

Status of Drug-Eluting Coronary Stents

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EVOLUTION OF PERCUTANEOUS CORONARY INTERVENTIONAL TECHNOLOGIES

The introduction of **percutaneous transluminal coronary angioplasty (PTCA)** in the late 1970s provided a new, non-surgical approach to the treatment of selected patients with symptomatic coronary artery disease. Throughout the next decade, adjunctive technologies, including rotational and directional atherectomy, expanded the range of coronary lesions which could be approached percutaneously. PTCA continued to be limited, however, by the problems of abrupt vessel closure and late restenosis.

Abrupt vessel closure occurred as a consequence of large intimal dissections, vasospasm and thrombus formation and usually happened during or immediately after the procedure. As a consequence, surgical backup was required for all PTCA procedures and the incidence of emergency CABG, acute myocardial infarction and death was about 1.0%.¹

Late restenosis tended to occur about 3-6 months after the procedure and was usually heralded by the recurrence of anginal symptoms. Restenosis was a significant problem with 40% of patients demonstrating angiographic re-narrowing (of $\geq 50\%$ of the vessel diameter), and 20 to 30% of patients requiring repeat revascularization within the year. Intravascular ultrasound studies demonstrated a dual mechanism for restenosis, including components of elastic recoil of the vessel wall and intimal hyperplasia of the underlying smooth muscle cells of the medial layer.¹

CORONARY STENTING

Coronary stents were developed in the late 1980s to improve the results of PTCA and better manage the problems of abrupt vessel closure and restenosis. Stents produced better immediate in-lab results with less residual stenosis, and more importantly the ability to stabilize dissection flaps, resulting in significantly lower rates of emergency CABG, periprocedural MI and death (0.1%). In

addition, stents virtually eliminated the elastic recoil component of restenosis, allowing for a greater acute luminal gain and reducing the overall incidence of restenosis. Following **Food and Drug Administration (FDA)** approval of **bare metal stents (BMS)** in 1994, there was a significant reduction in the rate of angiographic restenosis (20-30%) and in the frequency of target lesion revascularization (10-15%).¹

The improved and very predictable clinical and angiographic success of BMS expanded the scope of **percutaneous coronary interventions (PCI)** to multiple lesions, more complex coronary anatomy and to patients with acute myocardial infarction. Clinical restenosis after bare-metal stenting continued to occur within the first 12 months and was related predominantly to intimal hyperplasia. Increased risk factors for restenosis included longer lesion segments ($>20\text{mm}$) and smaller vessel diameters ($<2.5\text{mm}$) frequently found in women and diabetics. Recurrent ischemia more than a year after stenting was much more likely to be due to new or progressive disease at another site rather than to restenosis.²

The significant advantages of stenting, however, were associated with a new and previously unrecognized clinical event, "sub-acute" vessel closure, related to thrombus formation at the stent site, and occurring several days to weeks after the procedure. The initial incidence of "sub-acute thrombosis" was not insignificant—ranging from 0.5 – 2%.

Pioneering work from Antonio Colombo and others demonstrated that the risk of sub-acute stent thrombosis could be minimized by optimal stent deployment with high pressure balloon inflations. In addition, large multi-center trials (STARS) of different post-stent anticoagulation regimens demonstrated that aspirin plus a thienopyridine—"dual anti-platelet therapy" (DAT)—substantially reduced the risk of sub-acute thrombosis to ~ 0.5%.

Continued improvements in stent design, allowing for greater flexibility and improved access to more distal stenotic

lesions, combined with the efficacy of DAT, propelled bare metal stents into the forefront of percutaneous coronary intervention. By 2001, almost two million coronary interventions were performed worldwide, with an estimated annual increase of 8%.

DRUG-ELUTING STENTS

Restenosis rates, however, remained in the 10 – 15% range, and in-stent restenosis was particularly difficult to treat. Initial forays with brachytherapy (localized radiation therapy) for in-stent restenosis demonstrated some clinical benefit compared to PTCA alone but the technique was clinically cumbersome, requiring the collaboration of interventionalists, radiation oncologists and radiation physicists, and necessitating life-long DAT due to the risk of sub-acute stent thrombosis at the irradiated site.

