the ACIP study of 1997 have been supported by a number of other studies. For example the BARI study (Bypass Angioplasty Revascularization Investigation), with its final report published in 2007, showed the following:

1. 10-year survival after PCI: Overall survival 89.5%, survival with single-vessel disease 95%, survival with multi-vessel disease 81%.
2. 5-year survival after PCI: Overall survival 86.3% (infarct free survival overall 78.7%), two-vessel disease 87.6%, three-vessel disease 84.7%.

This study did not compare survival of medically treated patients vs. patients treated with PCI. With increased use worldwide of PCI as the treatment of choice for CAD, it has become very difficult to find reasonable studies of survival of medically treated CAD patients in the literature. One such study was done by Ogawa in Japan giving the 10-year survival rate for patients with single-vessel CAD and an MI at 90.4%.

The following table is a graphical representation of the 10-year mortality rates found by the BARI study and the medical treatment only mortality rates in the Ogawa study:

10-Year Mortality Rates in Patients Treated with PCI (BARI) and by Medical Therapy Alone (Ogawa)



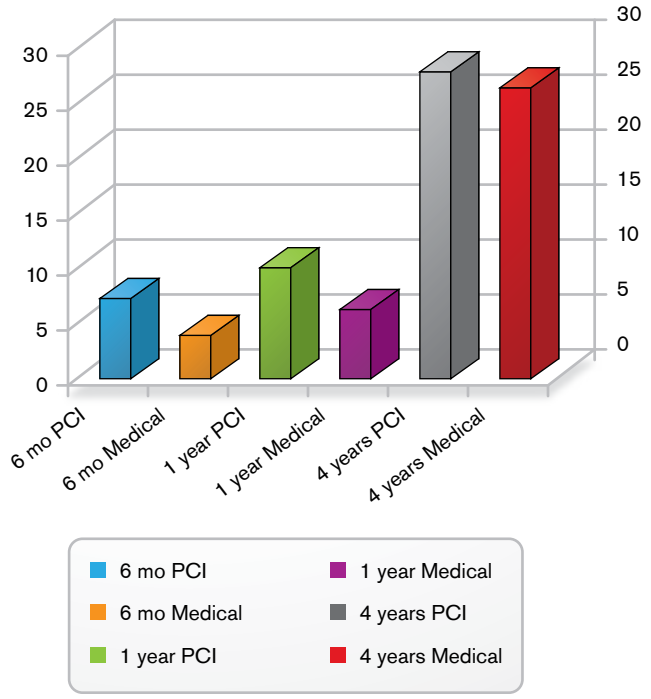
One of the factors that should be very clear from this chart is that the risk associated with CAD varies with a number of different factors – certainly with the number of vessels involved and with the type to treatment given. However there are many other factors that determine the severity of CAD and the expected outcome with PCI or other forms of treatment. The ACC has published a list of these factors which increase the risk of poor overall outcomes with PCI treatment:

Causes of increased risk for poor outcomes with PCI

1. Advanced age.
2. Female gender.
3. Diabetes Mellitus.
4. A prior history of an MI.
5. Left Main Coronary Artery (LMCA) disease.
6. Pre-existing poor left ventricular or renal function.
7. Total occlusion of a coronary artery.

Some of these groups with increased risk for poor outcomes after PCI have been studied independently. The TIME study (Trial of Invasive Medical Therapy in Elderly patients) reported the long-term outcomes of PCI and medical therapy in an octogenarian population with clinical class 3 angina pectoris, and severe heart disease, defined as a history of heart failure with an ejection fraction less or equal to 45% and two other comorbidities. The elderly patients treated with PCI in this study had a lower incidence of non-fatal cardiac events than those receiving medical treatments, but the difference in overall mortality at four years was not statistically significant for both groups. It should be noted that the mortality outcome for this octogenarian population with severe heart disease treated medically or with PCI is significantly worse than that of the general population.

