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Guest Editorial

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PERCUTANEOUS CORONARY INTERVENTION:
A CONTEMPORARY ASSESSMENT

It has been known for more than three centuries that chronic stable angina pectoris is most commonly caused by narrowing of one or more epicardial arteries. Andreas Grüntzig’s brilliant development of percutaneous transluminal coronary angioplasty (PTCA) in 1977 to relieve coronary obstruction was the first and most important step in the development of modern percutaneous coronary intervention (PCI), and represents one of the triumphs of twentieth-century medicine. Coronary revascularization by PTCA soon became a widely used and effective approach for the treatment of angina. When compared with coronary artery bypass surgery (CABG), PCI proved to be equally efficacious in the majority of patients. To the chagrin of cardiac surgeons, an increasing fraction of patients with disabling chronic stable angina selected PCI over surgery because it causes little discomfort and requires only a brief hospitalization and convalescence. Furthermore, it does not exclude subsequent surgery, should it be necessary.

As a result of the development of PCI, an important new specialty, interventional cardiology, developed and interventional cardiologists quickly became the “darlings” of both the profession and the public. In the early 1980s in North America and to a lesser extent in Western Europe, coronary angiography and PCI were carried out in patients with progressively less disabling angina. The “oculostenotic reflex” soon became widespread, viz, if a stenosis on the coronary arteriogram was visualized, then its immediate relief by PCI would be carried out almost reflexly by the interventional cardiologist.

However, three problems with PTCA soon emerged. The first was the development of restenosis caused by neointimal hyperplasia of fibromuscular tissue in the dilated coronary artery. This occurred in 35% to 40% of patients, requiring one and in some instances multiple repeat procedures. The second problem, fortunately much less...
The development, in 1986, of metal stents, at first bare-metal stents (BMS), inserted into the coronary artery following balloon angioplasty, was the second of the three major advances of PCI, since it essentially eliminated procedural coronary occlusions. Although BMS reduced coronary restenosis by one third, to about 20% to 25%, this remained a stubborn residual problem that did not yield to a large number of pharmacologic approaches that were explored. BMS also brought with them an uncommon, but often devastating, early complication—platelet-driven stent thrombosis. To avoid this, dual antiplatelet therapy, ie, aspirin and a thienopyridine, first ticlopidine and more recently clopidogrel, was required. This treatment was associated with its own risk—bleeding that was spontaneous or which accompanied cardiac (or other) surgery.

The development of drug-eluting stents (DES) in 2001 represents the third important advance of PCI. DES are coated by a carrier polymer and anti-inflammatory antiproliferative agents and have been successful in reducing restenosis substantially, to between 5% and 10%. DES have not eliminated the early stent thrombosis with its attendant high risk that was noted with BMS. Indeed, it appears that late stent thrombosis, ie, between 30 days and 1 year, and very late stent thrombosis (after 1 year), may actually be more frequent with DES than with BMS. Such late thromboses may occur because the anti-proliferative activity of the coating, which reduces the risk of restenosis, also inhibits reendothelialization, leaving the stent as a nidus for platelet aggregation. This complication may occur despite prolonged dual antiplatelet therapy, although patients who develop stent thrombosis despite such therapy often exhibit hyporesponsiveness to one or both of the antiplatelet drugs.

Moreover, patients with DES who discontinue dual antiplatelet therapy prematurely are at especially high risk of stent thrombosis, which, like coronary occlusion after PTCA, is associated with a very high incidence of mortality or massive nonfatal myocardial infarction. Long-term compliance with dual antiplatelet therapy is problematic and the need to interrupt it because of the occurrence of serious bleeding or because of refusal of payers to continue long-term reimbursement for thienopyridines may become re-
sponsible for a growing number of DES thromboses in the future. The duration of dual antiplatelet therapy required to minimize the risk of DES thrombosis has not yet been determined, but probably exceeds 1 year. In addition, DES may also cause local hypersensitivity reactions.

Where do we go from here? First, a rededication to meticulous deployment regardless of the composition or configuration of the stent is necessary. Second, continued research on DES should be strongly encouraged. New stents must steer a course between the Scylla of inadequate reendothelialization and the Charybdis of excessive neointimal hyperplasia. Ultimately, fully resorbable DES are likely to become standard. Formal prospective registries to ascertain long-term outcomes of patients with newly approved stents are essential to ensure maximum patient safety.

Second, a new look at the platelet P2Y12 component of dual antiplatelet therapy is indicated. Detection of hyporesponsiveness to clopidogrel and/or aspirin with a number of portable devices is now possible. In the not inconsiderable number of patients who exhibit hyporesponsiveness, the doses of these drugs could be increased. Prasugrel, a novel thienopyridine, has been shown to reduce both early and late stent thrombosis by half, albeit at the cost of an increased risk of bleeding. This drug is now wending its way through the regulatory process. Very potent nonthienopyridine P2Y12 blockers are also under active investigation.

Finally, and perhaps most importantly, a reconsideration of the indications for PCI is in order. While this procedure successfully eliminates or reduces the severity of stable angina pectoris, PCI has never been demonstrated to improve survival or reduce the incidence of acute myocardial infarction in these patients. Intensive medical management of angina has improved considerably since the introduction of PCI in the 1970s, and a trial of such therapy should be attempted before allowing the “oculostenotic reflex” to prevail. A medical strategy could be even more important when patients with asymptomatic or mildly symptomatic coronary obstruction are identified in increasing numbers as multislice computed tomographic coronary angiography becomes more widespread. Of course, if optimum medical therapy fails in a patient with severe angina, mechanical reperfusion is required; the specific method—PCI or CABG—depends on the coronary anatomy and left ventricular function.

The situation differs in patients with acute coronary syndromes. PCI, if carried out without delay after the onset of symptoms in patients with ST-segment–elevation myocardial infarction (STEMI) has been shown to be life saving and is now the treatment of choice for patients with this condition. When the thrombosis occurs in a large proximal coronary artery, as is often the case, late lumen loss and restenosis may be of less concern than when it occurs in a smaller coronary artery. Since PCI must be carried...
out immediately on presentation of patients with acute STEMI, it is often difficult in the very few minutes available to ascertain if the patient is likely to adhere to dual antiplatelet therapy for a prolonged period. Thus, DES may not be the stents of choice in these patients. In patients with unstable angina and non-ST-segment–elevation myocardial infarction, the need for PCI is also clear, since the composite end point of death or myocardial infarction is reduced by this procedure, DES may be quite useful in patients with this condition.

A number of dazzling advances in cardiovascular therapeutics have occurred during the last half century. However, none of these have been free of problems, either limitations of efficacy and/or the development of adverse effects. All have required continuous reassessment. PCI certainly stands tall among these advances. This issue of *Dialogues in Cardiovascular Medicine* provides a thoughtful, contemporary assessment of this important therapy.
Drug-eluting coronary stents: stents and stent-ability

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Stents are endoprosthetic scaffolding devices designed to enlarge the vessel lumen, seal dissections and create a rounder, smoother channel. Their advent has significantly advanced the field of interventional cardiology. Yet, metallic stents are associated with intima proliferation, causing in-stent restenosis and subsequent need for reintervention in a substantial number of patients. Considerable efforts have gone into the development of stents covered by an active coating designed to inhibit in-stent restenosis—the drug-eluting stent (DES). They proved to be highly efficacious in reducing reintervention rates, but by inhibiting stent-driven intima hyperplasia, they also delay vascular healing after the procedure, which exposes treated patients to the need for prolonged dual antiplatelet treatment and to the risk of delayed abrupt stent closure. Moreover, the synthetic nonbioerodable polymer containing the drug may be an important trigger of local vascular inflammation, which may ultimately contribute to long-term vulnerability of the implanted stent. Second-generation DES engineered with more biocompatible or even reabsorbable polymers are being developed, which hopefully will make DES equally safe as well as more efficacious than currently available bare metal stents.

HISTORICAL PERSPECTIVES

More than 30 years have passed since the beginning of clinical interventional cardiology on the occasion of the first angioplasty procedure performed by Andreas Grünzig on September 16, 1977. With the launch of a new era of device-based therapies, his legacy has translated into several new chapters in the history of medicine, pushing every other discipline, not just cardiovascular care, toward less invasive forms of treatment (Figure 1, page 240).

The first patient to undergo transluminal balloon dilatation was 38 years old (the same age as Grünzig) and had a discrete lesion in the proximal anterior descending coronary artery and disabling angina. Bernhard Meier, who as a resident in Zurich was taking care of the patient at the time, recounts that even though Grünzig told the patient that he was the first to undergo the procedure, the patient was enthusiastic to have an alternative to bypass surgery. With all the senior staff of the hospital in attendance, Grünzig performed the procedure, and recalled1:


SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
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<th>ABBREVIATION</th>
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<tr>
<td>BENESTENT</td>
<td>Belgian Netherland STENT [trial]</td>
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<tr>
<td>BMS</td>
<td>bare-metal stent</td>
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<td>DES</td>
<td>drug-eluting stent</td>
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<td>FIM</td>
<td>First-in-Man [trial]</td>
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<td>MACE</td>
<td>major adverse cardiac event</td>
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<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>SIRIUS</td>
<td>Sirolimus-eluting stent in de novo native coronary lesions [trial]</td>
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<td>STRESS</td>
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The catheter wedged the stenosis so that there was no antegrade flow and the distal coronary pressure was very low. To the surprise of all of us, no ST elevation, ventricular fibrillation or even extrasystole occurred and the patient had no chest pain. At this moment I decided not to start the coronary perfusion with the roller pump. After the first balloon deflation, the distal coronary pressure rose nicely. Encouraged by the positive response, I inflated the balloon a second time to relieve the residual gradient. Everyone was surprised about the ease of the procedure and I started to realize that my dreams had come true.

This patient remained free of angina, and when he underwent repeat catheterization on September 16, 1987, the anterior descending coronary artery was widely patent. Ten years later, he remained asymptomatic and in September 1997, he performed a maximal bicycle ergometric test with normal results.

In the early days of angioplasty, the guide catheters were made of Teflon and were extremely stiff. The balloon catheters were of a double-lumen design with a closed end and a short, nonmovable, and barely steerable guidewire attached directly at the tip of the balloon. The catheters were high profile, and recrossing the plaque after dilatation attempts was considered extremely dangerous. The procedure was guided by angiographic assessment, of poor quality at the time, and by measurement of the change in pressure gradient across the lesion. Pressures were measured from the tip of the balloon catheter and at the coronary ostium through the guide catheter. Even though the balloon catheter was high profile, which was causing a pressure gradient by itself, a significant reduction in translesional gradient could be documented after successful dilatations. Because of the lack of steerability of the balloon catheter, it was necessary to achieve selective intubation or at least selective direction of the guide catheter toward the artery to be intubated.

In 1982, at the urging of John Simpson and others, companies began to make steerable guidewires, which represented the first of a series of incremental quantum leaps in technology such that today, virtually all segments of the coronary tree can be reached without much difficulty.

Soon the initial enthusiasm was tempered by the high rate of stenosis recurrence, the restenosis process, a major problem in over 30% of patients undergoing angioplasty. Numerous reports on the incidence of restenosis began to appear. The pathological mechanisms of restenosis have been studied by a number of investigators. The restenotic lesion was found to be composed of cells very similar to smooth muscle cells with a great deal of extracellular matrix. Various correlates of restenosis were identified. Early randomized trials addressed the problem of restenosis by comparing anticoagulation regimens, without much success. Although antiplatelet agents were effective in preventing acute complications, none of these studies showed that antiplatelet or anticoagulant strategies influenced restenosis rates. Many other drugs were tested both in animal models and in humans. All of them eventually failed to have a significant impact on restenosis rates after balloon angioplasty.

This set the stage for the development of coronary stents. Stents are endoprosthetic scaffolding devices designed to enlarge the vessel lumen, seal dissections, and create a rounder, smoother channel. The first human implants of coronary stents occurred in 1986. The stent was the interwoven helical self-expanding design (Wallstent), which was used by Jacques Puel in Toulouse, France, and Ulrich Sigwart, in Lausanne, Switzerland. At the beginning, stents were mainly intended to be used as a backup after balloon angioplasty in cases of abrupt and/or threatened closure of the...
coronary artery following balloon dilatation. Abrupt vessel closure, complicating 6% to 8% of balloon angioplasty procedures, was associated with a 5% mortality, 40% rate of myocardial infarction, and 40% rate of emergency coronary artery bypass grafting. Not only were stents shown to significantly reduce these adverse events, it soon became obvious that much more effective and predictable dilatation results could be obtained.\(^\text{17,18}\) Subsequently, two landmark investigations proved that the systematic use of stents was associated with improved outcome and reduced restenosis rate compared with balloon angioplasty. Patients studied in the BElgian NEtherlands STENT study (BENESTENT)\(^\text{19}\) and the STress RESRestenosis Study (STRESS)\(^\text{20}\) underwent single-lesion angioplasty in vessels ranging from 3 to 4 mm in diameter. The reduction in restenosis was from 42% to 32% in STRESS and from 32% to 22% in BENESTENT. Many additional studies showed in a consistent manner that the use of stents was leading to predictable initial outcome and reduced restenosis rate, both contributing to decreasing the need for reintervention as compared with balloon angioplasty (Figure 2).

Yet, stented angioplasty has been plagued from the onset by early stent thrombosis (<30 days after index procedure). Indeed, initially, stent thrombosis rates as high as 24% raised serious doubts as to the viability of the therapy.\(^\text{21}\) Moreover, restenosis, now specifically due to in-stent neointimal proliferation of matrix and vascular smooth muscle cells, was not abolished by bare-metal stents (BMS), remaining at 30% to 40% with repeat revascularization still occurring in 15% to 20% of cases. Two further major developments revolutionized the practice and results of stented angioplasty. Paul Barragan in Marseille, and others in France, began to use antiplatelet therapy consisting of aspirin and ticlopidine instead of the cocktail of virtually all available anticoagulants given so far in attempting to prevent stent thrombosis.\(^\text{22}\) This practice spread rapidly throughout France and other countries. An understanding of the improved results with antiplatelet therapy was provided by Schomig and the group in Munich.\(^\text{23,24}\) Their study, comparing aspirin and ticlopidine therapy with warfarin therapy, demonstrated that the platelet activation occurring with the latter was not present when antiplatelet therapy alone was used. This is the likely explanation for the reduced (sub)acute throm-

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**Figure 2.**

A. **Upper left:** A blank picture of the right coronary artery shows the metallic stent struts of a previously implanted drug-eluting stent (arrow) and the heavily calcified vessel wall downstream. **Upper right:** Contrast injection shows diffuse in-stent restenosis with subocclusive luminal narrowing. **Lower left:** Intravascular ultrasound images inside the stent (level A) showing irregular and narrow lumen (green contours). The stent struts (thick hyperechogenic dots) have remained apposed against the vessel wall, but neointimal tissue has proliferated through stent struts, causing re-narrowing. **Lower right:** Intravascular ultrasound images recorded distally (level B) show the circular and superficial calcifications, preventing penetration of ultrasound in the deeper vessel layers (shadowing effect).