Ongoing research to reduce the incidence of in-stent restenosis ultimately led to the development of "drug-eluting" stents (DES). DES consist of a standard stainless steel stent backbone, a polymer coating, and an anti-inflammatory drug affixed to the polymer and gradually released or "eluted" into the surrounding tissues over a period of several weeks to modify the local healing response.

Clinical trials of **sirolimus-eluting stents (SES)** and **paclitaxel-eluting stents (PES)** demonstrated a marked reduction in the incidence of restenosis and target lesion revascularization compared to bare metal stents. The benefit of drug-eluting stents compared to BMS resulted from the inhibition of neointimal hyperplasia, leading to a lesser degree of late in-stent lumen loss at six to twelve months. In fact, long-term follow up studies with intra-vascular ultrasound have shown that the neointimal suppression following DES placement may be present as long as two years following stent deployment.^{3,4}

Based on the significant reduction in restenosis rates with DES, in 2003 and 2004 the FDA approved two drug-eluting stents for routine clinical use in selected patients.

CLINICAL TRIALS OF DES

A 2006 meta-analysis of 19 clinical trials with 7060 patients (the three largest trials were SIRIUS, TAXUS IV, and TAXUS V) concluded that, compared to BMS, DES conferred a significant reduction in both angiographic restenosis as well as in target vessel revascularization. In particular, target lesion revascularization was reduced from 16.6 % (BMS) to 6.2% (DES). Despite the reduction in restenosis, however, there was no significant difference in either one-year mortality or myocardial infarction, consistent with previous findings that the majority of restenosis patients present with recurrent symptoms of angina, as opposed to acute myocardial infarction or sudden cardiac death.⁵

As a result of the marked reduction in restenosis and target vessel revascularization, DES usage, particularly in the United States, grew exponentially from 2004 through 2006, accounting for almost 90% of all stent implantations.

In the fall of 2006 the long-term safety of DES came into question with reports in the European literature of an increased incidence of “late” stent thrombosis.

TIMING OF STENT THROMBOSIS

Stent thrombosis can occur “acutely” (within 24 hours), “sub-acutely” (between one and 30 days), “late” (from 30 days to one year), or “very late” (more than one year) after stent placement. Stent thrombosis within the first year following implantation appears to occur with equal frequency in patients with BMS or DES, as long as patients with DES are treated with the recommended duration of dual anti-platelet therapy.

Two studies published in 2006—one a small randomized trial of BMS versus DES, and the other a meta-analysis of previously published DES trials—raised concerns of an increased incidence of “very late” stent thrombosis in DES patients, which caused an uproar in the lay press. [In both studies, the protocols called for discontinuation of the thienopyridine after six months of DAT therapy.] These concerns led to intense scrutiny and retrospective examination of the use of drug-eluting stents. Risk factors predisposing to a higher rate of DES thrombosis were more frequently related to off-label usage,

including longer stented segments, complex bifurcation lesions, and smaller vessel diameters. Technical and clinical factors were also identified and included suboptimal stent expansion and inadequate stent strut apposition, diabetes mellitus, chronic renal insufficiency, and resistance to anti-platelet agents. Perhaps most importantly, premature discontinuation of dual anti-platelet therapy was identified as one of the major risk factors for late stent thrombosis.^{5,6}

In 2007, several larger studies re-examined the risk of late thrombosis in DES-treated patients. In one study, angiographically proven stent thrombosis occurred in 152 of 8146 patients (1.9%) who received DES for both on and off-label indications during up to three years (mean 1.73 years) of follow up. “Sub-acute” stent thrombosis was seen in 91 patients (1.1 %), with a median timing of four days. This figure alone was higher than the historically reported rate of 0.5 – 1.0% seen in BMS patients who were treated with DAT therapy. In addition, both “late” and “very late” thrombosis were seen in an additional 61 patients (0.75%), and events continued at a steady rate of 0.6% per year during the first three years. The estimated cumulative incidence of stent thrombosis was 2.9% at three years.⁴