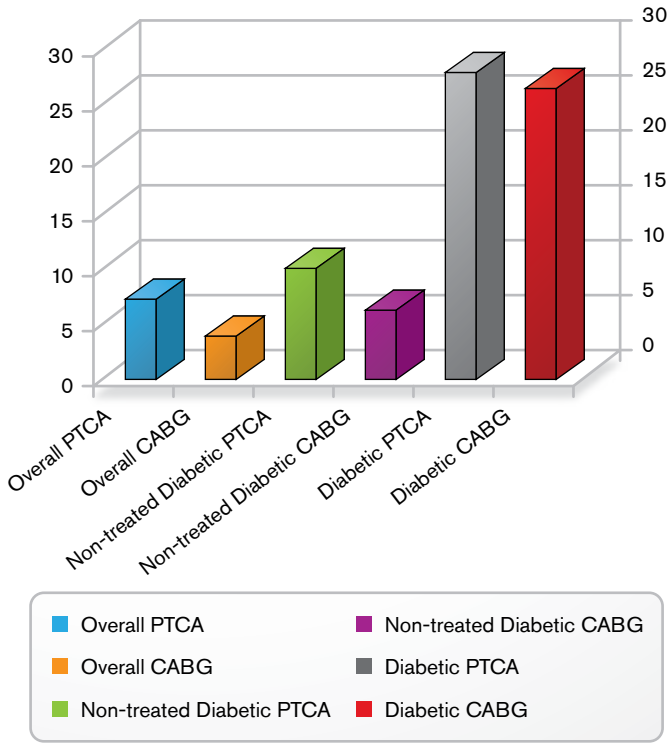
4-Year Mortality in Octogenarians Treated with PCI vs. Medical Treatment Alone



The mortality outcomes are much worse for diabetics than for the octogenarians with severe heart disease. The BARI

study included a subgroup of patients who were diabetics. This diabetic subgroup mortality outcome after treatment with PTCA or CABG was compared with a matched (not under diabetic treatment) subgroup's outcome with similar treatments. There was no comparison with medical therapy in this study subgroup. This diabetic study subgroup divided the patients into two groups: those with treated diabetes, and those receiving no treatment for diabetes. There was no distinction made (not enough patients) between single vessel and multivessel disease outcomes. The overall 10-year survival of these patients was 71.0% for those treated with PTCA, and 73.5% for those treated with CABG. Among the patients with no treatment for diabetes, the overall survival for those treated with PTCA and those treated with CABG was identical (77.0% and 77.3% respectively). However, the survival rate for patients with treated diabetes was much worse and favored treatment with CABG, 45.5% survival after PCI vs. 57.8% survival after CABG. These results clearly show a much worse outcome for diabetics with CAD vs. the general population with CAD, as well as a somewhat improved survival after CABG compared with the survival after treatment with PCI.

10-Year Mortality for Diabetics vs. Non-Diabetics and PCI vs. CABG



Patients with chronic total occlusion of a coronary artery comprise one of the groupings of patients with the lowest success rate after PCI. There are distinct technical problems in crossing the areas of total coronary artery occlusion with the guide-wires used to insert the catheters. The restenosis problem in cases of total coronary artery occlusion is very high, even when the wire can be passed successfully across the lesion. With the use of stents the restenosis rates can be as high as 30% – 55%.

In cases of high-grade but incomplete obstruction of a coronary artery, the incidence of restenosis is as high as 30% – 50% of all cases treated with simple PTCA and 10% – 30% of all patients receiving stents. This is an area where the use of bare metal stents and drug-eluting stents show great promise as documented by the Mayo Clinic experience report.