B. **Coronary angiography of the coronary vessel (2 projections) after overexpansion of a new drug-eluting stent deployed inside the previously implanted one, restoring a widely patent lumen.**
basis rate that has been seen in all published studies using antiplatelet therapy alone. These observations were then confirmed by numerous clinical trials.\textsuperscript{25,26} During the same time period, Antonio Colombo in Milan, Italy, who was pioneering intravascular ultrasound imaging, observed that many times stents were not fully expanded and were in poor apposition against the vessel wall, potentially a risk factor for thrombosis. These features were not discernible by angiography and his observations led to the use of high-pressure post-stent balloon inflations for more complete expansion of the metallic stent struts.\textsuperscript{27}

With the combined prescription of thienopyridines and aspirin for 4 to 8 weeks,\textsuperscript{28,29} together with proper stent deployment techniques,\textsuperscript{27} early stent thrombosis rates decreased to what was felt to be an unavoidable and acceptable 1% to 1.5%. Notably, it remains unknown still today what is the minimal time period during which it is indispensable to prescribe dual antiplatelet therapy after implantation of a given stent type. Stent implantation, inherently a thrombogenic procedure, initiates a complex interaction between the blood components and the metallic surface of the stent, which includes the deposition of protein, the activation of platelets, the complement system, and coagulation factors. Eventually, thrombi will propagate over the surface of the stent creating a confluent endothelial monolayer. Modifications of the metallic stent surface and various biologically inert surface coatings, such as carbon, platinum, phosphorylcholine, and gold have been applied to stainless-steel stents in an attempt to reduce thrombosis and restenosis, but the clinical effectiveness of these strategies has not been proven. Instead, gold coating resulted in increased rates of restenosis.\textsuperscript{30} Continuously ongoing efforts to reduce the \textasciitilde{30} late in-stent restenosis rates through various systemic pharmacological approaches remained unsuccessful until local radiation, a strong antiproliferative therapy (vascular brachytherapy), was applied to prevent or treat this condition.\textsuperscript{31-33}

While successful in reducing restenosis, vascular brachytherapy was the first illustration that delayed healing might portend an increased risk of thrombosis together with the expected reduction in neointimal proliferation and the less desirable lack of endothelialization. Indeed, stent thrombosis rates increased again up to 5.3%,\textsuperscript{34} and the time window of event occurrence was extended beyond 1 year so that the initial clinical benefit would eventually erode as time went by, a sequence of pathogenetic events that would repeat itself later as radiation was replaced by cytotoxic drugs.

**THE ADVENT OF DRUG-ELUTING STENTS**

Considerable efforts have gone into the development of stents covered by an active coating designed to inhibit in-stent restenosis—the drug-eluting stent (DES). The components of a DES can be divided into a platform (the stent), a carrier (usually a polymer), and an agent (a drug) to prevent restenosis. Stents are ideal delivery systems because they allow the local delivery of the active agent to the area of vascular injury, averting the need to deliver high doses systemically. The development of a suitable carrier to transport an appropriate agent has been challenging, since it must have mechanical resistance to abrasion during implantation, be nonthrombogenic, be the cause of inflammation of the vessel wall and tissue.\textsuperscript{26} Various types of coatings have been developed, including phosphorylcholine, biocompatible nonerodable, biodegradable, or bioabsorbable polymers, as well as ceramic layers. A drug that is successfully eluted should inhibit the complex cascade of events that leads to neointimal formation after stent implantation. The inflammatory and proliferative mechanisms of the general tissue-healing response and specific blood and vessel-wall components of the vascular reparative processes are potential targets for therapeutic approaches aimed at reducing neointimal proliferation (Figure 3). The success of eluting devices is highly dependent on each component of the complex, as well as on the interactions among these elements. Therefore, different DES brands will not share a class effect, since there is a myriad of possible iterations on each component of the drug-device combinations that may have significant therapeutic implications. Many proposed devices did not work and different DES differ in their ability to inhibit neointimal growth. Finally, because the results of short-term experiments in animal models cannot be directly translated to humans, specific clinical trials were required in order to establish the efficacy and safety for each device.

**FIRST-GENERATION DRUG-ELUTING STENTS**

The first positive clinical data on DES came from trials examining sirolimus-coated stents. Sirolimus, a natural macrocyclic lactone with potent antiproliferative, anti-inflammatory, and immunosuppressive effects, acts by inhibiting the activation of the mammalian target of rapamycin (mTOR), ultimately causing arrest of the cell cycle (Figure 3). The Cypher sirolimus-elut-
ing stent (Cordis, Johnson & Johnson) is produced by coating a stainless-steel stent with a thin layer of a nonerodable polymer containing sirolimus. The seminal first implantations of slow- and fast-release sirolimus-eluting stents, in the First-in-Man (FIM) clinical study, were performed by de Souza in São Paulo, Brazil, and Serruys in Rotterdam, the Netherlands. Four months after implantation, both formulations were associated with minimal neointimal hyperplasia, as measured by intravascular ultrasonography and quantitative coronary angiography. The slow-release formulation was subsequently selected for clinical use. In the Brazilian study, intravascular ultrasonography at 4 years revealed continued suppression of intimal hyperplasia in the group of 30 patients with the slow-release sirolimus-eluting stent, with an event-free survival rate of 87%. The results of the randomized, double-blind SIRIUS trial (SIRollimUS-eluting stent in de novo native coronary lesions), involving 1055 patients, were used to gain approval of the device by the Food and Drug Administration (FDA) in the United States in 2003. This pivotal trial confirmed the efficacy and short-term safety of the sirolimus-eluting stent in single, previously untreated coronary artery lesions, with a 91% relative reduction in angiographic restenosis compared with the otherwise identical BMS: 3.2% vs 35.4% (P<0.001).

Figure 3. Mechanisms of restenosis after stent implantation and targets of therapy with sirolimus including other “limus” agents and paclitaxel. Sirolimus analogs act through the same pathway as sirolimus. The restenosis cascade that is initiated after stent implantation is shown in green. The mechanism of action of sirolimus (and analogs) is shown in blue, whereas the mechanism of action of paclitaxel is shown in yellow.

The second DES that was released on the market was the polymer-based paclitaxel-eluting stent. Paclitaxel is a potent antiproliferative agent that inhibits the disassembly of microtubules (Figure 3). A series of studies (TAXUS) were conducted to collect data on 3 iterations of the stent platform, the Nir, the Express, and the Liberte stents (Boston Scientific). A copolymer coating (Transluete, Angiotech) is used for the biphasic release of paclitaxel, with an initial burst in the first 2 days, followed by lower-level release for 10 days. Unlike the sirolimus-eluting stent, a considerable amount of drug is kept within the polymer (ie, not fully released). The biologic and clinical consequences of this specific release kinetics remain elusive today. The randomized TAXUS-IV trial, involving 1314 patients, assessed the safety and efficacy of the slow-release paclitaxel-eluting stent in single, previously untreated lesions and led to FDA approval in 2004.30 Nine months after stenting, the need for a repeated procedure in the treated vessel was 4.7% in the group that received paclitaxel-eluting stents, as compared with 12.0% in the group that received BMS (P<0.001).

From the literature, the Cypher and Taxus stents appear to yield similar rates of repeat revascularization, although most comparative studies suggest that the luminal preservation achieved by the Cypher stent and measured by coronary angiography or intravascular ultrasound is slightly superior to that of the Taxus stent.31 Recent meta-analyses of all randomized comparisons between these two stents suggest that the use of Cypher is associated with a slightly lower need for reintervention in the previously instrumented vessel as compared with Taxus.32,33

**NEWER-GENERATION DRUG-ELUTING STENTS**

Despite considerable reductions in angiographic restenosis and need for repeat revascularization procedures, continued attention to the safety, efficacy, and deliverability of first-generation DES has led to the development of new antiproliferative agents with alternative stent platforms and different drug carrier systems. Numerous drug-device combinations have been tested, of which over 20 have received the CE (Conformité Européenne) certificate that is necessary for use in the European Union.34 So far, only two of these new-generation DES have received positive reviews by the FDA. Zotarolimus is a novel pharmacologic therapy that shares similar structure and biologic activity with the antirestenotic agent sirolimus, ie, it blocks the function of mTOR (Figure 3). The Endeavor stent is a cobalt-based alloy stent with a phosphorylcholine polymer loaded with zotarolimus at a dose concentration of 10-μg/mm stent length. It has been shown in preclinical studies that approximately 95% of zotarolimus is eluted from the stent within 15 days of implantation, although drug concentrations within surrounding vascular tissue may be detected as late as 30 days after stent deployment (data on file, Medtronic Vascular). To date, following the pivotal ENDEAVOR II study,35 4 additional clinical trials evaluating the safety and efficacy of zotarolimus-eluting stents have been completed. The ENDEAVOR IV study recently compared the zotarolimus-eluting stent with the paclitaxel-eluting stent in 1578 patients presenting with single de novo lesion in 2.5-3.5 diameter vessels with an overall lesion length of less than 28 mm.36 The primary end point of the study was target-vessel failure at 9 months with a prespecified noninferiority absolute margin of 3.8%. A subset of 328 patients underwent angiographic follow-up at 8 months. While in-stent late loss (ie, the largest loss of lumen diameter at follow-up that is due to intimal hyperplasia, Figure 4) was significantly higher in the Endeavor stent (0.67±0.49 mm vs 0.42±0.50 mm, P<0.001), this did not translate into a difference in terms of the primary end point (6.6% in the Endeavor vs 7.2% in the Taxus group), which satisfied the noninferiority end point (P<0.001 for noninferiority of the Endeavor compared with Taxus stent.

The everolimus-eluting coronary stent system is made available by two companies (Xience-V by Abbott Vascular company, IL, USA and Promus by Boston Scientific, MA, USA). Xience-V is comprised of the Multilink Vision stent and a drug-eluting coating. Everolimus is blended on a nonerodable polymer, coated over another nonerodable polymer primer layer. The coating comprises acyclic- and fluoropolymers, both approved for use in blood-contacting applications. This layer of everolimus-polymer matrix with a thickness of 5-6 microns is applied to the surface of the stent and is loaded with 100 μg/cm² of everolimus with no topcoat polymer layer. The stent is designed to release approximately 80% of the drug within 30 days after implantation. As a sirolimus analog, everolimus also inhibits mTOR (Figure 3). In the SPIRIT II trial, 300 patients were randomized to either everolimus- or paclitaxel-eluting stents in a 3:1 ratio. At 1 year, there was a significant difference in terms of major adverse cardiac events (MACE) in favor of the everolimus-eluting stent (2.7% vs 9.2% P=0.04).37 These results have recently been duplicated in the SPIRIT III study, involving 1002 patients recruited in 62 clinical sites in the US, which recently led to a favorable FDA review.38
LATE STENT THROMBOSIS: AN ISSUE OF DELAYED VASCULAR HEALING

While all four FDA-approved DES have shown superiority in terms of angiographic recurrence and clinical reintervention rates compared with uncoated stents, there is increasing evidence for both sirolimus- and paclitaxel-eluting stents that late adverse events related to abrupt stent closure (ie, late or very late stent thrombosis) are more frequent than with the use of BMS. Most striking is the fact that abrupt thrombosis might occur at later time points (beyond 1 year), which is reminiscent of acute coronary occlusions seen after radiation therapy. These thrombosis events are rare, but clinically severe, associated with sudden death or myocardial infarction in half of the cases. Absolute rates are difficult to capture because death and myocardial infarction can be the expression of the disease process itself. Definitions and criteria have varied from very specific to more inclusive, resulting in a range of underestimated to overestimated figures. The most conservative estimates indicate a 0.6% yearly incidence up to 4 years, corresponding to an incidence density of 1 case/100 patient years. Comparisons between devices will require the use of standardized definitions, such as provided by the Academic Research Consortium. Time will tell whether this incremental risk of late stent thrombosis also applies to the newer-generation DES, although available data up to 4 years following implant of the Endeavor stent seem to indicate that no such incremental risk is present with use of this specific drug-device combination. Autopsy studies have shown that after BMS deployment an inflammatory reaction takes place in the vessel wall that involves macrophages and T lymphocytes with few B lymphocytes and giant cells. After implantation of first-generation DES, a more pronounced inflammatory response has been described that may occasionally be associated with a local hypersensitivity reaction and eosinophilic infiltration. The synthetic nonbioerodable polymer containing the drug may be an important trigger of local vascular inflammation, even though the metal struts or the drug itself may participate in this phenomenon. Virmani and colleagues first described a case of local hypersensitivity reaction with extensive vasculitis of intima, media, and adventitia consisting predominantly of lymphocytes and eosinophils in a patient presenting with very late thrombosis after sirolimus-eluting stent implantation. Histopathological analysis revealed aneurysmal dilatation of the vessel wall within the stented segment with evidence of stent malapposition and thick fibrin thrombus between the stent and the arterial wall. Incidence and clinical relevance of hypersensitivity reactions stems from a registry, with 17 of 5783 patients reporting hypersensitivity symptoms probably or certainly related to DES. Chronic vessel inflammation may lead to positive vessel remodeling and stent malaposition. A pooled analysis of intravascular ultrasound studies after sirolimus-eluting stent (8.5% vs 0%, P<0.05) and paclitaxel-eluting stent (8.4% vs 3.5%, P<0.05) implantation revealed a higher incidence of incomplete stent apposition with DES compared with BMS that was not associated with MACE in the short term. In

Figure 4. Left: In-stent late loss. The lumen diameter inside the stent is measured by computerized quantitative coronary angiography. The focal point of minimum lumen diameter (MLD) is identified on the immediate postimplantation angiogram (upper row, post--drug-eluting stent [DES]) and repeated on the late angiogram (typically acquired 6 to 9 months later). Late loss as the difference between minimum lumen diameters (early minus late) is an angiographic metric of restenosis propensity of coronary stents. Middle: The computer searches for the minimum diameter inside the stent as well as on the native vessel on both stent edges (about 5 mm on each side). Right: In-segment late loss. Figures are representative of those observed in the SIRIUS trial (SIRolImUS-eluting stent in de novo native coronary lesions) after implantation of a short sirolimus-eluting stent in a 3-mm vessel.
contrast, a study of 13 DES patients undergoing intra-coronary ultrasound before emergency percutaneous coronary intervention (PCI) at the time of very late stent thrombosis showed a higher incidence and larger area of incomplete stent apposition compared with a control group of 144 event-free DES patients (frequency, 77% vs 12%; \( P<0.001 \)). The following pathological mechanisms were identified as associated or possibly causally related to DES thrombosis: chronic inflammation/hypersensitivity reaction, stenting over major side branches, or bifurcation stenting using the crush technique, overlapping DES edges, malapposition related to positive arterial remodeling or incomplete stent expansion, in-stent restenosis with superimposed thrombus, resolution of mural thrombus initially jailed by stent struts, and penetration of necrotic core by stent struts.