In a series of 38 cases of stent thrombosis occurring after DES implantation in 2974 consecutive patients, stent thrombosis was significantly more common following premature discontinuation of clopidogrel (37% of patients with stent thrombosis versus 11% in those without stent thrombosis). The mean duration between cessation of clopidogrel and stent thrombosis was nine days in patients with sub-acute stent thrombosis and 153 days in those with late stent thrombosis. A similar analysis from Rotterdam described a cohort of 2,006 patients who received DES, and in whom 8 cases of late stent thrombosis occurred (0.4%). All 8 patients developed late stent thrombosis following discontinuation of clopidogrel (5 continued on aspirin monotherapy).^{7,8}

“OFF-LABEL” USAGE OF STENTS

The FDA approved DES for “stable patients, without serious co-morbidities, who have newly diagnosed lesions, less than 28 to 30 mm in length, greater than

2.5 mm in vessel diameter, and not involving a major vessel bifurcation”. Less is known about the risk for patients in whom stents are placed for off-label indications, which may account for as many as 50-60% of all stent procedures in this country. Off-label indications include patients with complex anatomy (vessels with high risk features including multiple lesions, small vessel diameter, long lesion segments, ostial and bifurcation lesions, restenotic lesions and saphenous vein graft lesions) and patients with acute MI. Preliminary data from the DEScover and EVENT registries suggested worse cardiovascular outcomes in this setting. However, a retrospective analysis in the *New England Journal of Medicine* evaluated adverse events in 6551 patients enrolled in the NHLBI Dynamic Registry. This study concluded that the use of drug-eluting stents was not associated with an increased risk of death or myocardial infarction in patients with off-label indications but was associated with a lower rate of repeat revascularization at 1 year, as compared with bare-metal stents. These findings support the use of drug-eluting stents for off-label indications, based on a one-year duration of follow-up.^{9,10,11}

PATHOGENESIS OF DES THROMBOSIS

An important explanation for the increased risk of thrombosis in DES compared to BMS patients is delayed endothelial healing, particularly incomplete neointimal coverage of the stent struts. (Figure 1) Delayed neointimal coverage was confirmed in a long-term study of 17 DES and 11 BMS patients in whom angiography was performed at 4, 10, and 21 months. Neointimal coverage was complete in all but one of the BMS patients at 3.6 months while the majority of DES patients still had incomplete neointimal coverage at 21 months. Similarly, an autopsy series comparing 23 DES with 25 BMS patients with evidence of late stent thrombosis (>30days) demonstrated inadequate or absent endothelialization of the stent struts in 14 of the 23 DES patients but in none of the BMS patients. In addition, some DES patients demonstrated areas of local inflammation suggesting the possibility of an additional hypersensitivity reaction.^{12,13}

