

# **The Society for Cardiovascular Angiography and Interventions**

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**Public Statement to**

**The FDA Circulatory System Devices Panel**

**of the Medical Devices Advisory Committee**

**Meeting on December 7 – 8, 2006**

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## **INTRODUCTION**

I am Gregory J. Dehmer, a practicing interventional cardiologist, and the President of the Society for Cardiovascular Angiography and Interventions. On behalf of the Society, I appreciate the opportunity to provide comments to the panel on this important topic. The Society for Cardiovascular Angiography and Interventions (SCAI) is a professional association now representing over 3,700 invasive and interventional cardiologists. We are the Society that represents the great majority of physicians who perform invasive cardiac procedures, including the placement of coronary artery stents. For the past 30 years, the Society has diligently promoted excellence in cardiac catheterization, cardiovascular angiography, and interventional cardiology through physician education and representation, the development of clinical guidelines and promotion of quality standards to enhance patient care.

In fulfillment of that mission, SCAI has been – and will continue to be -- at the forefront in providing guidance to physicians regarding the use of drug-eluting stents. Among the guidelines and advisories recently produced are two on the use of drug-eluting stents. These guidelines and advisories (as is true for all SCAI official statements) represent the consensus of our profession's leading experts, based on objective review of current research and best practices, with the goal of providing the best quality of care for our patients.

Our [first position statement](#) was released in 2003 shortly before drug-eluting stents were released for use.<sup>1</sup> Subsequently we organized a Task Force to review critical issues surrounding drug eluting stents and their introduction into clinical practice. The [report of this Task](#) force was published in 2004.<sup>2</sup> We later joined the American College of Cardiology and the American Heart Association on [updated guidelines](#) for percutaneous coronary interventions.<sup>3</sup> A third Clinical Alert on drug-eluting stents is currently under development and will be issued later this month. As the main professional organization dedicated to the

subspeciality of invasive and interventional cardiology, it is the goal of the SCAI to provide the best possible information to physicians and patients.

## **BACKGROUND**

Recent analyses of late follow-up data from the initial randomized trials of drug-eluting stents suggest the infrequent occurrence of late stent thrombosis after implantation of a drug-eluting stent, but at rates greater than observed for bare metal stents. Since these observations have come into light, many have expressed diverse comments about the safety of drug-eluting stents. These concerns have been highlighted in high-profile news reports causing some patients who have received these stents to become unduly alarmed. I do not come today presenting new or dramatic data. Rather, my goal is to put these recent observations and reports into perspective and present what SCAI believes are reasonable actions for the advisory panel to consider.

Like me, a practicing interventional cardiologist for the past 25 years, many members of the panel have lived through the history I am about to recount. My purpose is to place the current concerns about drug-eluting stents into a reasonable perspective and to frame these concerns properly within the evolution of interventional cardiology.

During the early days of percutaneous coronary intervention, or PCI, the only treatment was balloon angioplasty. This provided an exciting alternative to coronary artery bypass graft surgery (CABG), yet 3 to 5 % of patients required emergency CABG surgery with considerable morbidity and mortality. Furthermore, approximately 40% of patients suffered renarrowing of the artery and a substantial portion of these patients required a repeat procedure with its associated risks. Multiple drugs were tried to treat restenosis and had no effect. Other newer devices, such a rotational atherectomy and directional

atherectomy, were developed and proved useful in treating a subset of patients, but had a higher incidence of vessel perforation -- a potentially fatal complication of interventional treatment.

The next major clinical advance occurred in 1993 when the FDA approved the first stents for clinical use in the U.S. Data from pivotal trials like STRESS and Benestent clearly showed a reduction in restenosis and the need for subsequent revascularization procedures and formed the basis for their approval.

However, these devices were not devoid of problems. Despite what was thought to be appropriate anticoagulation with warfarin and aspirin, early stent thrombosis occurred in 1-2% of patients - - sometimes just after leaving the hospital - - usually resulting in an acute myocardial infarction.

Better stent deployment techniques coupled with the use of dual-antiplatelet therapy (aspirin and a thienopyridine like clopidogrel) all but eliminated early stent thrombosis as a clinical problem. Although restenosis was reduced by bare metal stents, it was not eliminated; when it occurred, restenosis in those situations was frequently more difficult to treat. Balloon angioplasty and other techniques were largely ineffective for the treatment of in-stent restenosis and actually led to the development of an entirely new therapy – intravascular radiation or brachytherapy. Intravascular radiation was superior to balloon angioplasty for the treatment of in-stent stenosis, but was not a perfect therapy. Similar to the issue now of concern with the drug-eluting stents, there was delayed healing after brachytherapy, a higher incidence of late thrombosis, and prolonged dual-antiplatelet therapy was recommended. The very late effects of brachytherapy as yet are incompletely known.