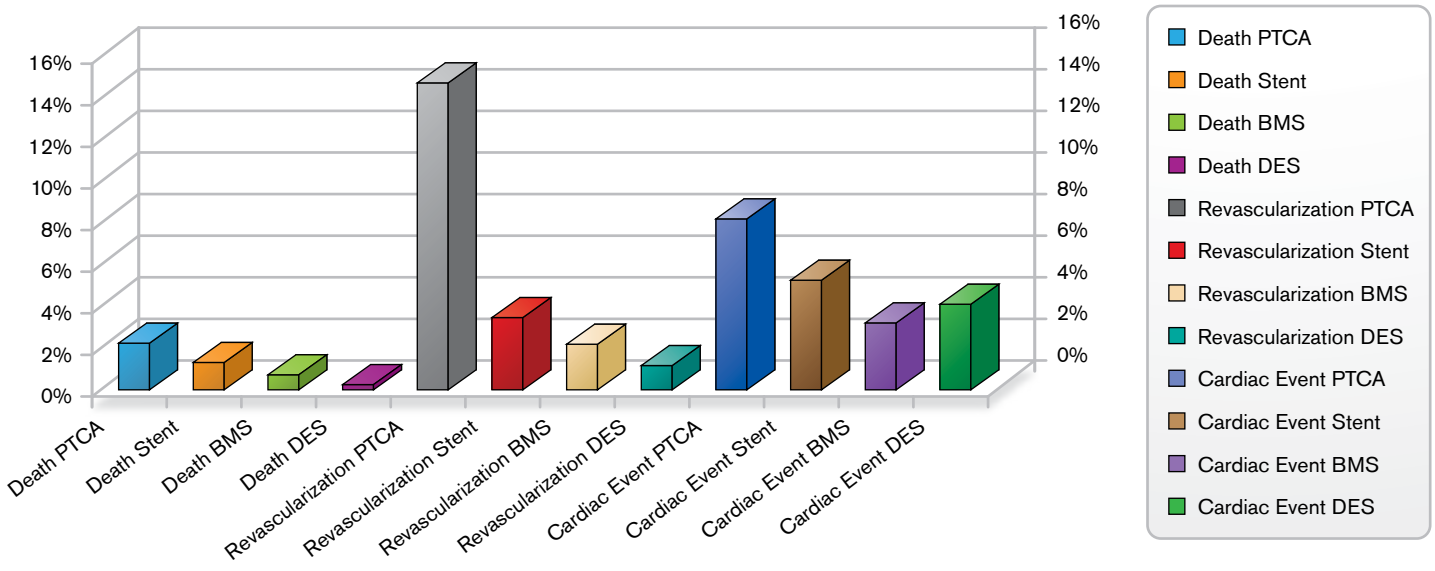
The Mayo Clinic published their overall 25-year experience with coronary revascularization in 2007. A total of 1,262 patients were treated using different PCI techniques at this center during this period of time. This study reported only hospital and peri-operative experience with these techniques: no long-term outcome results were included. The comparison of the various techniques showed significant differences in the rates of death, revascularization by CABG, and other cardiac events. This series indicates significant decreases in all of these complications with the use of bare metal stents (BMS) and drug-eluting stents (DES) when compared with standard PTCA or stents, as shown in the chart at the top of the following page.

To summarize, it can be stated that PCI is a safe and effective form of treatment for CAD that generally provides improved survival over medical treatment used alone. In certain impaired populations, particularly the elderly and diabetics, the long-term survival outcome after PCI is significantly reduced compared with the survival outcome after PCI of the general population. The PCI procedure itself is not free of risk and multiple complications may occur during the peri-operative period, including some deaths. However, after the peri-operative period is over, the vast majority of patients undergoing PCI for the treatment of CAD do well, with a decreased number of repeat cardiac events and, with the exception of specific high-risk populations, an increased survival rate.

The role of some of the newer types of stents and the long-term outcomes that may be associated with their use, particularly when used in conjunction with recently introduced anti-platelet protocols, appears very promising at this time. However not enough information is currently available to reach conclusions in this regard.

From an underwriting point of view, the underwriting of these cases requires complete information so that adequate

Mayo Clinic Complication Rate by Type of Procedure Used



decisions may be reached. The initial case presented in this article clearly demonstrates how limited information can affect the underwriting decision. It must be remembered that all population subgroups will not have the same type of favorable outcomes as those of the general population and this knowledge must be applied to the underwriting of these cases.

This second case demonstrates once more the difficulties presented by the evaluation of such cases for underwriting purposes.

CASE #2

Female, 58 years of age. Non-smoking. Not diabetic. No family history of early cardiac disease or sudden death. High cholesterol, under treatment with Lipitor, current value 262. History of a blood clot 10 years prior with no details.

This woman had a history of a prior MI at age 49. In the early summer of 2000 she presented with increasing chest pain, clinically diagnosed as angina, and had an EKG read by her doctor as showing a septal MI. She had a TM with a stress echo performed for diagnostic purposes. The TM was not diagnostic for ischemia after exercise of 10:30 min. The stress echo showed mild septal hypokinesia with exercise, and was read as positive for ischemia.