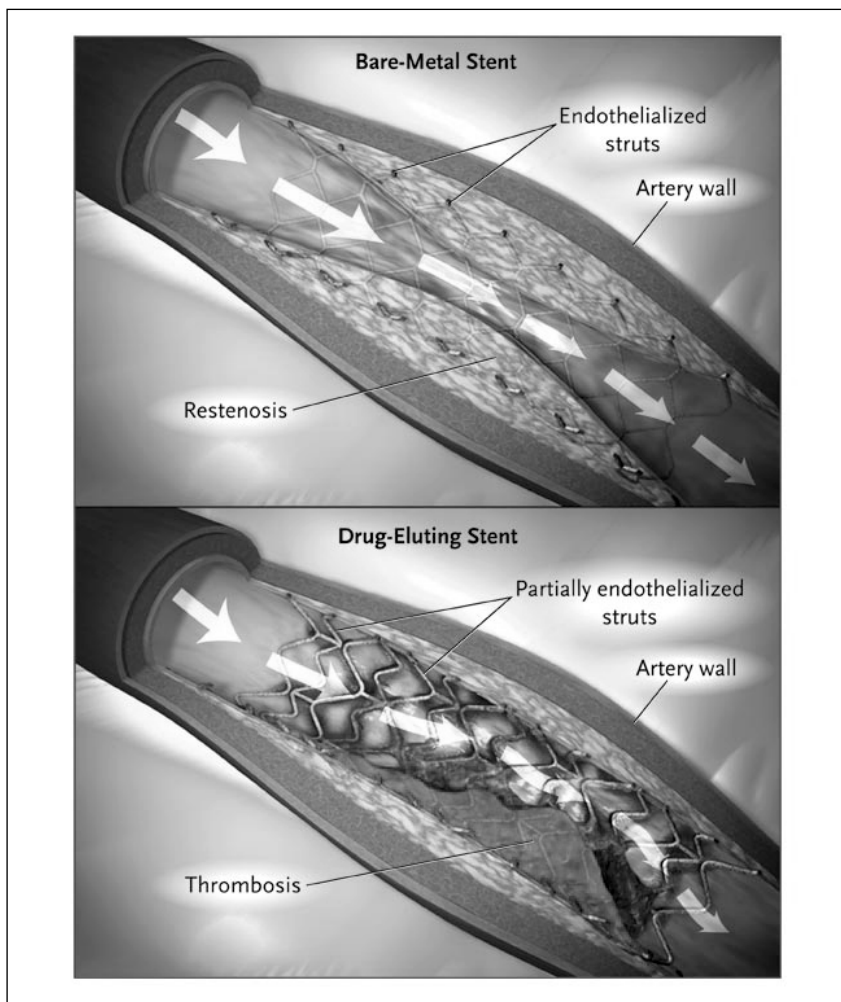


Figure 1. Pathophysiology of restenosis and stent thrombosis (with permission from the NEJM). This figure illustrates the potential complications of coronary stenting: restenosis in a bare-metal stent and late thrombosis in a drug-eluting stent.

Thus, long-term follow-up of DES patients indicates a short term advantage compared to BMS due to a significant reduction in one year re-stenosis events, but an ongoing, low-level risk of late stent thrombosis which may be reduced by optimal patient selection (Table 1) and a longer duration of dual-anti-platelet therapy.

CURRENT RECOMMENDATIONS FOR DURATION OF DAT

The initial FDA and manufacturer's recommendations for the prevention of stent thrombosis after coronary stent implantation required dual anti-platelet therapy with 325mg of ASA and 75mg of clopidogrel for 1 month after BMS implantation, 3 months after sirolimus DES implantation and 6 months after paclitaxel DES implantation. These recommendations were based on the anti-

platelet regimens used in the initial pre-market trials that led to FDA approval for DES (i.e. low-risk patients with low-risk lesions).¹⁴

The current clinical practice has been to continue DAT for a longer period for DES patients, especially for procedures performed for off-label indications, including higher-risk lesions, higher risk patients and multiple vessels

in a single patient. An updated FDA statement on duration of DAT after DES noted that while the "optimal duration of antiplatelet therapy ...is unknown", DAT therapy "should be extended to 12 months in patients at a low risk of bleeding". In our clinical practice we have opted to extend the duration of DAT therapy in DES patients to a minimum of one to two years in all patients, and to continue DAT indefinitely in patients at higher risk of developing late thrombosis (e.g. diabetics and patients with complex lesions or multiple stents), unless bleeding arises.

Long-term therapy with DAT is not without risk. Clearly either aspirin or clopidogrel therapy alone increases the risk of bleeding compared with placebo. And when clopidogrel is combined with aspirin and administered for prolonged duration (up to 28 months), randomized trials have demonstrated a small increase in major bleeding (ranging from 0.4% to 1.0%), compared with aspirin alone.¹⁵

CONSEQUENCES OF STENT THROMBOSIS

Sub-acute stent thrombosis carries a high risk of significant morbidity and mortality. In some series mortality rates have been as high as 45%; hence, compliance with the recommended post-stent anti-platelet regimen is crucial.