The development of drug-eluting stents and subsequent approval in 2003 represented another milestone in interventional cardiology. Restenosis, a problem frequently referred to as the Achilles' heel of PCI, was dramatically reduced to less than 10% in the initial pivotal trials. In October 2003, shortly after the first drug-eluting stent was released, the FDA notified physicians about reports of increased stent thrombosis

within the first 30 days after implantation. After further analysis and additional reporting, a second report to physicians was issued on November 25, 2003, stating that the risk of early thrombosis was within the expected rate for any stent. As everyone knows, the use of drug-eluting stents has grown rapidly, capturing up to 90% of the stent market by most estimates.

So, why is this historical review important to the current issue at hand? My point is that throughout the evolution of interventional cardiology, there have been challenges and subsequent solutions to these challenges. In fact, it is difficult to think of any area in medical care where challenges – and solutions – did NOT occur during introduction of a new therapy into practice. We are now faced with evidence of a possible problem with drug-eluting stents – very late stent thrombosis. Like all of the problems which preceded it, we firmly believe this too will have a rational solution.

## **FINDINGS**

First, is this a genuine problem or a statistical fluke? The concerns about late thromboses have grown from some small observational studies, but primarily from several meta-analyses using the pivotal trial data. Meta-analysis is a powerful and increasingly popular method used to combine trial data, yet there are limitations resulting from the combination of different datasets. However, because the occurrence of late stent thrombosis is infrequent, signals of this event were difficult to detect in any single trial.

Moreover, varying definitions for this event among trials and assumptions about the cause of death when stent thrombosis is suspected, but not proven angiographically, hamper this assessment. Despite all of these concerns and potential limitations, SCAI believes this is a real, but infrequent event. Many others at this meeting will present the best current estimates for the occurrence of late stent thrombosis. These range from 1 excess event in 200 to 500 patient-years in those treated with a drug-eluting stents compared with bare metal stents. Clearly, this risk is small, but it is not zero. Concern for this event is magnified by the fact that late stent thrombosis frequently presents as an acute myocardial infarction.

This new concern about drug-eluting stents mandates that we reevaluate the benefits of drug-eluting stents. Many have focused on the dramatic numerical reduction in restenosis, which is striking, but the percent of vessel narrowing is just a number. The real benefit to patients is the related reduction in subsequent revascularization procedures whether they are repeat PCIs or bypass surgeries. In this reevaluation of the benefits and risks of drug-eluting stents now before this panel there are two important aspects to consider. First, for years we have often said that restenosis, while very troublesome for the patient and costly to the healthcare system, is not a life-threatening condition and is often successfully treated by a second revascularization procedure. More recent analyses, however, have shown that more than one third of in-stent-restenosis episodes among patients treated with bare metal stents present as a myocardial infarction or unstable angina requiring hospitalization.<sup>4</sup> Furthermore, although rare, late stent thrombosis has been reported with bare metal stents.<sup>5</sup> Thus, restenosis may not be as benign as once thought, but understand that just like late stent thrombosis after drug-eluting stents, we are talking about a very small minority of the total cohort of patients successfully treated by bare metal stents. The repeat percutaneous revascularization procedures necessary to treat restenosis are not without some risks of harm, albeit small. Second, Medicare billing data show that the number of CABG procedures performed on Medicare patients alone declined 14% between 2003 and 2005. This reduction of 42,868 procedures is a real number and would be even larger if all age groups were considered. I would not want a single person in the room to think I am claiming this entire reduction in CABG surgery is related to drug-eluting stents. We all understand it is much more complicated than that, but I think it is fair to conclude that, because of drug-eluting stents, some patients avoid CABG and its risks, including a 1-2% chance of death. My point is fairly simple. We all would agree that drug-eluting stents reduce the need for subsequent revascularization procedures. However, the small risk of late stent thrombosis from drug-eluting stents must be considered in the context of the number of morbid complications occurring because a revascularization procedure was necessary for restenosis. Although the risk of harm from drug-eluting

stents we are now discussing may be as high as 1 event in 200 patient years, we cannot lose focus on the fact that the other patients have experienced no harm and received the potential benefits of drug-eluting stents -- primarily avoiding the risk of further revascularization procedures. We cannot simply focus on the risk side of this equation without appropriately considering the benefit side. So I ask the panel in their deliberations to consider the number of patients helped by drug-eluting stents.