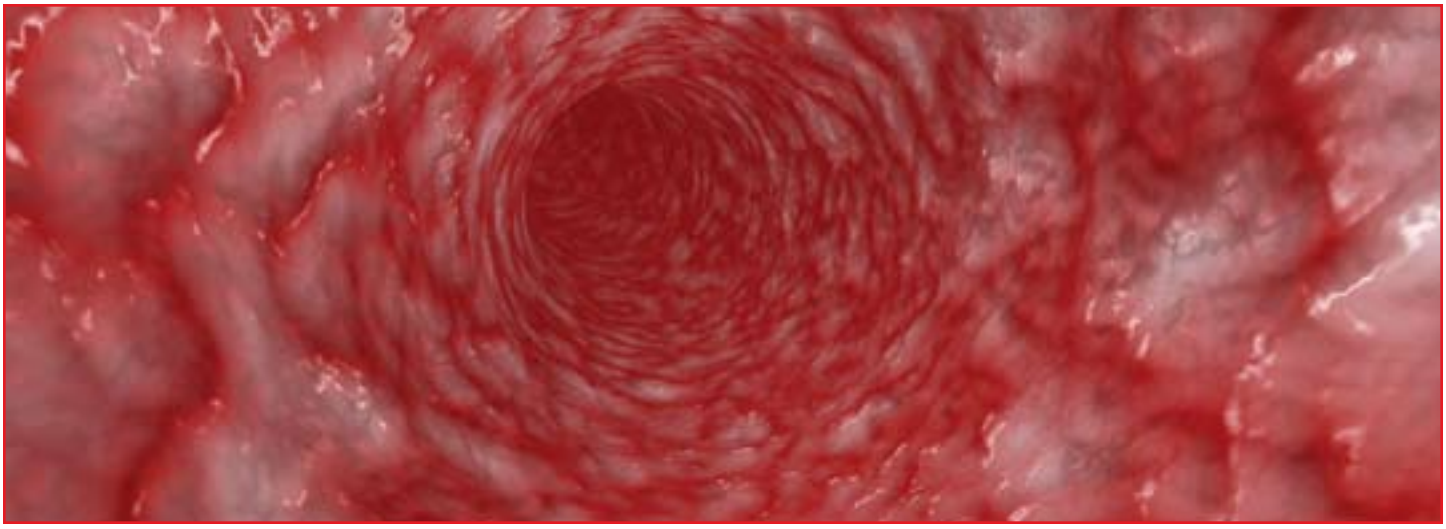
How convincing is this history of CAD? And what severity of CAD is expected in this patient given her early age and the data supplied? If this was all the information available it would appear reasonable to classify her as having moderate to severe CAD, in my opinion.

A cardiac catheterization was done after the initial work-up. It showed no evidence of CAD, but the LAD (Left Anterior Descending Coronary Artery) was found to be the only functional artery in the left side, with a tiny close–to-absent circumflex artery of congenital origin. The official reading of the coronary angiogram was: “Normal coronary arteries, rudimentary possibly absent left circumflex artery.”

This applicant was treated medically.

This case documents the difficulty in evaluating CAD cases without full information. It is obvious that this woman has a congenitally deficient left-side heart circulation, not obstructive CAD. As it stands, her condition is stable, not progressive like obstructive CAD cases are. PCI cannot be performed in this case because there is no vascular tree present in this case that can be treated this way, therefore the only feasible treatment in this case is medical. This case shows some issues that might confuse even well trained underwriters and which document the need for complete information in evaluating these cases.

In conclusion, the treatment of CAD has undergone many advances in the last two decades, with improved long-term survival and a decreased rate of complications for most



people with this disease. The prospects for further improvements by using combinations of medical anti-platelet protocols and specialized stents appear bright, even for traditionally difficult-to-treat or complicated cases. However, certain population subgroups, particularly diabetics and very old people, remain at high risk and have a high mortality despite these advances in the treatment of CAD. This is a disorder that cannot be underwritten lightly – it requires full documentation, particularly in regard to these high risk subgroups. ■

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