Premature cessation of thienopyridine drugs may occur for several reasons. The cost of clopidogrel (approximately \$4 per day) has been cited as one reason patients discontinue (or fail to renew) their therapy. In an analysis from the PREMIER registry, factors associated with premature discontinuation of thienopyridine therapy included: older age, not having completed a high school education, not being married, not receiving discharge instructions for medi-

Table 1. Predictors of Drug-Eluting Stent Thrombosis (adapted from Grines, CL et al: *Circulation* 2007; 115: 813-8)

CLINICAL	ANGIOGRAPHIC
Advanced age	Long stented segment
Acute coronary syndrome	Multiple lesions
Diabetes mellitus	Overlapping stents
Low ejection fraction	Ostial or bifurcation lesions
Prior restenosis or brachytherapy	Small vessel diameter
Renal failure	Suboptimal stent results

cation use, not being referred for cardiac rehabilitation, greater likelihood of having preexistent cardiovascular disease or anemia, and history of avoiding health care because of cost. The authors concluded that “additional patient education about the rationale for and importance of continuing thienopyridine treatment may be needed—particularly for patients with less formal education.”¹⁶

Concerned about excessive bleeding, physicians, dentists and other healthcare providers who are planning an invasive or surgical procedure often stop anti-platelet therapy. Unfortunately, many patients are instructed to stop “blood thinners” without distinction be-

tween warfarin and anti-platelet agents and without consideration of the rationale for their use. Many procedures (e.g., minor surgery, dental cleaning, and dental extraction) can usually be performed at no or only minor risk of bleeding with patients on anti-platelet therapy, or could be delayed until the prescribed anti-platelet regimen has been completed.

DENTAL PROCEDURES IN PATIENTS WHO HAVE RECEIVED DES

Although dental practitioners have long been concerned about the possibility of prolonged bleeding during and after invasive dental procedures on patients receiving anti-platelet drugs, a recent

prospective study of single tooth extractions on patients randomized to aspirin versus a placebo failed to show a statistically significant difference in postoperative bleeding. Although there are no prospective studies of invasive dental procedures on patients taking a thienopyridine alone or in combination with aspirin, there are also no well-documented cases of clinically significant bleeding after dental procedures, including multiple dental extractions. Given the relative ease with which the incidence and severity of oral bleeding can be reduced with local measures during surgery (e.g. absorbable gelatin sponge and sutures) and the unlikely occurrence of bleeding once an initial clot has formed, there is little or no indication to interrupt anti-platelet therapy for dental procedures.

CONSENSUS STATEMENT FROM THE AHA/ACC/SCAI/ACS AND ADA

In February 2007, a science advisory and consensus statement was published in *Circulation* aimed at prevention of thrombotic events in patients who had received coronary stents. A summary of their recommendations follows:¹⁷

- 1) Discuss the requirement for anti-platelet drugs with patients prior to stenting and assess their risk for premature discontinuation of DAT.
- 2) Avoid the use of DES, and consider bare-metal stents in:
 - a. Potentially non-compliant patients
 - b. Patients who may discontinue drugs for economic reasons
 - c. Patients likely to require invasive or surgical procedures within the ensuing 12 months
- 3) Increase efforts to educate patients
 - a. Regarding the reasons for prescribing DAT and the risks associated with premature discontinuation
 - b. Not to discontinue any anti-platelet therapy unless specifically cleared to do so by their cardiologist
- 4) Educate healthcare providers who perform invasive or surgical procedures
 - a. Regarding the potentially life-