In a recent necropsy comparison of 23 DES cases with 25 BMS cases (>30 days after the index procedure), delayed healing manifested by persistent fibrin deposition and incomplete reendothelialization emerged as an important discriminator between BMS and DES (Figure 5) \(^{49} \). Endothelialization (27%±26% versus 66%±25% versus 90%±21%) was reduced, whereas fibrin scores (3.0%±0.9% versus 1.9%±1.1% versus 0.9%±0.8%) were increased in DES patients with late stent thrombosis, different from both patients with patent DES and BMS. Endothelialization was nearly complete in BMS specimens examined beyond 6 months, whereas incomplete endothelialization in DES specimens persisted beyond 40 months. Poor stent strut coverage was confirmed in humans by angioscopic examination of the inner lining of the stented vessel segment. \(^{50} \)

Several recent clinical investigations support the notion of reduced or dysfunctional endothelialization after DES implantation. \(^{51-53} \) Normal vasodilatory responses to various stimuli such as exercise, pacing, or intracoronary delivery of acetylcholine were blunted or replaced by constriction in coronary segments proximal and distal to the stented area. Functional abnormalities tended to be more pronounced with some DES brands than with others. \(^{53} \) Finally, drugs released from the drug-polymer combination may exert a thrombogenic effect on their own. Paclitaxel and sirolimus have been
reported to enhance endothelial tissue factor expres-
sion, a cell surface receptor for coagulation factor VII, the principal activator of the coagulation cascade that activates factors IX and X.54,55

In summary, delayed healing and impaired endothelial-
ization are common features of most cases of late and
very late stent thrombosis, and represent the likely
due to this severe adverse event. In contradistinc-
tion to the thick layer of neointima that forms after balloon
angioplasty or BMS implantation, the surface cover-
age on a DES may be thin and brittle or even absent
and thus prone to rupture, not unlike a vulnerable
plaque. It remains to be explained why sirolimus-elut-
ing stents are not more susceptible to this problem
than paclitaxel-eluting stents in light of their attested
thinner neointimal coverage. Inhomogeneity of neo-
timal hyperplasia with the paclitaxel-eluting stent (thin
on struts, thicker between struts) may account for this.
Long-term follow-up of newer DES will be pivotal to
assess the incidence of late and very late stent throm-
bosis for these devices that are intended to reconcile
absence of restenosis and late safety without interfer-
ing with vascular healing and endothelial function.

SYSTEMIC ANTIPLATELET THERAPY

Recognizing that the pathogenesis of late stent throm-
bosis is multifactorial and the importance of local
factors, one should not underestimate the key role of
systemic factors. Poor response to antiplatelet therapy
and the many conditions causing a permanent or tran-
sient increase in the propensity for arterial thrombo-
sis will both contribute to an increased risk of stent
thrombosis. Whether or not a patient is at increased
risk for stent thrombosis and for how long will depend
on the complex interplay between the many possible
combinations of any of the abovementioned local and
systemic factors. With the use of first-generation DES,
an empirical approach has been to prolong the duration of
dual antiplatelet effect so as to match the presumed
window of increased risk. A retrospective analysis of
the Duke database suggested that there is possible
benefit associated with extension of dual antiplatelet
therapy from 6 months to 1 year.56 This practice is now
endorsed by international guidelines57,58 Protagonists
argue that long-term antiplatelet therapy might have
a favorable effect on the natural course of coronary
patients in whom events are also caused by systemic
atherosclerosis. There are, however, several drawbacks
to this approach. All subjects receive blanket therapy,
while only few might actually be at risk, for a variable,
device-specific time period. Presently, these individu-
als at risk who could benefit from the prolonged ther-
apy cannot be identified. Under these circumstances,
blanket pharmacological prevention of a rare event
makes little sense from an epidemiological perspective
and can simply not be cost-effective. Secondly, this
approach weakens the weaker even further. Elderly pa-
tients or patients with severe comorbidities are more
likely to be in need of noncardiac diagnostic or surgi-
cal interventions that either require treatment inter-
ruption or will be associated with increased complica-
tion rates when performed under dual antiplatelet
therapy. Thirdly, long-term dual antiplatelet therapy
has been associated with excess bleeding in all previ-
ously published large trials, including the recently re-
ported TRITON study.59 Finally, enforcing an obligatory
long-term systemic drug-device combination annihi-
lates the fundamental promise of DES, which was based
on local delivery of tiny amounts of drug, therefore
devoid of systemic side effects. From a cost perspec-
tive, one is not easily inclined to add yet another drug
to the already long list of medicines that are prescribed
to coronary patients. These important issues are dis-
cussed in greater detail in the contribution by Pfisterer
et al in the present issue.

Thus for the time being, the option of extending the
duration of dual antiplatelet therapy ... forever (?) is
empirically envisaged after implantation of first-gener-
ation DES, but does not represent a true, sustainable
solution to the problem for the future. Poor responders
to antiplatelet agents obviously represent an except-
on.60 When properly identified at the time of stent im-
plantation, these patients will require a systemic solu-
tion to their systemic problem, be it an increase in the
dose of clopidogrel or prescription of a more potent
drug such as prasugrel.

PRECLINICAL AND CLINICAL
EVALUATION OF FUTURE
DRUG-ELUTING STENTS

Until the concerns with late stent thrombosis were rec-
ognized, attention was primarily, if not exclusively,
247
focused on the antirestenosis properties of DES.61,62
Today, the emphasis is placed on their efficacy-safety
ratio, which appears to depend on the balance between
the early benefit, namely the desired antirestenosis ef-
fect, and the late hazard, driven by the rare, but severe,
complication of stent thrombosis. This new concept,
at times called “net clinical benefit,” is increasingly
often recommended as an appropriate, patient-driven
end point for evaluation of newer-generation devices.
Much more attention will be given to safety indicators
Drug-eluting coronary stents: stents and stent-ability - Wijns and Valgimigli

EVALUATION PATHWAYS FOR DES

<table>
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<tr>
<th>1st generation</th>
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<tr>
<td>Preclinical</td>
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<td>First-in-Man (FIM)</td>
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<tr>
<td>(Dose-response &amp; kinetics)</td>
<td>(Dose-response &amp; kinetics)</td>
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<tr>
<td>Pivotal randomized trial</td>
<td>Pivotal randomized trial</td>
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Superiority vs BMS
Powered for combined clinical/angiographic end points
- Complex lesion/patient subset
- Real-life registry

Noninferiority vs 1st DES
Powered for angiographic efficacy end points
- Complex lesion/patient subset
- Real-life registry

Table 1. Preclinical and clinical evaluation scheme of drug-eluting stents (DES). New drug-device combinations are tested for noninferiority against first-generation DES (Cypher or Taxus). The Endeavor stent has been tested for superiority against bare-metal stent (BMS) and noninferiority against both Cypher and Taxus. None of the published stent trials are powered for clinical outcome (death, nonfatal myocardial infarction). The value and limitations of these evaluation schemes are discussed in the contribution by Shah and Schulman in this issue.

Among the many options, one could mention the everolimus-eluting stent\(^{37,38}\) and the Resolute zotarolimus-eluting stent\(^{65}\), both are using durable, as well as more biocompatible, polymers. Other options have incorporated biodegradable polymers, namely the biolimus-A9 eluting program that was applied to several stent platforms\(^{66}\) or the sirolimus-eluting device using the modified stent platforms in which the drug is released from tiny reservoirs. Several research teams are developing fully biodegradable stents in combination with drug elution.\(^{67,68}\) The objective is to provide the necessary mechanical scaffold and prevention of restenosis for a finite period of time after which the vessel would regain its natural state, without leaving behind a permanent implant and the appended downsides. This concept would be devoid of many currently faced issues such as chronic inflammation, delayed vessel healing, disturbed vasomotion or incompatibility with radiation-based or magnetic resonance imaging and later bypass surgery.

All these novel options, some of which have reached an advanced stage of clinical evaluation, are indicative of the wide spectrum of higher effectiveness in combination with increased biocompatibility that will eventually be achievable with the future generations of DES. How the availability of DES will continue to impact on treatment choices for patients with coronary artery disease is discussed by Adgey et al in the present issue of Dialogues in Cardiovascular Medicine.
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Randomized comparison of Nobori, Biolimus A9 drug-eluting coronary stent with a Taxus, paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the Nobori 1 trial.

Comparison of in vivo acute stent recoil between the bioabsorbable everolimus-eluting coronary stent and the everolimus-eluting cobalt chromium coronary stent: insights from the ABSORB and SPIRIT trials.

Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial.
Drug-Eluting Stents in Angina

Expert Answers to Three Key Questions

1. Medical therapy, surgery, or PCI: does (or should) the availability of drug-eluting stents influence the decision?
   
   A. A. J. Adgey, B. M. Glover, S. J. Walsh

2. Antiplatelet therapy: what to do if the patient with a drug-eluting stent needs elective noncardiac surgery?

   M. Pfisterer, M. J. Zellweger, M. Filipovic, F. Nietlispach

3. What are the regulatory and economic challenges posed by drug-eluting stents?

   B. R. Shah, K. A. Schulman
While optimal medical therapy improves prognosis in a significant number of patients with stable coronary artery disease (CAD), revascularization either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is often required. This may be to reduce symptoms and/or improve prognosis in certain subgroups using PCI. Drug-eluting stents (DES) have been shown to reduce in-stent restenosis and target-vessel revascularization compared with bare-metal stents. This has led to the hypothesis that outcomes after multivessel coronary stenting with DES might be comparable to surgical revascularization for some patient groups. We review the evidence for medical therapy in CAD, and assess when patients should be considered for PCI or CABG, DES, and the risks associated with DES implantation.

**Keywords:** stable coronary artery disease; revascularization; drug-eluting stent; sirolimus; paclitaxel

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**WHAT EVIDENCE DO WE HAVE FOR MEDICAL THERAPY, CABG, OR PCI?**

There is considerable debate regarding the benefits of optimal medical therapy in patients with stable angina who may constitute up to 85% of patients undergoing percutaneous coronary intervention (PCI) in the US.\(^1\) The Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation (COURAGE) trial in patients with stable coronary artery disease compared all-cause deaths or nonfatal myocardial infarction (MI) in >2000 patients randomized to either optimal medical therapy with or without PCI.\(^2\) There was no difference in either the primary end point for either group (over a median of 4.6 years). Although there was no difference in the frequency of angina at 5 years, one third of patients in the optimal medical therapy group subsequently underwent a revascularization procedure. Therefore, the results of this study support the role of PCI in symptom relief in patients with stable coronary artery disease. It should also be noted that patients who are known to improve prognostically from revascularization were not included in

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BARI</td>
<td>Bypass Angioplasty Revascularization Investigation</td>
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<td>BMS</td>
<td>bare-metal stent</td>
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<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<td>CASS</td>
<td>Coronary Artery Surgery Study</td>
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<td>COURAGE</td>
<td>Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation</td>
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<td>DES</td>
<td>drug-eluting stent</td>
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<td>LMCA</td>
<td>left main coronary artery</td>
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<td>MASS II</td>
<td>Medicine, Angioplasty, or Surgery Study–2</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>NSTEMI</td>
<td>non-ST-segment–elevation myocardial infarction</td>
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<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>POBA</td>
<td>plain old balloon angioplasty</td>
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this trial such as those with ongoing unstable symptoms, prognostically unfavorable stress tests, left main stem disease, and multivessel disease with significant left ventricular dysfunction. It is therefore reasonable to postulate that CABG would not have led to a significant survival benefit either, over modern optimal medical therapy for the population who were investigated. In the Medicine, Angioplasty, or Surgery Study–2 (MASS II) study there was no survival benefit for either PCI or coronary artery bypass grafting (CABG) above medical therapy over 1 year when lower-risk patients were treated. Of those undergoing PCI in the UK, in approximately 50% it is associated with acute coronary syndromes and the results of COURAGE do not apply to these patients (<2% of COURAGE patients had Canadian Cardiovascular Society (CCS) class 4 angina at presentation). As with any population of patients with coronary disease, there is a spectrum of patients who will require revascularization by either PCI or CABG for symptom reduction or to improve prognosis. For the majority of these patients, there are no overwhelming data to support either strategy at present. Ultimately, some patients are not suitable for either modality of revascularization due to technical limitations or severe comorbidity. In addition, those with stable symptoms do not require revascularization either prognostically or for symptomatic benefit and do well with medical therapy. Physicians must help make choices for individual patients on the clinical information, the available evidence, and the wishes of the patient. Up-to-date evidence demonstrating improved prognosis of CABG over optimal medical management is limited. Many studies were carried out before the development and widespread use of contemporary treatments and also modern surgical techniques. It should be remembered that the initial results of the Coronary Artery Surgery Study (CASS) demonstrated no survival benefit for surgery over medical therapy over a 5-year period in patients with normal ventricular function. The survival advantage for CABG over medical therapy in patients with significant LMCA stenosis is generally accepted and also applied to LMCA equivalents (>70% ostial left anterior descending and left circumflex). At present, historical rather than contemporary trial data continue to drive practice toward surgical revascularization for patients with reduced LV function (ejection fraction >30% and <50%) and for those with diabetes. Those with severe impairment of LV function (ejection fraction <30%) are rarely entered into surgical trials. Direct comparisons between PCI and CABG are also hindered by a lack of contemporary evidence. The long-term results of the Bypass Angioplasty Revascularization Investigation (BARI) study demonstrate a
significant survival advantage for patients with diabetes undergoing CABG. Despite, in this trial, the comparison of angioplasty and CABG, there is almost identical long-term survival in nondiabetic patients. While it is accepted that there is a clear need for an increase in repeated revascularization with bare-metal stents (BMS) compared with CABG, there are no clear benefits in survival for the vast majority of patients who undergo surgical revascularization.