To further emphasize this point I will present two examples using medications familiar to any physician – aspirin and warfarin. As cardiologists, we recommend aspirin to nearly all of our patients and are judged deficient in compliance to JCAHO Core Measures if we fail to administer aspirin to a patient with a heart attack. Although aspirin is widely prescribed, we all know aspirin has important complications especially at higher doses. Major complications,<sup>6</sup> occur at a rate of 1.1 to 3.5 per 100 patient years and fatal complications occur at a rate of 0.2 to 0.9 per 100 patient-years<sup>7, 8</sup>. Of course, this small risk of serious complications must be off-set by the benefits of aspirin therapy. A meta-analysis of randomized controlled trials using aspirin showed that a mean dose of 273 mg/day increased the absolute risk of hemorrhagic stroke to 12 events per 10,000 people.<sup>9</sup> This relatively small increase must be weighed against the reduced risk of myocardial infarction (to 137 events per 10,000) and ischemic stroke (to 39 events per 10,000). Thus, there will be 1 fatal complication per 200 patient-years from aspirin, a widely used over-the counter medicine.

Even more dramatic, consider the potential serious complications from warfarin, another drug used widely in patients with cardiovascular disease. The rate of major complications varies from 0 to as high as 25 per 100 patient-years in some early studies. The occurrence of fatal complications also varies from 0 to 6.6 per 100 patient-years among studies.<sup>7, 8, 10, 11, 12</sup> Thus, the rate of fatal events from this commonly

used therapy are of the same or greater magnitude as those we are now considering as the newly identified risk of drug-eluting stents.

Perhaps we could derive some lessons from what we teach medical students about using warfarin and apply these to drug-eluting stents. We do not teach them warfarin is a bad drug that should not be used, but we teach them respect for warfarin and its potential hazards. So, what do we teach? First, and this is perhaps self-evident, but we teach them not to use this drug unless there is a good indication because there are risks. Second, although there may be a good clinical indication, we teach them to not use warfarin if the patient is at high risk for a bleeding complication because the risk outweighs the benefit. Third, we teach them how to use warfarin properly with careful monitoring of anticoagulation. Finally, we teach them that they must educate the patient about the risks and benefits of warfarin and, if possible, involve the patient in the decision process. With this practical example derived from a drug used in clinical practice for years as a template, SCAI makes the following recommendations to this panel.

## **Recommendations**

### **1. Adherence to established guidelines for percutaneous coronary interventions (PCI)**

Similar to warfarin, physicians must use appropriate indications for PCI even before considering whether or not to use a drug-eluting stent. The current treatment guidelines developed jointly by the ACC/AHA and SCAI outline the clinical situations where PCI is appropriate and inappropriate for use and these remain a valid guide to clinicians for selecting patients for PCI.<sup>3</sup> Lesions of intermediate severity may require further evaluation in the catheterization laboratory using techniques such as intravascular ultrasound or fractional flow reserve to determine their appropriateness for PCI. It must be emphasized, however, that the recommendations in the guideline apply to most patients, but may require modification by existing situations that only the primary treating healthcare provider can evaluate properly. Given these new concerns about drug-eluting stents, their use to treat lesions that have no clear indication for



PCI is inappropriate. Outside of the pivotal trials that included a predominance of non-complex lesions, we have gained considerable experience using drug-eluting stents in complex lesions considered to be “off-label” uses. These lesions have a higher risk of restenosis and have been shown to derive the greatest benefit from drug-eluting stents. After consideration of the risk/benefit ratio for specific patients, many of these lesions may be best treated by drug-eluting stents and it would be unfortunate for the panel to restrict the use of drug-eluting stents to the non-complex lesions included in the pivotal trials. Since the benefit of drug-eluting stents is a reduction in restenosis, clinicians must weigh the potential risks of restenosis for a particular patient or lesion against the potential risks of a drug-eluting stent. In situations such as large diameter vessels with focal lesions, the risk of restenosis with a bare metal stent is low and provides a reasonable alternative to a drug-eluting stent.

## **2. Determine if the patient is an appropriate candidate for a drug-eluting stent**

The patient may have an appropriate clinical indication for PCI and drug-eluting stent placement, but may not be an appropriate candidate for this therapy. There are multiple reports describing acute stent thrombosis occurring shortly after antiplatelet therapy is discontinued within the recommended treatment duration of 3-6 months. Moreover, careful pathologic studies have clearly documented delayed re-endothelization with drug-eluting stents and many have recommended an extended duration of dual-antiplatelet therapy following placement. Similar to assessing whether the patient is an appropriate candidate for warfarin, clinicians must determine whether the patient is an appropriate candidate for prolonged dual-antiplatelet therapy. Physicians must make every effort to ensure that their patients can and will take the necessary antiplatelet therapy for at least 6 months before they consider implanting a drug-eluting stent. Strict adherence to dual antiplatelet therapy is necessary and we support the current Class I ACC/AHA/SCAI guideline recommendation that this therapy be continued for 12 months in patients who are not at high risk for bleeding. At the present time, we do not believe it is necessary to mandate the indefinite use of dual antiplatelet therapy in patients with drug-eluting stents, but this is an

option best left to the judgment of the clinician. In situations where, in the judgment of the clinician, the patient is not a candidate for prolonged antiplatelet therapy, use of an alternative device or revascularization strategy is appropriate.