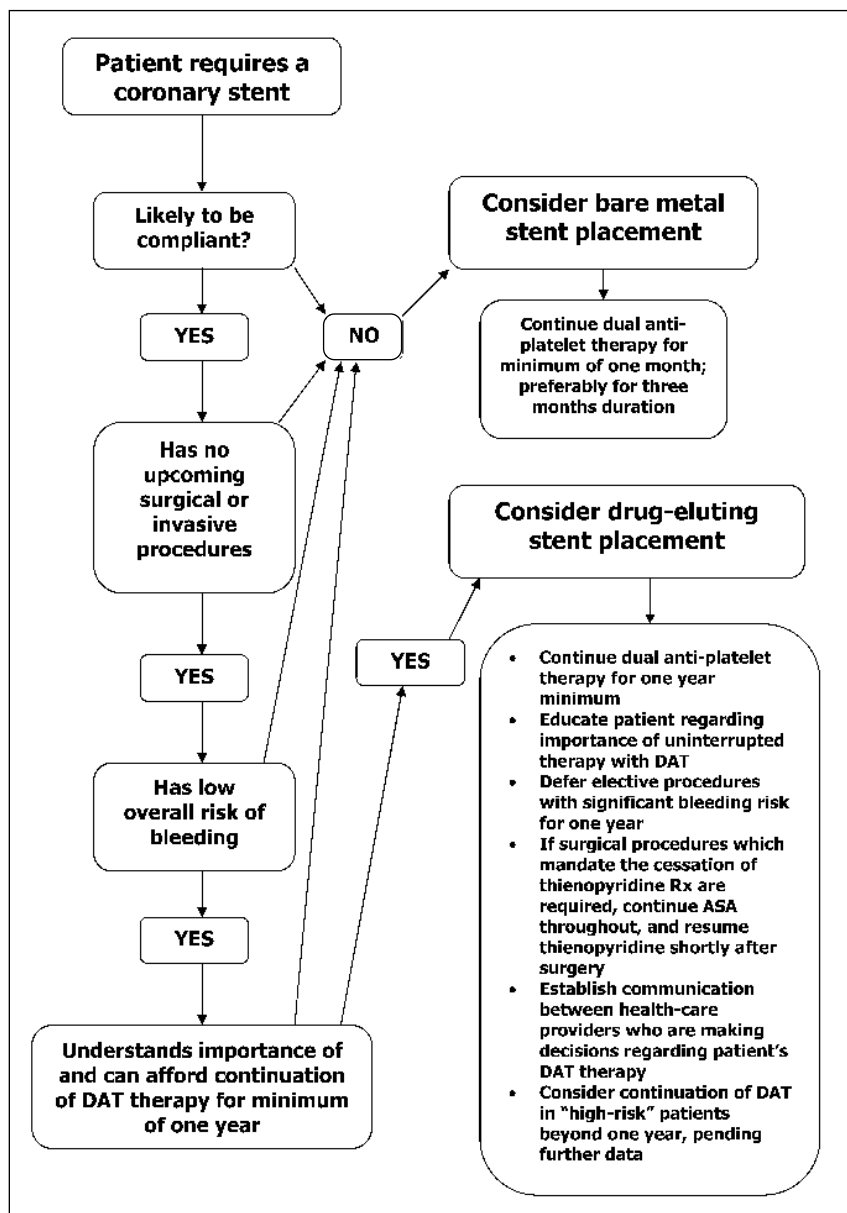


Figure 2. Stent decision-making algorithm

threatening risk of premature discontinuation of DAT in stented patients

b. To contact the patient's cardiologist to discuss optimal patient management strategy prior to surgery

- 5) Elective procedures with significant risk of peri- and post-operative bleeding should be deferred for:
 - a. 12 months after DES
 - b. 1 month after bare-metal stenting
- 6) For patients who have received DES within the past year and who must undergo procedures that mandate discontinuation of thienopyridine therapy, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure to reduce the risk of "late" stent thrombosis

Based on these recommendations, we constructed an algorithm regarding the decision making prior to placing a coronary stent, and the recommendations following stent placement. (Figure 2)

Perhaps the most important guideline to follow in treating patients who have received DES is to ensure adequate communication between the patient, the cardiologist, and other health-care providers who are adjusting the patient's anti-platelet regimen.

SUMMARY

Significant advances in interventional cardiology have occurred over the past 30 years, leading to substantial increases in the number and anatomic complexity of treated patients, the long-term success of these procedures, and a reduction in the need for coronary bypass surgery. While the risk of restenosis has been dramatically reduced by drug-eluting stents, delayed neo-intimal healing has led to a small, but significant occurrence of "late" stent thrombosis. This thrombotic risk is substantially reduced by continuation of dual-anti-platelet therapy for one or more years following DES placement.

Current guidelines for patient selection for DES, for duration of DAT following DES, and for facing surgical and invasive procedures after DES were discussed, and the avoidance of early discontinuation of anti-platelet therapy following DES was emphasized.

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Discussion of off-label usage of a product: drug eluting stents

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