Relatively recent studies have also documented no benefit of surgery for reducing major adverse cardiovascular events with CABG over PCI. Furthermore, there are no long-term differences in survival for CABG patients compared to those treated by PCI in the Arterial Revascularization Therapies Study [ARTS], ERACI II (not an acronym), or the MASS II studies. A recent comprehensive meta-analysis of almost 10,000 patients in randomized studies comparing these revascularization strategies (CABG versus PCI both with or without coronary stents) reaches the same conclusion. CABG confers no survival benefit for the patients enrolled in these trials.

It may be that over a very long period of time (greater than 10 years) any advantages of CABG are lost progressively due to worsening graft disease. As graft failure increases with time, clinical events will undoubtedly increase and it seems reasonable to assume that mortality will also accelerate as this occurs.

Current guidelines advocate an early invasive strategy for the majority of patients with non-ST-segment–elevation acute coronary syndromes, especially those at highest risk. While a symptom-driven conservative strategy may be warranted in some patients with a stabilized non-ST-segment–elevation myocardial infarction (NSTEMI), there is sufficient evidence of a reduction in death, MI, or hospitalization in the long-term to support early consideration of revascularization for patients with non-ST-segment–elevation acute coronary syndromes.

In general, patients with these forms of acute coronary syndromes will be at increased risk of future cardiac events. Those with LMCA disease, diabetics with multivessel disease, and patients with significant left ventricular systolic dysfunction (although severe dysfunction precludes surgery) will usually be considered for CABG. Of those, patients with severe comorbidities will usually be referred for PCI as they are unsuitable for CABG due to an unacceptable operative risk. A large proportion of patients do not fall into these categories, and where revascularization is indicated, it is most frequently performed by PCI.

Contemporary trial data that specifically compare outcomes for patients with non-ST-segment elevation acute coronary syndromes managed medically, by PCI or surgery are lacking. The Veterans’ Affairs Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial found comparable survival with CABG and PCI for those at high operative risk at 3 years follow up. All patients had ongoing unstable ischemia and one third of the patients had had an MI within 7 days of randomization. Interestingly, just over half the PCI patients had stents deployed. Similarly, the Arterial Revascularization Therapy Study (ARTS), which compared PCI with CABG also included =1/3 of patients with unstable angina, found identical 3-year survival rates without stroke or MI in addition. Both studies reported more repeat revascularization procedures with PCI.

**DRUG-ELUTING STENTS: A BALANCED VIEW OF THE EVIDENCE IN 2008**

The use of intracoronary stents has been routine in clinical practice for over a decade. It is widely accepted that these improve clinical outcomes over plain old balloon angioplasty (POBA), principally by reducing early acute vessel closure and subsequently restenosis of target lesions. This results in a reduced need for repeat revascularization procedures compared with POBA. However, with BMS there is still a significant incidence of neoimtimal proliferation, vessel lumen compromise, and recurrent angina. This has been reported to result in a revascularization rate of 10% to 25% within 1 year of PCI (BMS) in the UK. In order to reduce this problem, stents coated with an antiproliferative agent have been developed: drug-eluting stents (DES). Many trials have now been carried out that demonstrate a highly significant reduction in in-stent restenosis and the need for target-vessel revascularization when DES are compared with BMS.

In-stent thrombosis, although much less common than in-stent restenosis, generally results in an acute MI and also has a significant mortality. Historically, this complication occurred with BMS before reintervention had occurred and it is less common in BMS 4 weeks after implantation. Recently, it has become apparent that there is a small, but significant, increased risk of very late stent thrombosis associated with DES. This is mainly attributed to incomplete endothelialization of these devices, although there may be additional pathophysiological mechanisms involved (such as chronic inflammation associated with the stent coating). Beyond the first year after DES im-
plantation there is an accumulation of very late stent thrombosis events at around 0.4% to 0.6% per annum.\textsuperscript{23} The increased event rates in DES patients were unmasked after 18 months of follow-up in the seminal DES studies.\textsuperscript{24} Overall, in terms of mortality and MI, the late incidence of stent thrombosis with DES is counteracted by previously unrecognized thrombotic events and the increased risks of in-stent restenosis in BMS (Figure 2).\textsuperscript{25,26} It is now apparent that BMS restenosis is associated with a significant number of MIs. Therefore, while late thrombotic events result in an excess of adverse events with DES, it is important to remember that the benefit conferred by these devices is a large reduction in target-vessel revascularization and that they do not lead to less major clinical events (death or MI).

![Figure 2](image.png)

**Figure 2.** A comparison of the evidence for drug-eluting stents versus bare-metal stents for: (A) Major adverse cardiac events (MACE); (B) In-stent restenosis; (C) Mortality (all-cause); (D) Subacute thrombosis.

In view of these findings, most current clinical practice is based on the clinical scenario. In acute MI (where there is increased thrombogenicity), there are still concerns regarding late stent thrombosis with DES implantation. Ongoing randomized studies will shed further light on the use of DES in these patients. In smaller vessels, longer lesions, and patients with diabetes mellitus, where the risk of in-stent restenosis is high, and in patients who have already had an episode of BMS in-stent restenosis, there is a clear advantage of DES. DES are also frequently used for treating other lesions such as LMCA disease, bifurcation lesions, chronic total occlusions, and saphenous vein grafts, despite the lack of availability of robust randomized clinical trial data. These lesions are all known to be at high risk of restenosis and it is reasonable to postulate that DES would lead to significant benefits for these patients over BMS.

Several drugs have now been investigated on different stent platforms and/or with different polymer coatings (that may have biological effects of their own that are distinct from the eluted drug). The most studied drugs to date are sirolimus and paclitaxel. Investigations are currently ongoing with these drugs as well as with stents coated with zotarolimus, everolimus, tacrolimus and other novel agents.

At present, the cost-benefit of DES is a hotly contested debate. This subject is currently being examined in the United Kingdom by the National Institute of Clinical Excellence. Evidence continues to accumulate that the cost of DES (at present prices) may well be in excess of the benefits that are conferred to patients and thus health care systems. DES are most cost-effective for patients when the risk of restenosis is highest. This is particularly the case in those with 2 or 3 risk factors for restenosis, ie, small vessels (<3.0 mm in diameter), long lesions (>20 mm), and in diabetics.

**DOES (OR SHOULD) THE AVAILABILITY OF DRUG-ELUTING STENTS INFLUENCE THE DECISION?**

The reality of clinical medicine is that randomized controlled trials cannot provide answers to all of our clinical dilemmas. There are circumstances where, on the basis of current evidence and practice guidelines, CABG is the preferred method of revascularization. Until there are data to the contrary, patients with LMCA disease and diabetics with multivessel disease and left ventricular dysfunction should be considered for surgery when it is clinically feasible.

As discussed previously, the majority of studies of patients who were randomized to CABG or PCI with BMS consistently demonstrate no difference in outcomes for death or major adverse cardiovascular events in the medium or long term. However, there is a very clear risk of increased repeat revascularization procedures with PCI using BMS compared with CABG.

It is apparent that DES will greatly reduce this complication. We already know that these devices are highly effective at preventing in-stent restenosis and subsequent target-vessel revascularization on the basis of large-scale multicenter randomized controlled trials that have enrolled many thousands of patients. There are already some non-randomized data to show that these devices confer these benefits to patients with multivessel disease who are also treatable by CABG.

Furthermore, as we strive to achieve complete revascularization for these patients, we will be treating longer, more complex lesions in smaller vessels and a significant proportion of patients will be diabetics. These are the patients who have most to gain from DES use. The forthcoming randomized studies (SYNTAX and FREEDOM [not acronyms]) will provide robust scientific evidence that reflects best medical care as well as contemporary interventional and surgical practice. These studies will help to answer which patients are best served by either procedure.

DES are clearly needed for patients with multivessel disease and their availability is important when interventionalists consider the best treatment option for their patients. Furthermore, the second-generation of these devices is likely to be more biocompatible and/or absorbable. It is likely that further improvements in DES technology will further reduce the risk of late thrombotic events and improve the benefits offered by DES. The availability of DES is important for our patients and should influence the decision regarding the mode of revascularization for patients who require this treatment.

**CONCLUSION**

In summary, DES are a safe and effective technology. These devices are effective for reducing in-stent restenosis and target-vessel revascularization after PCI. BMS restenosis is not a benign phenomenon and there is a clear need for DES use in certain patients. This efficacy comes at a small risk of very late stent thrombosis, although preventing events that would otherwise be associated with BMS offsets this risk over the long term. DES do not produce an excess number of deaths or MIs up to 4 years. These devices
are a relatively expensive technology when cost-benefit ratios are examined for universal use during percutaneous revascularization procedures. The next generation of DES will be specifically designed to obviate the risk of late thrombotic events and may lead to further benefits over BMS if this goal can be achieved.

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Arterial Revascularization Therapies Study part II—Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions.
Drug-eluting stents (DES) reduce restenosis, but carry a small risk of late stent thrombosis. Dual antiplatelet therapy is the treatment of choice after DES implantation. Early discontinuation of this therapy, eg, in patients in need of noncardiac surgery, is an important risk factor for stent thrombosis with a high risk of death or myocardial infarction. Therefore, such surgery should be delayed for up to 12 months. If it cannot be, one has to balance risks and benefits of continued antiplatelet therapy. Generally, the risk of stopping dual antiplatelet therapy in the perioperative period appears higher than to perform surgery on continued therapy, except for brain surgery. We discuss evidence-based data that go into this risk-benefit analysis and how to manage these situations practically.

**Keywords:** drug-eluting stent; antiplatelet therapy; noncardiac surgery; stent thrombosis; myocardial infarction

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>BASKET-LATE</td>
<td>BAse Stent Kosten-Effektivitäts Trial–LAte Thrombotic Events</td>
</tr>
<tr>
<td>BMS</td>
<td>bare-metal stent</td>
</tr>
<tr>
<td>CURE</td>
<td>Clopidogrel in Unstable angina to prevent Recurrent Events (trial)</td>
</tr>
<tr>
<td>DES</td>
<td>drug-eluting stents</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>PREMIER</td>
<td>PReterax in albuminuria rEgRession</td>
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**Figure 1:**
In BASKET-LATE, these late stent thrombosis events occurred after stopping clopidogrel, and therefore the question arose whether even longer dual antiplatelet therapy may prevent these events. Unfortunately, no randomized controlled trial has been performed so far to
answer this question. An observational registry study from the Duke Clinical Research Institute suggested that there was a better 2-year outcome if DES patients were still on dual antiplatelet therapy after 12 months. This led to recommendations by the Food and Drug Administration and new European Society of Cardiology guidelines to use dual antiplatelet therapy after DES implantation for 12 months in patients not at increased risk of bleeding. The notion that dual antiplatelet therapy may in fact prevent these late stent thrombosis events is, however, questioned by observations from two large prospective registry findings showing that late stent thrombosis occurs in about 25% of patients despite dual antiplatelet therapy, and that in multivariate analysis dual antiplatelet therapy cessation is a predictor of such events only within the first 6 months, but not thereafter. Still, most interventional cardiologists seem to follow at present the recommendation to use dual antiplatelet therapy at least for 12 months.

However, if elective surgery is proposed as is the case in at least 5% of patients for prostate surgery, hip replacement, etc., the question will be whether dual antiplatelet therapy can/should be stopped prematurely or whether surgery can/should be postponed and how long. This means that the risk of bleeding during surgery on dual antiplatelet therapy has to be balanced against the risk of stent thrombosis following premature discontinuation of dual antiplatelet therapy. The American College of Cardiologists/American Heart Association (ACC/AHA) guidelines suggest, based on expert opinions, postponing surgery for at least 12 months in patients with DES.

There is no question that emergency surgery, if indicated, has to be performed in patients with DES on the current treatment, which will be dual antiplatelet therapy within the first 12 months after stenting. There is no question that emergency surgery, if indicated, has to be performed in patients with DES on the current treatment, which will be dual antiplatelet therapy within the first 12 months after stenting.

Unfortunately, there are no large scale randomized controlled trials to assess the bleeding risk in these procedures with and without antiplatelet therapy. The Antithrombotic Trialists Collaboration determined a rate of spontaneous bleeding on dual antiplatelet therapy of 0.7% to 1.13% (relative risk increase of 37%) compared with aspirin alone and this was 2.7% to 3.7% (27% increase in relative risk) in the Clopidogrel in Unstable angina to prevent Re-Current Events (CURE) trial. A large meta-analysis of more than 400 studies assessing the impact of aspirin alone on preoperative blood loss showed an increased hemorrhagic risk of aspirin by a factor of 1.5, however, without increases in surgical morbidity or mortality. Therefore, it seems documented that antiplatelet therapy does increase perioperative surgical bleeding by at least 50%, with, however, mostly minor bleedings, but that surgical outcomes, morbidity, and mortality are not significantly changed, except for intracranial surgery.