### **3) Drug-eluting stents must be implanted properly**

Many lessons were learned about the proper methods for the deployment of bare metal stents that are equally applicable to drug-eluting stents. Stents must be appropriately sized for the artery, must be adequately expanded and must be well-apposed to all areas of the vessel wall. Intravascular ultrasound is an excellent tool to examine these characteristics of stent deployment but may not be feasible or practical in every case. Nevertheless, optimal stent sizing and deployment, guided by intravascular ultrasound imaging, can reduce the occurrence of technical problems that are associated with complications such as stent thrombosis.

### **4) Increase patient and physicians education about drug-eluting stents**

Physicians need to advise their patients of the most current information about the risks and benefits of drug-eluting stents. Whenever possible, this discussion should occur before the anticipated procedure. Several reports have highlighted situations where healthcare providers unfamiliar with the importance of dual-antiplatelet therapy after drug-eluting stent placement have advised patients to stop these drugs only to have the patient present shortly thereafter with stent thrombosis. Patients also discontinue these medications for a variety of reasons, including lack of appropriate patient education. It is strongly recommended that all patients receive counseling about the importance of continuing dual-antiplatelet therapy both before and after stent placement and that there be greater education provided for all healthcare workers about the need for this therapy.

## **Unresolved Issues**

### **1. The incidence of stent thrombosis with drug-eluting stents**

It must be acknowledged that the true incidence of stent thrombosis is unknown at present. SCAI believes this is a real, but uncommon event. Further data must be collected to better understand the magnitude of this event and better define potential corrective actions. Some patients who have developed late stent thrombosis do so after being off dual-antiplatelet therapy for months. If delayed endothelialization of the stent is the cause, the obvious question is - - Why did the stent thrombosis occur months after stopping the drugs? We know that stent thrombosis (both bare metal and drug-eluting) has occurred in the post-operative period after antiplatelets were recently discontinued and understand that surgery itself induces a procoagulant state. Are there as yet unknown procoagulant events occurring in the small cohort of patients with late stent thrombosis?

### **2. The role of drug resistance**

Aspirin and clopidogrel resistance are emerging clinical entities with potentially severe consequences. The mechanisms of resistance remains incompletely defined, but there are specific clinical, cellular, and genetic factors that influence therapeutic failure. The extent to which drug resistance or tolerance is related to late stent thrombosis is unknown.

### **3. Patients with a drug-eluting stent already implanted**

Finally, patients who have already received a drug-eluting stent should consult with the physician who implanted the device or a cardiologist who has carefully reviewed the data and issues surrounding late stent thrombosis and the appropriate use of anti-platelet therapy. We will be encouraging all physicians to read and consider our upcoming Clinical Alert when advising their patients. Patients who have already stopped their dual-antiplatelet therapy for more than one month should likely remain on aspirin alone. For patients who are still taking dual-antiplatelet therapy, we advise physicians to weigh the risks and

benefits based on the individual case when deciding how long to continue dual therapy. The AHA in collaboration with the SCAI and ACC will shortly issue a Scientific Advisory on the premature discontinuation of antiplatelet therapy in patients with drug-eluting stents.

Physicians should work with industry, the FDA, professional societies and perhaps CMS in gathering more data on the risks of late stent thrombosis. More studies are needed and events occurring outside of clinical trials need to be carefully documented and reported to the appropriate bodies. Data collection with groups such as the ACC National Cardiovascular Data Registry should be considered and the NCDR™ should work to develop ways to link its data with CMS data to review long-term outcomes on patients receiving drug-eluting stents.

### **Conclusion**

We look forward to the panel's deliberations on the subject of drug-eluting stents and late stent thrombosis. We commend the FDA for holding this hearing in a timely fashion and the FDA's willingness to hear and consider data and opinions from all involved in this issue.

After considering the data and analyses presented at this meeting and elsewhere, and this panel's recommendations, SCAI in collaboration with the AHA and ACC will issue a Clinical Alert to physicians (and their patients) with our recommendations regarding the appropriate use of drug-eluting stents.

## **Endnotes**

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