In order to avoid excessive perioperative bleeding, surgeons and anesthesiologists usually ask for withdrawal of antiplatelet therapy before surgery. However, this is associated with several risks by itself: there is a certain rebound effect, even after stopping aspirin, and aspirin withdrawal was associated with a 3 times higher cardiac complication rate in a meta-analysis of 50 279 secondary prevention patients (odds ratio [OR] 3.14; P=0.0001). This risk was higher (OR 89.8) in patients after...
Drug-eluting stents and noncardiac surgery - Pfister and others

stenting and the delay between stopping aspirin and these thrombotic events was 10 to 14 days.\textsuperscript{9,10} In the PREtension registry (PREMIE\textsuperscript{R}) registry, premature stopping of clopidogrel was associated with a 9-fold increased mortality within 1 year,\textsuperscript{11} indicating the high mortality in such patients. This increased bleeding risk is also seen in coronary artery bypass grafting on dual antiplatelet therapy.\textsuperscript{12}

After stent implantation, the risk of antiplatelet therapy discontinuation seems to be different early, i.e., within the first 6 (to 12) months, and thereafter. There are numerous studies documenting the catastrophic effect of early stopping of clopidogrel or even dual antiplatelet therapy.\textsuperscript{12,13} Independent predictors of early stent thrombosis (i.e., within the initial 6 to 12 months after stenting) were identified as small vessel stenting, stenting of bifurcation lesions, patients with diabetes or renal failure, a suboptimal angiographic result, and early cessation of dual antiplatelet therapy.\textsuperscript{14–19} In contrast, the relation between dual antiplatelet therapy and late or very late stent thrombosis seems less clear after 6 to 12 months. Stent thrombosis and related clinical events may occur during this late phase despite continued antiplatelet therapy. In addition, no clustering of the occurrence of stent thrombosis events was noted after stopping clopidogrel, neither in BASKET-LATE\textsuperscript{2} nor in the Berne-Rotterdam registry.\textsuperscript{4} Stopping clopidogrel was no predictor of stent thrombosis after 6 months in another Italian-German study.\textsuperscript{5} Acute coronary syndrome seems to be the only independent predictor of stent thrombosis after 6 to 12 months.\textsuperscript{2,4,5} Thus, whereas there is strong evidence for the danger of stopping dual antiplatelet therapy during the initial 6 months after DES placement, this is much less clear and even questioned after (6 to) 12 months. This led to an ACC/AHA Task Force statement warning not to stop dual antiplatelet therapy prematurely.\textsuperscript{20}

**HOW SHOULD DES PATIENTS IN NEED OF NONCARDIAC SURGERY BE MANAGED?**

In front of a patient with a DES in need of noncardiac surgery, the first question will always be whether surgery cannot be delayed up to after the initial 6—or preferably 12 months—after DES implantation, when the risk of stent thrombosis is lower. If that is possible, then stopping clopidogrel after 12 months is an option and surgery may be performed on aspirin alone. Still, the risk for late stent thrombosis remains and exposes the patient to a somewhat higher risk of cardiac events compared with the general population.\textsuperscript{21} If postponing surgery is not possible, one has to balance the risks of surgical bleedings on dual antiplatelet therapy against those of stent thrombosis after premature stopping of dual antiplatelet therapy. In view of the data showing that surgical bleeding rates are increased by at least 50% without significantly altering overall surgical outcomes and the possibility of managing perioperative bleeding complications by transfusions of red blood cells or fresh thrombocytes on the one hand, and the catastrophic clinical outcomes of perioperative stent thrombosis with up to greater than 80% death or MI risk, which can only partly be managed by risky coronary reinterventions on the other hand, the recommendation has to be to carry out surgery on continued dual antiplatelet therapy. In other words, the risks of stopping dual antiplatelet therapy in the perioperative period appear generally higher than to perform surgery on continued therapy. Taking into account the prothrombotic environment during or after surgery, the current ACC/AHA Guidelines even suggest continuing clopidogrel perioperatively beyond 1 year in high-risk patients (e.g., patients with previous stent thrombosis, after left main coronary artery stenting, after multivessel stenting, after stenting of the last remaining vessel).\textsuperscript{6} However, this benefit-risk balance is different for brain surgery or surgery close to the spinal cord; here it may be mandatory to stop antiplatelet therapy.

Obviously, surgery on dual antiplatelet therapy has to be planned well and performed by a skilled surgical, anesthesiological, and intensive care team aware of possible bleeding complications and how to manage them. This means, in the absence of antidotes to antiplatelet drugs, that fresh thrombocytes have to be available immediately to stop bleeding if necessary. However, because this treatment carries a risk of side effects per se, fibrinogen substitution may be considered as an alternative. All patients with coronary artery disease being operated on are at increased surgical risk and this is true despite previous successful revascularization.\textsuperscript{22} In fact, the value of preoperative revascularization as a general rule has been questioned and is not generally recommended.\textsuperscript{23} Therefore, these patients need special electrocardiographic and cardiac monitoring and evidence of transient or persistent perioperative ischemia has to be taken seriously, with immediate consultation with a cardiologist. This implies that such surgery is performed most safely in hospitals with interventional cardiac facilities. General anesthesia, compared with regional anesthesia, leads to an even more prothrom-
nhibitory state may thereby enhance the risk of coronary complications. However, spinal or epidural anesthesia is generally considered to be contraindicated in the presence of dual antiplatelet therapy. If dual antiplatelet therapy had to be stopped as in neurocranial surgery, it should be reinstated as quickly as possible after surgery. Unfortunately, heparins will not prevent stent thrombosis from occurring and there are no data showing that glycoprotein IIb/IIIa inhibitors may serve periparatively to “bridge” a critical phase without oral antiplatelet drugs.


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What are the regulatory and economic challenges posed by drug-eluting stents?

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Medical devices are complex therapeutics that pose unique regulatory, ethical, legal, and financial challenges. Drug-eluting stents were heralded initially as a breakthrough in the treatment of coronary artery disease. However, later revelations about the safety and efficacy of drug-eluting stents would highlight challenges in the regulatory approval of medical devices. In this paper, we discuss a few key issues that arose from debates about drug-eluting stents: Are trials for medical devices adequately designed to examine long-term safety? What are the ethics of phase 1 research for medical devices when long-term complications are unknown? What are the intellectual property rights issues for medical technology? How do payment systems create incentives that encourage overuse of medical devices?

Keywords: drug-eluting stent; ethics; research; health care economics and organizations; FDA

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When coronary angioplasty was introduced in the late 1970s, it ushered in the modern age of cardiology. However, the long-term success of balloon angioplasty was hindered by high rates of reocclusion of treated vessels. The introduction of bare-metal stents—essentially metal scaffolds used to prevent reocclusion in arteries after successful angioplasty—was described as the golden age of interventional cardiology. However, the Achilles heel of bare-metal stents was the high rate of in-stent thrombosis, and it was not until the importance of dual antiplatelet therapy with aspirin and thienopyridines (such as clopidogrel or ticlopidine) was discovered that coronary stents were widely adopted. But this discovery did not totally resolve concerns about high restenosis rates, which could only be overcome with restenting or brachytherapy (and even then with limited success).

When the first drug-eluting stent was approved in the United States by the Food and Drug Administration (FDA), cardiologists heralded the new technology as a breakthrough for the treatment of coronary artery disease.1,2 Drug-eluting stents were rapidly adopted into clinical practice (Figure 1, page 268), and it was estimated at one time that more than 80% of coronary stents used in the United States were drug-eluting stents.3 However, concerns among researchers about late stent thrombosis leading to myocardial infarction and possible cardiovascular-related death began to make the headlines.4 Researchers were also concerned about the widespread off-label use of drug-eluting stents (ie, for scenarios that had yet to be formally tested or approved by the FDA).5 Compounding these concerns were longer-term medical data suggesting that drug-eluting stents had no significant impact on the occurrence of myocardial infarction and death compared with alternative medical or surgical therapies.6

THE FDA APPROVAL PROCESS

The modern FDA was conceived by the Federal Food, Drug, and Cosmetic Act of 1938, a Congressional mandate prompted by several deaths related to sulfanilamide that had been compounded as an elixir using diethylene glycol. This lethal combination was brought to market without clinical testing, and the incident exposed deficiencies in the Food and Drugs Act of 1906, which did not require safety studies for new drugs.7 The 1938 legislation was largely credited with the current operating framework of the FDA. It was the first legislation to require drug labeling with adequate directions for safe use. The act mandated premarket approval of all new drugs and required manufacturers to demonstrate safety to the FDA be-
fore selling their drug products. However, the act did not include provisions for the oversight of medical devices.8

A series of medical device injuries in the late 1960s and early 1970s, and a 1970 report from the National Heart and Lung Institute documenting over 10,000 injuries and 731 deaths linked to medical devices, once again prompted Congress to act. The Medical Device Amendments of 1976 gave the FDA the authority to regulate medical devices based on the complexity and perceived risk of the device. The legislation was later criticized for giving the FDA little power to require manufacturers to report failures or adverse events. This power to mandate postmarket surveillance and reporting of device-related injuries and deaths was granted to the FDA by the Safe Medical Devices Act of 1990 and the Medical Device Amendments of 1992.9 With the enactment of these provisions, 224,197 device-related injuries, malfunctions, and deaths were reported in 2006 alone.10

**DEVICE APPROVAL IN THE EUROPEAN UNION**

The European Union has a different regulatory approval model than the United States, but the structure of clinical research for medical devices is similar in the two markets. To obtain approval to market and sell a device in the European Union without meeting the testing requirements of each member state, device makers must receive a Conformité Européenne (CE) mark certifying that the product meets European Union health, safety, and environmental requirements. CEs are issued by independent, private commercial entities called “notified bodies,” which are regulated and audited by relevant regulatory bodies in the member states. Device companies can choose from more than 50 notified bodies in the European Union, resulting in competition among the notified bodies, which are viewed as less bureaucratic and more nimble than the FDA. Nevertheless, because of the variety among notified bodies, device approval can be variable and fragmented and can result in the approval of devices and drugs that have not received approval in the United States. Unlike the United States, where a manufacturer must prove to the FDA both safety and efficacy, the European Union requires only that the manufacturer demonstrate that the device is safe and operates as the manufacturer intended.11

**REGULATORY APPROVAL FOR DRUG-ELUTING STENTS**

Cordis Corporation’s Cypher sirolimus-eluting stent received a CE mark in April 2002 for “treatment of de novo coronary artery lesions (less than or equal to 30 mm in length) in native coronary arteries with reference diameters ranging from 2.25 to 5.0 mm” based on data from 238 patients enrolled in Europe and Latin America.12 In April 2003, the FDA approved the same device for “improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions of the length ≤30 mm in native coronary arteries with a reference vessel diameter of ≥2.5 mm to ≤3.5 mm. Long-term outcome (beyond 12 months) for this permanent implant is unknown at present.” The FDA letter of approval also required clinical outcomes through 5 years post-procedure on at least 80% of patients in the clinical trial used for approval of the device, plus information on 2000 patients with the device implanted after the approval.13
Three months after the approval, Cordis issued a letter to inform health professionals of the possibility stent thrombosis could occur shortly after implantation and recommended that professionals choose the appropriate stent size, appropriate patients, correct antiplatelet regimen, and proper techniques for stent deployment. In October 2003, the FDA released a preliminary public health notification of more than 290 reports of subacute stent thrombosis associated with the Cypher stent. More than 60 reports were associated with death, and the remaining reports were associated with injuries requiring medical or surgical intervention. The FDA acknowledged that it did not have sufficient data to establish rates for these events, to compare drug-eluting stents with bare-metal stents, or to describe a definable cause for the events. By this time, Cordis had distributed more than 450,000 Cypher stents worldwide. Despite the warning signals, the FDA approved Boston Scientific’s Taxus paclitaxel-eluting stent in March 2004.

In the spring of 2006, conflicting study results presented at a meeting of the European Society of Cardiology fueled concerns about the safety of drug-eluting stents. To address these issues, the FDA’s Circulatory System Devices Advisory Panel convened a group of regulators, research physicians, and patient and industry representatives in December 2006. At the end of a 2-day conference, the panel concluded that drug-eluting stents were associated with a decrease in the need for repeat cardiac catheterization compared with bare-metal stents, but noted an increase in the frequency of stent thrombosis, the magnitude of which was unknown, but was clearly higher with off-label use. The panel concluded that dual antiplatelet therapy be continued for at least 1 year based in part on recent data on this issue, but the exact duration was still unknown.

REGULATORY ISSUES

The approval of drug-eluting stents was predicated on the premise of efficacy (reduced total revascularization rates) and safety (no stent thrombosis or deaths) in both the United States and the European Union. The approval process application for the Cypher stent involved approximately 1000 patients (with fewer for the European Union approval) in two studies with narrowly defined inclusion criteria. However, at the time these trials were conducted, the populations of patients receiving stents were much broader than what the approved labeling included and, more importantly, excluded. Although the participants had been randomly assigned, the small number of carefully selected patients resulted in approvals informed by underpowered studies with low event rates, essentially missing any ability to detect rare, serious complications such as stent thrombosis. By the time safety signals began to emerge, over a half million of the devices had been implanted worldwide.

In its approval letter for the first drug-eluting stent, the FDA highlighted areas of limited data for the new technology: more complex lesions and patients, the duration of clopidogrel, and the impact on hard end points. These deficiencies in the approval data would later emerge as the areas of concern regarding the safety and efficacy of drug-eluting stents. The FDA correctly identified the issues at the outset, but neither the United States nor European Union regulatory authorities required the manufacturers to produce additional data or align their postmarket surveillance to mitigate the concerns as the stents entered broader clinical use. When the concerns became widespread, the agencies were forced to react to anecdotal reports and pooled studies with insufficient primary data.

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The medical device industry focuses on incremental and continuous improvement processes on a smaller range of products with perceived lower risk with each iteration. To better gauge safety in the approval process, the challenge for medical device manufacturers is to balance larger trials and longer follow-up with the costs and burdens of doing so. Balancing patient safety with expected market returns, the $220 billion global medical device market could be expected to invest in more rigorous trials if the current reimbursement incentive structure is preserved. Furthermore, device manufacturers could test iterative or even new products on more enriched patient populations to better simulate real-world clinical use and outcomes. Such a requirement would allow for better assessment of product safety and efficacy and would allow regulatory agencies to make a more informed approval decisions.

OFF-LABEL USE

AND POSTMARKET SURVEILLANCE

Regulators in the United States and the European Union do not explicitly regulate physician behavior or approve the procedures by which devices are implanted. Furthermore, even when a physician uses a device off-label, the manufacturer is absolved of product liability. As a result, once a therapy is approved, it can be used in clinical scenarios that fall outside the guidelines for which it was approved with almost no liability to the manufacturer.
What are the regulatory and economic challenges posed by drug-eluting stents? - Shah and Schulman

Postmarket surveillance registries mandated by regulators can be used to monitor the safety of an approved therapy, particularly in populations and clinical scenarios not represented in the original clinical studies. However, experience with drug-eluting stents exemplifies the rapidity of medical technology development and the limitations of the current regulatory framework to adequately monitor both existing and new technologies and their iterations in clinical practice. Currently, postmarket surveillance is conducted using some combination of mandated postmarket surveillance registries, national registries, claims data, and regulatory reporting systems, and each has inherent limitations. A centralized, systematic registry using an easily accessible electronic database including device make and model information and medication data could be used as a real-time clinical monitoring tool to alert regulators, manufacturers, and providers of safety signals.

Feedback could also be provided to identify safety and efficacy trends in the clinical use of a newly approved therapy. The initial capital costs of such a system would not be insignificant; however, once implemented, the marginal cost for each additional patient tracked and monitored would be minimal and could be funded by a public-private partnership to the benefit of providers, manufacturers, and regulators.

**ETHICAL CONSIDERATIONS**

An overriding issue for any new device or drug is the ethics of the informed consent process for first-in-human studies. More than 75% of phase 1 clinical trials are performed outside of the United States, because regulatory barriers add significant costs to the development process. As a result, many of these trials are conducted in emerging markets where participants may find it attractive to participate in a trial to receive free or discounted care that they would not receive otherwise. Moreover, most intracoronary device therapies are permanent and, by definition, removable only by extreme measures. Concerns about stent thrombosis emerged almost 7 years after the phase 1 drug-eluting stent trials were completed, making it nearly impossible to remove the devices if there had been a more significant risk of morbidity or mortality. As a result, patients who participated in phase 1 trials could have suffered a much graver scenario, particularly those whose access to medical care and resources was limited. There must be equipoise in the testing of any new therapy, but the rapid adoption of many medical devices presents a challenge in how to address problems with permanent indwelling devices that cannot be easily extracted.

Other issues with phase 1 trials are subjects’ perceptions of the trade-off between device safety and therapeutic outcome. The trade-off is likely different than that ascribed to phase 1 research for oncology therapeutics, as stents confer no mortality benefit. Unlike explaining the risk of death to a patient, it is unclear how patients would value the trade-off between the need for target vessel revascularization and stent thrombosis, where the mortality rate for the latter is unclear.

**INTELLECTUAL PROPERTY ISSUES**

Medical devices are subject to the same intellectual property and patent protections afforded to other technologies. For example, in February 2008, a Texas jury ruled that Boston Scientific’s drug-eluting stent infringed on a patent by a radiologist issued in 1997. The original patent described how fractures in bones could be healed if a thin, flexible material with small pores could allow the flow of large molecules in and out of the injured bone, also describing how this method could apply to stents to control the delivery of drugs to a blood vessel wall. Also, Cordis’ parent company, Johnson & Johnson, sued Medtronic for patent infringement, which resulted in a countersuit. In other parts of the world, patents for drugs and devices are loosely regulated, allowing entrepreneurs and businesses in local markets to manufacture and sell copycat products without paying royalties or licensing fees. Given the significant loss of revenue or royalties from infringement of intellectual property, manufacturers and entrepreneurs spend
REIMBURSEMENT AND ECONOMICS

Little data exist on the diffusion of medical technology into medical practice and the barriers and incentives that affect adoption. However, with the approval of drug-eluting stents in the United States and the European Union, the devices were disseminated into the market rapidly despite costing two to three times more than their bare-metal counterparts. This rapid adoption could be explained in part by the reimbursement climate in the United States. In an unprecedented move, the Centers for Medicare & Medicaid Services (CMS) approved reimbursement of the incremental cost of the use of a single drug-eluting stent compared to the use of bare-metal stents. Prior to this decision, a new medical technology was only reimbursed by CMS after it had been used on the market and the prospective annual reimbursement scale was adjusted on the basis of review of retrospective cost data for specific diagnosis-related groups. In practice, this resulted in an increase in payment 2 years after market entry (unless the technology qualified for special reimbursement consideration under a technology pass-through program). However, by creating a favorable reimbursement climate, CMS encouraged rapid adoption of drug-eluting stents.

The price of drug-eluting stents was justified initially by a reduction in the need for repeat revascularization for restenosis (although initial models suggested that drug-eluting stents would not save money and might actually add costs to the system). However, this benefit extends to only 10% to 15% of patients, making it difficult to predict which patients are at risk for restenosis and for whom the increased cost would be justified. The true value of drug-eluting stents depends on the perspective taken. For patients, increased costs for drug-eluting stents could be justified by the potential reduction in events and repeat revascularization for restenosis. This perspective would be shared by physicians, but could be offset by decreased revenue from performing fewer procedures. Before the Medicare fee schedule change, hospitals were in crisis over the potential diffusion of drug-eluting stents. However, after the payment policy changed, their incentives to impede the dissemination of the technology evaporated.

CONCLUSIONS

Medical devices can provide improved quality of life and longevity to many patients. Device technologies are rapidly evolving and almost as rapidly being adopted in clinical practice. However, the case of drug-eluting stents illustrates the complex risk-benefit trade-off for new devices. The informed consent process for phase 1 research in developing countries places a disproportionate burden of long-term complications of permanent, indwelling devices in populations with limited access to health care and resources. Moreover, differing regulatory schemes for premarket approval reflect differences in requirements for demonstration of clinical efficacy, safety, and post-market surveillance. Reimbursement systems can accelerate or moderate adoption of approved devices. Taken together, these issues highlight the complexities and challenges of bringing new medical technologies into clinical practice.

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Matters @ Heart

Dr Patterson and his missing gene

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It has been said that death and taxes are inevitable and dreaded evils. As scientists we can add a third, the writing of a grant proposal. Why is the business of writing a grant proposal so disliked? There are a number of reasons: the principal investigator, as he is called to lower his self-esteem, must compress his ideas into a mold which has been ordained by the granting agencies; he must express his ideas in an idiom with which he may not be familiar; he must be mindful that he must please the reviewers, whose scientific interest and experience may be that of a competitor; he must realize that the reviewers, in order to appear intelligent, must find fault with his application, finally to be successful, the proposal should deal with a subject of current interest, not necessarily his own. A scientist who can wrap his ideas into the mantle of sophistication, without interfering or competing with the reviewers’ territory, is endowed with the specific gene of grantsmanship. The location of this gene is not known and it has as yet not been cloned. This gene can be absent in great scientists and the defect is compatible with scientific excellence.

An example is Clair C. Patterson (1922-1995). The Archives of the California Institute of Technology possess in their files an interview with Clair C. Patterson who was a member of the division of geology and planetary science at the California Institute of Technology. Despite his missing gene he was a great scientist. His scientific life was highly successful, although he was congenitally unable to get his work funded. His scientific career is a triumph of will over an inborn genetic defect.

Patterson was born in Iowa, attended Grinnell College, moved to the University of Iowa, and then to the University of Chicago to work on the Manhattan (Atomic Bomb) project. He transferred to Oakridge, Tennessee, to continue on the Manhattan project, where he became familiar with mass spectrometry, a technique which became the basis of his future research. He also became acquainted with Harrison Brown, the geophysicist who was interested in meteorites to define the elemental abundance of the solar system. Harrison Brown, his mentor and chief, had worked on the concept that lead in iron meteorites was the kind that existed in the solar system when it was first formed. Patterson was able in 1953 to measure the isotopic composition of primordial lead, from which he determined the age of the earth. “But we could do it because the isotopic composition of the lead was changing—it was dynamic because uranium was decaying all the time and there were three radioactive progenitors of three different isotopes in this lead that were being added all the time...”
the earth was there. The proportions of lead and uranium and thorium would change for millions and hundreds of millions of years at different areas, and the lead within would have a different isotopic composition and you could track this. You could follow it. This work also led to his second discovery, the contamination of the earth with lead; he estimated the lead concentration in blood of many Americans to be over 100 times that of the natural level and within a factor of two of the accepted limit for lead poisoning. He discovered that leaded gasoline was partially responsible. This finding did not endear him to the oil industry, which quickly withdrew funding. This got Patterson in trouble, particularly since he also published a warning on the amount of lead entering the food chain.

The first symptom produced by the missing gene for grantsmanship appeared when Patterson, after getting his PhD, asked for funds to measure the age of the earth and get the lead out of the meteorite. “So I wrote a little proposal to the U.S. Atomic Energy Commission—since they had financed us for work that led up to this. They turned me down, because they were not interested in measuring the age of the earth.” His chief rewrote the proposal in his name. “You know, he is very good in explaining things to people in a nonscientific way—so he wrote the darn thing. Boom. I was awarded a fellowship, a postdoc.” Apparently Dr Harrison Brown’s genome fully expressed the gene for grantsmanship!

Patterson then wanted to study the evolution of the earth by determining the isotopic composition of lead in rocks. His request for funding was not approved: “they were trying to prove that I was wrong.” Again his chief came to the rescue and obtained money from the Atomic Energy Commission; he told them that there was enough uranium in rocks, so they would get enough to use it in an atomic generator. Apparently this sales pitch was successful. Patterson bemoans his inability to please the granting agencies. He wrote a paper stating that lead is coming from leaded gasoline. “When they stopped my research they went around and tried to stop all my funding.”

How did Patterson compensate for his missing gene? He would go to other universities and submit joint cooperative proposals. Others would write the proposals and his name would
be on the joint proposal and part of the money would come to him. As he wrote: “I have been turned down throughout the years. If I wrote a proposal with science—down, no way out.”

Recently I received a pamphlet from a medical school, which proudly reports an advance in their rating, because research grants had increased by millions of dollars. Their pride is justified; bad research is usually not funded, a good application has to be well organized and sophisticated. And yet—there is the case history of Dr Patterson and others like him with the missing gene. There are also those who have a brilliant idea, not yet clothed in the mantle of sophistication! The only solution for those with this missing gene is to hitch their scientific wagon to someone whose genome is intact. Otherwise there is only the satisfaction that goes with the creation of a new idea. Alas, there is no dollar sign attached!

The author expresses his appreciation for the help and encouragement from the Archives of the California Institute of Technology. All quotations are from an interview with Dr Patterson held at the California Institute of Technology in March 1995. The Caltech Archives have issued permission for publication.
Drug-Eluting Stents in Angina

Summaries of Ten Seminal Papers

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1. One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease…

2. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis
C. Stettler and others. Lancet. 2007

3. Clinical end points in coronary stent trials: a case for standardized definitions
D. E. Cutlip and others. Circulation. 2007

4. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern
E. Camenzind and others. Circulation. 2007

5. Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents? Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents


7. Cyphering the complexity of coronary artery disease using the Syntax score to predict clinical outcome...
M. Valgimigli and others. Am J Cardiol. 2007

8. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice…
J. Daemen and others. Lancet. 2007

9. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization
A. V. Finn and others. Circulation. 2007

10. Balancing the risks of restenosis and stent thrombosis in bare-metal versus drug-eluting stents. Results of a decision analytic model

Selection of seminal papers by William Wijns, MD, PhD, FESC
Cardiovascular Center Aalst - Aalst - Belgium

Highlights of the years by Ian Mudway, MD
Lung Biology - Division of Life Sciences - Franklin Williams Building
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One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials


J Thorac Cardiovasc Surg. 2005;130:512-519

With the advent of a safe and progressively more effective percutaneous coronary intervention (PCI) for coronary artery disease (CAD) as opposed to traditional coronary artery bypass grafting (CABG), the choice as to the best revascularization strategy for multivessel disease patients remains today still very challenging. Many previous meta-analyses have pooled together available randomized controlled studies comparing percutaneous versus surgical revascularization in such patient populations. However, they are limited by inclusion of patients treated with balloon angioplasty, with use of bare-metal stents restricted to bailout situations. The results of trials that antedated the stent era are not reflective of the current practice of coronary revascularization because coronary stents are nowadays implanted in approximately 90% or more of all procedures and adjunctive pharmacologic therapy with glycoprotein IIb/IIIa inhibitors is frequently used.

This systematic overview based on individual patient data from recent clinical trials comparing angioplasty with multiple stenting against CABG surgery thus provides the clinician caring for patients with multivessel disease with meaningful treatment effect estimates regarding the advantages and drawbacks of each treatment strategy. The authors created an individual patient database composed of 4 trials (Arterial Revascularization Therapies Study [ARTS], Stent or Surgery [SOS] trial, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease–2 [ERACI-2], and Medicine, Angioplasty, or Surgery Study–2 [MASS-2]) that compared percutaneous coronary intervention with multiple bare-metal stenting (N=1518) versus CABG (N=1533). One year after the initial procedure, PCI with multiple stenting and coronary artery bypass graft surgery provided a similar degree of protection against death, myocardial infarction, or stroke for patients with multisystem disease. Repeat revascularization procedures remain high after PCI, but the difference with CABG surgery has narrowed in the era of bare-metal stenting. In particular, the observed gap with CABG surgery has narrowed from approximately 30% reported in the pre-stent era to approximately 14% in the present report.

While this analysis is largely consistent with the data reported by single studies comparing PCI versus CABG and the results showed in previous meta-analyses, there are some outstanding considerations, which should be kept in mind when interpreting the data. The main limitation of this meta-analysis is the relatively short follow-up period limited to 1 year. Long-term (5-year) follow-up of this cohort of patients is planned and will likely be reported soon. It is also likely that the patients included may represent a selected population of low-to-moderate risk patients with multisystem disease, thus limiting the generalizability of the results to more complex subsets of patients. Finally, the use of drug-eluting stents may significantly impact on the performance of PCI versus CABG in this patient population. With unrestricted use of drug-eluting stents, the difference in reintervention disfavoring the PCI approach may further be reduced without affecting the overall composite of death, myocardial infarction, or stroke. This is what has been shown in the ARTS II study in which 606 multivessel disease patients undergoing treatment with sirolimus-eluting stents were compared with historical results obtained in the CABG arm of ARTS I. The SYNTAX study (SYnergy between PCI with TAXus and cardiac surgery) compared in a prospective randomized manner multiple DES implantation versus CABG in patients with 3-vessel disease and/or left main stem-stenosis. The 1-year primary end point results of this study were presented at the European Society of Cardiology annual congress in September 2008.

2005

King Fahd of Saudi Arabia dies at the age of 83 and Crown Prince Abdullah accedes to the throne; Cuban singer Ibrahim Ferrer, vocalist of the Buena Vista Social Club, dies aged 78 years; and Phil Mickelson wins the 2005 PGA Championship
The long-term safety of the first two polymer-based drug-eluting stents (DES) approved by the US Food and Drug Administration (FDA)—a sirolimus-eluting stent and a paclitaxel-eluting stent—is a matter of intense and ongoing debate, with some studies reporting increased rates of death, myocardial infarction, or late stent thrombosis compared with bare-metal stents (BMS). These studies were, however, hampered by the small number of patients, limited durations of follow-up, or observational study designs.

Network meta-analyses allow a unified, coherent analysis of all randomized controlled trials that have compared either of the two DES with BMS or the two DES head-to-head, while fully respecting randomization. The authors set up a collaborative group of investigators who provided trial data based on standardized definitions of outcomes and performed a network meta-analysis. Thirty-eight trials (18,023 patients) were included with a follow-up of up to 4 years. Trialists and manufacturers were also contacted to provide additional data on clinical outcomes for 29 trials. This network meta-analysis showed that DES and BMS were associated with similar rates of overall and cardiac mortality, and that use of sirolimus-eluting stents was associated with a reduction in the risk of myocardial infarction compared with use of BMS and paclitaxel-eluting stents. About 100 patients must receive sirolimus-eluting stents, rather than BMS or paclitaxel-eluting stents, to prevent 1 myocardial infarction over 4 years. Although there was little evidence of an overall increase in definite stent thrombosis associated with DES, paclitaxel-eluting stents were found to be associated with an increased incidence of late stent thrombosis compared with BMS and sirolimus-eluting stents. About 100 patients must receive sirolimus-eluting stents rather than a BMS to prevent 1 target lesion revascularization over 4 years; 35 would need to receive a sirolimus-eluting rather than a paclitaxel-eluting stent to prevent 1 such event. Lastly, there was little evidence of an increased risk of mortality associated with either DES in diabetic patients, but again wide confidence intervals precluded definite conclusions.

A secondary analysis showed a marked reduction in target-lesion revascularization with both DES, which was more pronounced for sirolimus-eluting stents than for paclitaxel-eluting stents. About 6 patients must receive a sirolimus-eluting stent rather than a BMS to prevent 1 target lesion revascularization over 4 years; 35 would need to receive a sirolimus-eluting rather than a paclitaxel-eluting stent to prevent 1 such event. Lastly, there was little evidence of an increased risk of mortality associated with either DES in diabetic patients, but again wide confidence intervals precluded definite conclusions.

This network meta-analysis integrated evidence from direct and indirect comparisons while fully preserving randomization. The considerably higher number of patients and events in this study, compared with previous analyses resulted in a relevant gain in statistical precision, particularly for the hazard ratio of death, myocardial infarction, and stent thrombosis. Network meta-analysis makes similar assumptions to standard meta-analysis of direct within-trial comparisons, but requires that these assumptions hold over the entire set of trials in the network, including the assumption that relative treatment effects comparing two interventions in different trials are from the same common distribution. The smaller the heterogeneity between trials, the more likely relative treatment effects originate from the same distribution. Additional assumptions are that the model fits the data and that the network of trials is consistent. Importantly, all assumptions were satisfied for all outcomes, except for stent thrombosis and target-lesion revascularization. Critics have argued that not all bare-metal stents included in the trials perform equally well, which makes pooling of outcomes problematic.
Clinical end points in coronary stent trials: a case for standardized definitions


_Circulation_. 2007;115:2344-2351

For every clinical cardiologist and cardiovascular researcher, this consensus article calling for standardized outcome definitions in coronary stent trials should be compulsory reading. Variability in end point definitions creates a formidable barrier to the understanding of results across clinical trials or the pooling of results for the detection of rare safety signals. With the recognition that consistency across well-considered end point definitions is critical to this process, 4 academic research organizations involved in the design and management of current drug-eluting stent (DES) clinical trials combined efforts in an informal collaboration termed the Academic Research Consortium (ARC) to orchestrate a set of consensus definitions for DES study end points.

While this consensus document focuses on the definitions and standardization of all clinical cardiac and cardiovascular end points that may be applicable to coronary stent trials, including death, myocardial infarction, reintervention in the target vessel and cerebrovascular accidents, the added value of this report is that it is the first attempt to propose a universal definition for stent thrombosis.

The ARC consensus is that both levels of evidence and timing of events can be stratified to define varying degrees of certainty and to imply different pathophysiological mechanisms, respectively. The triple level of certainty classification recommended is definite, probable, and possible stent thrombosis.

Definite stent thrombosis classification requires angio graphic or autopsy confirmation, is highly specific, and is patterned on the definition developed when these events were first detected during early brachytherapy clinical trials. Although it maximizes specificity, the definite classification may not be sufficiently sensitive for the capture of a relatively rare safety event. The categories of probable and possible stent thrombosis add such sensitivity, but the utility of these categories will vary depending on the quality of data available to the adjudication committee. This is particularly true for the least specific thrombosis category, possible, which could be assigned to all late deaths unless sufficient detail is provided for adjudication. It is important to avoid the dilution of a potential real difference in events with the use of an overly sensitive definition that may include cases unlikely to represent thrombosis. The ARC recommends the combination of adjudicated definite and probable stent thrombosis to best characterize this aspect of DES safety, however, the reporting of definite only and overall rates is also encouraged.

Since this report, the endorsement of this classification system for defining stent thrombosis has been widespread and consistent by both investigator- or sponsor-driven clinical trials, thereby resulting in a significant improvement in our understanding on the incidence, predictors, and clinical implications of stent thrombosis. This very sensitive definition of stent thrombosis, however, has clear limitations, which should also be acknowledged, including the fact that it labels as potential stent thrombosis almost any vessel or stent failure or even any unexplained fatal or nonfatal cardiac event in the presence of limited available information. This may be particularly problematic in studies recruiting patients who have an intrinsic risk of fatal or nonfatal recurrences, such as those with ongoing myocardial infarction. In such settings, the category of possible stent thrombosis remains questionable today. Similarly, it is likely that the specificity of probable and possible stent thrombosis categories decreases over time, which may impact on studies with long and clinical outcomes. A similar effort pertaining to appropriate end points for use in postmarketing surveillance registries would be welcome.

Eleven World Wrestling Entertainers are suspended for suspected steroid abuse; World Rally champion Colin McRae and his son are killed in a helicopter crash in Scotland; and melting sea ice in the Arctic Ocean opens up the Northwest Passage between Europe, Asia and North America.
Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern

E. Camenzind, P. G. Steg, W. Wijns

*Circulation.* 2007;115:1440-1455

At the European Society of Cardiology (ESC)/World Congress of Cardiology (WCC) in Barcelona in 2006, some of us were caught off guard by a plenary session combining three critical presentations by Edoardo Camenzind, Salim Yusuf, and Alain Nordmann, who raised serious concerns about the long-term safety profile of drug-eluting stents (DES). This session was dubbed the “ESC firestorm” and is very well known to all updated interventional cardiologists. The criticisms and concerns regarding the safety profile of the first-generation DES, namely, sirolimus-eluting and paclitaxel-eluting stents, are summarized in this comprehensive revision of the literature.

The first section of this paper is devoted to the pathophysiology of stent thrombosis, which is attributed to the so-called Rudolf Virchow’s triad: (i) abnormal vessel wall lining (eg, incomplete endothelialization); (ii) abnormal blood-flow pattern (eg, slow flow); and (iii) altered blood constituents (eg, increased blood thrombogenicity). Any of these items alone or in combination favors intravascular thrombus formation. The connection between the anti-restenosis effect of first-generation DES and late stent thrombosis resides in the fact that antiproliferative agents such as sirolimus or paclitaxel inhibit intimal hyperplasia growth and endothelial cell proliferation, which ultimately prevents stent strut coverage. First-generation DES inhibit or may even abolish vessel wall healing, leaving the struts in direct contact with flowing blood and blood elements. Complete or partial lack of reendothelialization of stent struts and vessel wall generates a long-lasting, if not permanent, unhealed vessel wall surface, favoring platelet adhesion and aggregation, which may eventually cause thrombus formation. Moreover, the chronic inflammatory process is possibly linked to the nonerodible polymer or the eluted drug itself may trigger positive vessel remodeling (ie, an increase in vessel lumenal diameter over time). Widening of the coronary lumen over time may reduce both intra-stent flow velocity and wall shear stress. Segmental slow flow may be caused by a local intravascular abnormality (eg, aneurysm or bifurcational stenting) or a global coronary perfusion abnormality (eg, diastolic coronary perfusion determined by variables such as tachycardia, increased telediastolic pressure, microangiopathy, distal embolization), and thereby give rise to prolonged interaction between vessel wall and blood constituents. According to this hypothesis, patients with delayed or poor stent healing after intervention who are at increased risk for late stent thrombosis are those who show no in-stent intima hyperplasia at follow-up and/or positive vessel remodeling. Thus, particularly those DES that are associated with lower late loss (ie, higher intima hyperplasia inhibition) may predispose to higher likelihood of stent thrombosis. This hypothesis is challenged by several reports showing that the probability of late and especially very late stent thrombosis is slightly higher with paclitaxel-eluting stents than sirolimus-eluting stents, yet negative late loss at angiographic follow-up is more frequently detected in the latter than in the former. While this hypothesis remains intriguing, it needs to be proven by scientific trial before being endorsed by the cardiological community.

The second part of the article focuses on the rate of overall death or Q-wave myocardial infarction in first-generation DES vs BMS studies. The discussion emphasizes the need for a standardized definition of major cardiovascular safety end points and calls for a more transparent and systematic report of long-term outcomes in these studies. This report triggered intense scrutiny of all related issues and “carved some peepholes in the DES industry firewalls” (Cook et al, *EurIntervention* 2008;3:535-537).

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2007

News Corporation’s CEO Rupert Murdoch announces a $5 billion takeover of Dow Jones & Co, the publisher of the Wall Street Journal; Street Sense wins the 133rd Kentucky Derby; and Floyd Mayweather Jr defeats Oscar De La Hoya in the highest grossing boxing match in history.
Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents? Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents

P. W. Serruys, J. Daemen
Circulation. 2007;115:1433-1439

This position paper, intended as a point-by-point rebuttal to the paper by Camenzind et al, is a thorough reanalysis of the issue of early and late stent thrombosis (ST), starting from the introduction of the bare-metal stent (BMS), through the advent of brachytherapy, and finally focusing on drug-eluting stent (DES) data.

The authors questioned the scientific value of the classic triad of Virchow (altered blood constituents, flow pattern, and endothelial lining) as an explanation for ST after DES implantation. Discontinuation of oral antiplatelet treatment (aspirin and/or clopidogrel) is associated with proinflammatory and prothrombotic effects in patients with coronary artery disease, and this proved to be a risk factor for coronary events regardless of whether a DES was implanted or not. The optimal duration of dual antiplatelet treatment after DES remains currently unknown and clopidogrel discontinuation may be a risk factor for ST only when interrupted in the early phase after stenting (first 6 months), whereas there are currently no sound data in favor of more prolonged dual antiplatelet treatment. In a limited number of DES patients, postmortem findings show dramatic and compelling evidence of impaired reendothelialization with uncovered stent struts in stented arteries. However, eminent pathologists are the first to admit that postmortem studies have failed to evidence a common denominator and that the number of patients treated with DES in whom “uncovered stent struts” do not lead to ST is unknown, but undoubtedly very large.

Although late acquired malapposition has been occasionally observed with BMS, it is more frequent with DES, and the question remains of whether it has an unfavorable prognosis with respect to late ST. Intravascular ultrasound studies in randomized trials (RAVEL, SIRIUS, and E-SIRIUS), are available in 325 patients and the incidence of incomplete stent apposition at 6 months was 29% in the sirolimus-eluting stent (SES) group vs 8% in the BMS group. The authors found no prognostic impact of incomplete stent apposition on death (2.2% with incomplete stent apposition vs 5.2% without) and major adverse cardiac events (8.9% with incomplete stent apposition vs 12.6% without) in patients treated with SES, at least in the short term. Late ST was observed in only 1 of 45 patients with incomplete stent apposition at a 6- to 8-month follow-up.

Finally, the authors critically reanalyzed the data presented at ESC 2006 by Camenzind et al during the “firestorm,” pointing out two potential methodological limitations:

- The meta-analysis was derived from data published at different time points of follow-up. Of note, more complete data only became available following the alarm.
- Camenzind took two hard clinical end points, total death and Q-wave myocardial infarction (MI), and disregarded non-Q-wave MI, which was indeed substantially lower in the Cypher group. By including all MI in the analysis, no increase in the composite of death or MI would be reached in the SES as compared with the BMS arm.

The authors concluded that late ST occurs both with DES and BMS. However, the chronology and circumstances of occurrence seem quite different. With DES, late ST occurs later than with BMS and seems to appear as primary thrombosis, whereas with BMS it may related to repeat interventions of the target lesion. It is not known to which extent crossover to DES for treatment of BMS restenosis contributes to these events. Dedicated research is warranted to further elucidate the role of endothelial dysfunction, malapposition, and prolonged antiplatelet therapy.

Currently, second-generation DES are attempting to resolve the problems posed so far by first-generation DES.

A tsunami occurs on the northern coast of Japan following a 6.9 magnitude earthquake; French presidential candidate Nicolas Sarkozy resigns as Interior Minister to concentrate on his campaign; and the European Union celebrates the 50th anniversary of its foundation.

J. Daemen, P. W. Serruys

Circulation. 2007;116:316-328 (Part I, issue No. 3)
Circulation. 2007;116:961-968 (Part II, issue No. 8)

**Part I** is a comprehensive review of the past, present, and foreseeable future of drug-eluting stents (DES), whose numbers keep growing in an exponential manner. They are all loaded with drugs that interfere with inflammation and neointimal proliferation pathways. The process of restenosis is a sequence of complex events that has been only partly elucidated over the last 2 decades. Locally acting DES provide an opportunity to interfere with the various mechanisms responsible for each step in the restenotic cascade, and a wide variety of different agents are currently available.

The limus family is discussed first, which includes sirolimus-, everolimus-, zotarolimus-, pimecrolimus-, biolimus-, and tacrolimus-eluting stents, followed by paclitaxel-eluting stents. The new coating and new platform chapters are worth reading for those of us who want to understand who is doing what in a complex system such as DES technology nowadays. The pro-healing section is entirely devoted to a dream that has still to come true: we do have to inhibit intimal hyperplasia, but at the same time we also have to promote complete healing shortly after the implantation of the stent to obtain both lower late loss and an ideal safety profile. The so-called “endothelial progenitor cell (EPC) capture stent” which is coated with anti-CD34 monoclonal antibodies is here extensively described. EPCs are, however, not only identified by the expression of CD34 antigen, so the concept of a stent, which, by binding to CD34+ circulating cells, is able to promote stent healing is, to some extent, conceptually misleading and still waiting for proof-of-concept evidence. Indeed, today there is no clear-cut evidence suggesting that this complex type of device actually promotes quicker and more complete healing than the bare-metal stent, while the results in terms of late loss are partially disappointing. The last paragraph emphasizes the importance of elution kinetics as one of the most important variables for obtaining enduring late loss inhibition over time and for avoiding the so called late "catch-up phenomenon."

**Part II** is entirely devoted to unsettled issues in the DES era. After a brief summary focusing on the value of DES implantation as an effective means to reduce late loss and subsequent target-lesion revascularization as compared with BMS, the article focuses on the pitfalls of DES.

First, DES have been shown to hamper the natural vascular healing process. Second, stent underexpansion (minimum stent area <5.0 mm²), a factor linked to restenosis, is significantly more frequent after DES implantation. Whereas stent underexpansion is observed in 20% of all restenotic BMS lesions, an incidence of up to nearly 70% is reported in restenotic DES lesions. This may simply reflect a less aggressive policy of stent overexpansion after DES implantation as compared with BMS, due to excessive confidence in the anticipated superior antirestenotic properties of DES. Third, DES implantation seems to be associated with significant impairment in endothelial function, which in turn has been repeatedly linked to a higher rate of late adverse events. Fourth, recent reports have shown a significantly lower rate of neointimal coverage with DES (13.3% to 66%) than with BMS (90% to 100%), and subclinical thrombi tended to be more common with DES (P<0.09). These observations are pertinent to the concerns with late stent thrombosis, which is here extensively discussed both in the context of on- and off-label use of DES as compared with BMS.

New species of scallop and octopi are discovered off the coast of Nova Scotia; Bollywood actor Sanjay Dutt is jailed for six years on charges of obtaining weapons from gangsters in a case associated with the 1993 Mumbai bombings; and New Zealand launches its first commercially available biofuel, consisting of 90% petrol and 10% bioethanol derived from cows’ milk.
Cyphering the complexity of coronary artery disease using the Syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention


Am J Cardiol. 2007;99:1072-1081

Since the earliest reports of coronary angiography, the extent of coronary artery narrowing has been considered a primary determinant of survival in patients with coronary artery disease. The simple division into one-, two-, and three-vessel disease has provided a convenient scheme for classifying patients and it has been extensively employed across the literature. This straightforward scoring system, however, is known to underestimate the prognostic importance of anatomy, especially in patients with complex and diffuse coronary artery disease. The Syntax score (SXscore) was developed in the context of the SYNTAX trial (SYNergy between PCI with TAXus and cardiac surgery) as a comprehensive angiographic tool. The score merges and tailors several previously validated scoring systems to the current era of intervention, and aims to assist in patient selection and risk-stratification for individuals with extensive coronary artery disease undergoing revascularization.

This report compares the predictive value of the Syntax score and of the modified American Heart Association (AHA) lesion classification system. The Syntax score was applied to 1292 lesions in 306 patients undergoing treatment for three-vessel disease in the Arterial Revascularization Therapies Study part II (ARTS II) to examine its role in predicting short- and long-term incidence of major adverse events.

The Syntax score predicted the rate of major adverse cardiac and cerebrovascular events (MACCE), with patients in the highest score tertile showing a significantly higher event rate at both 30 days and 1 year. After adjustment for all potential confounders, including clinical presentation and lesion characteristics, the Syntax score remained an independent predictor of MACCE at 1 year’s follow-up, with an almost threefold increase in the risk of events in patients in the highest compared to two lowest score tertiles. A better goodness of fit was obtained when modeling the risk provided by the Syntax score than that by the modified AHA lesion classification. This implies a closer relationship between observed and predicted event rates when the Syntax score is employed. In keeping with previous analysis, the area under the curve for the Syntax score was greater than the AHA score for MACCE at 30 days. Similarly, using a time-dependent analysis, based on the c-index computation, the prognostic accuracy provided by the Syntax score was confirmed to be significantly higher.

The ultimate goal for the Syntax score will be to discriminate outcome in surgically versus percutaneously treated patients, in view of selecting the best revascularization strategy for the individual patient. The prognostic implications of the Syntax score for patients with three-vessel and/or left main coronary artery disease undergoing either percutaneous or surgical coronary revascularization will be further evaluated in the ongoing trial. As soon as this dataset is available, each single item of the Syntax score will be “weighed” according to discrepancy between observed and predicted event rate in order to further optimize calibration and the interaction between the global score and its single components as well as with the mode of revascularization applied (ie, percutaneous versus surgical). While still clearly in its early phase, the Syntax score will likely be complemented in the future by surgical risk scores, such as the Euroscore or derived scores, to better determine the optimal revascularization strategy in patients with complex coronary artery disease.

India’s Essar Group buys Canadian steelmaker Algoma for $1.63 billion; Author Ray Bradbury and jazz saxophonist John Coltrane receive special citations at the 2007 Pulitzer Prize awards; and shootings at the Virginia Polytechnic Institute and State University leave 33 dead and 29 others wounded
Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study


Lancet. 2007;369:667-678

This cornerstone paper stems from the institutional databases of two tertiary referral centers in Europe, namely, Bern and Rotterdam. Between April 2002, and December 2005, 8146 patients underwent percutaneous coronary intervention in these two hospitals with either sirolimus-eluting stents (SES; n=3823) or paclitaxel-eluting stents (PES; n=4323). Angiographically documented stent thrombosis occurred in 152 patients (incidence density 1.3 per 100 person-years; cumulative incidence at 3 years 2.9%). Early stent thrombosis was noted in 91 (60%) patients, and late stent thrombosis in 61 (40%) patients. Definite late stent thrombosis occurred steadily at a constant rate of 0.6% per year up to 3 years after stent implantation. The incidence of early stent thrombosis was similar for SES (1.1%) and PES (1.3%), but late stent thrombosis was more frequent with PES (1.8%) than with SES (1.4%; \(P=0.031\)). At the time of stent thrombosis, dual antiplatelet therapy was being taken by 87% (early) and 23% (late) of patients (\(P<0.0001\)). Independent predictors of overall stent thrombosis were acute coronary syndrome at presentation (hazard ratio, 2.28, 95% CI, 1.29-4.03) and diabetes (2.03, 1.07-3.83). The median time to occurrence of early stent thrombosis was 4 days (inter-quartile range [IQR], 1-6). Of the 61 late stent thrombosis cases, 36 (59%) patients developed stent thrombosis 1 year or later after stent implantation (median, 451 days, IQR, 211-665). The cumulative incidence of stent thrombosis over time showed an initial steep rise with 50% of cases occurring within 9 days, followed by an almost linear increase in the remaining events up to 3 years. Notably, the absence of clopidogrel treatment did not seem to be associated with an increased risk of total and late stent thrombosis. The main value of this combined, yet retrospective analysis, consists in providing strong and worrisome evidence that the rate of late stent thrombosis does not decrease over time at least up to 3 years after drug-eluting stent (DES) implantation. Only longer-term follow-up studies will tell. Concomitantly, the major limitation of this analysis lies on the lack of a control group treated with bare-metal stent (BMS). Indeed, based on all randomized controlled studies conducted so far, it seems that the overall incidence of stent thrombosis does not differ in BMS- versus DES-treated patients. Thus, it is likely that BMS implantation is associated with a higher risk of stent thrombosis from 5 to 12 months after treatment, whereas DES use increases the likelihood of late stent thrombosis beyond 1 year. Based on these considerations, if the cumulative rate of late stent thrombosis will keep accruing over time after DES, at very long-term follow-up, the overall stent thrombosis rate may end up being significantly higher than after BMS implantation. This may translate into a net increase in the composite of death and myocardial infarction in the DES- compared with BMS-treated patients at very long-term follow-up. Careful long-term clinical surveillance of all DES and BMS patients so far recruited in randomized controlled studies will be pivotal for this purpose. Finally, in a consistent manner, PES was associated with slightly more late stent thrombosis than SES.

This has one major implication: even first-generation DES cannot be considered as one class of devices, and to some extent each single DES differs from the other, both in terms of efficacy and safety.

The hot issue we still need to clarify today is whether the rate of very late stent thrombosis will somehow flatten at longer-term follow-up or will this constant 0.6% rate per year be observed even beyond 3 to 4 years after DES implantation. Only longer-term follow-up studies will tell. Concomitantly, the major limitation of this analysis lies on the lack of a control group treated with bare-metal stent (BMS). Indeed, based on all randomized controlled studies conducted so far, it seems that the overall incidence of stent thrombosis does not differ in BMS- versus DES-treated patients. Thus, it is likely that BMS implantation is associated with a higher risk of stent thrombosis from 5 to 12 months after treatment, whereas DES use increases the likelihood of late stent thrombosis beyond 1 year. Based on these considerations, if the cumulative rate of late stent thrombosis will keep accruing over time after DES, at very long-term follow-up, the overall stent thrombosis rate may end up being significantly higher than after BMS implantation. This may translate into a net increase in the composite of death and myocardial infarction in the DES- compared with BMS-treated patients at very long-term follow-up. Careful long-term clinical surveillance of all DES and BMS patients so far recruited in randomized controlled studies will be pivotal for this purpose. Finally, in a consistent manner, PES was associated with slightly more late stent thrombosis than SES.

This has one major implication: even first-generation DES cannot be considered as one class of devices, and to some extent each single DES differs from the other, both in terms of efficacy and safety.

The Virginia General Assembly votes unanimously in favor of a motion expressing “profound regret” for Virginia’s role in the promotion of slavery; Mario Chanes de Armas, one of the leaders in the Cuban revolution, dies, aged 80 years; and “The Departed” wins four Academy Awards including Best Picture and Best Director for Martin Scorsese at the 79th Academy Awards.
Polymer-based sirolimus- (Cypher) and paclitaxel-eluting (Taxus) drug-eluting stents (DES) have become a treatment of choice for patients with symptomatic coronary artery disease undergoing percutaneous coronary revascularization. Although these stents have reduced rates of restenosis and late lumen loss compared with bare-metal stents, late thrombosis, a life-threatening complication of this technology, has emerged as a major concern. Although clinical predictors such as withdrawal of antiplatelet therapy are known to play a role in determining the probability of late stent thrombosis, the specific morphometric and histological parameters that significantly correlate with late thrombosis remained largely unknown.

This study reported by Finn et al was based on analysis of autopsy material and using a database of all patients dying >30 days after Cypher or Taxus DES implantation. It sought to determine the most powerful pathological risk factors for late thrombosis and identify the high-risk features of DES that might be clinically assessable. The main finding was that nonuniform healing with DES (as indicated by the number of uncovered struts per cross section) greatly increases the thrombotic risk.

Previous pathological studies have shown an association between lack of neointimal strut coverage and thrombus formation. Although the mechanisms by which the current-generation DES induce nonuniform incomplete healing are not fully understood, lesion characteristics, drug properties, dose, and distribution, and polymer biocompatibility together likely play an important role.

The underlying plaque morphology may affect the rate of healing when stent struts penetrate deeply into a necrotic core and are not in contact with cellular areas. Eccentric plaques may prevent uniform strut deployment, thereby increasing local toxicity resulting from higher concentrations of drug and polymer. Indeed, sections with evidence of thrombosis showed significantly lower inter-strut distances, which correlated with less neointimal growth. Local concentrations of drug are ultimately highly spacing-dependent, and the variance in distance between struts amplifies differences in concentrations, leading to biological effects. Heterogeneity in loaded dose of drug varies from strut to strut, and greater retention of lipophilic drugs in different regions of plaque affects arterial drug concentration and results in nonuniform healing. The relationship between local drug concentrations and cellular repair is underscored by data from overlapping versus nonoverlapping Cypher and Taxus stents in the rabbit iliac model.

This study was seminal in establishing a predictor of late stent thrombosis. The authors speculated that there might be a continuum of risk increasing with the ratio of uncovered to total struts per section. Using a univariate logistic regression model of occurrence of thrombus in a stent section versus ratio of uncovered to total struts per section, they showed that in a stent with 30% uncovered struts, the odds ratio for thrombus is 9.0 (95% confidence interval [CI], 3.5 to 22.0) compared with a stent with complete coverage. Based on this postulation, many groups around the world are now evaluating, in vivo, using optimal coherence tomography, the predictive value of uncovered struts to identify upfront patients at high risk for very late stent thrombosis. This may have relevant implications for long-term management, including intensification and/or tailoring of antiplatelet treatment to protect patients from potential catastrophic consequences. Prospective studies to validate these pathologic findings in vivo are warranted.
Balancing the risks of restenosis and stent thrombosis in bare-metal versus drug-eluting stents. Results of a decision analytic model

P. Garg, D. J. Cohen, T. Gaziano, L. Mauri

J Am Coll Cardiol. 2008;51:1844-1853

Decisions regarding percutaneous coronary intervention (PCI) for obstructive coronary disease have become increasingly challenging for patients and physicians since the observation of delayed stent thrombosis with drug-eluting stents (DES). The main risk attributable to bare-metal stenting (BMS) was restenosis, requiring repeat revascularization—a risk that largely ended within 1 year after stenting. Beyond this period, events attributable to the stent were rare. In particular, in-stent thrombotic complications occurred in <1% of patients, almost exclusively within the first month after BMS implantation. By limiting neointimal hyperplasia within the stent, the current generation of DES has reduced the relative risk of restenosis by 50% to 70%. However, there is concern that DES might be associated with increased risks of delayed stent thrombosis.

In this study, the authors sought to quantify the degree to which current uncertainty in the rate of very late thrombotic complications after DES implantation would affect the choice of one stent type versus the other. Because both the absolute risk and duration of risk of stent thrombosis after DES implantation are uncertain, the authors used the Markov model of decision analysis to define what threshold of incremental risk of thrombosis with DES would outweigh the benefits of reduced restenosis in clinical practice. They found, on the basis of the best data currently available, that the DES strategy was preferred for a prototypical PCI patient under the assumption of no difference in the rates of (very) late stent thrombosis. Although the benefit was small in absolute terms (0.014 QALYs, or quality-adjusted life years gained), this gain is plausible given the time-limited nature of the restenosis process and the absence of long-term mortality benefit associated with restenosis avoidance in most studies. This finding was confirmed to be robust, on the basis of probabilistic sensitivity analysis, which takes into account a range of plausible probabilities rather than relying on fixed estimates alone. Nonetheless, the authors also found their results to be highly sensitive to the absolute risk and duration of risk for late stent thrombosis, leading to uncertainty about optimal decision over a range of risk that is plausible on the basis of current data. In particular, for a prototypical patient, the authors found that even a small excess risk of very late stent thrombosis (>0.14%/year over 4 years) would be sufficient to negate any advantage of DES over BMS in terms of mean quality-adjusted life expectancy. Furthermore, if the at-risk period extended beyond 4 years, the incremental annual risk that could be tolerated was even smaller.

Whether the true risk of very late thrombosis with existing DES exceeds this risk is uncertain at present. Most likely, the risk depends on stent type and patient/lesion subsets. Restenosis risks can be predicted with reasonable precision in overall populations and according to well-understood patient and lesion-based factors, because restenosis was a frequent occurrence over the past decade of practice. In contrast, stent thrombosis risks have only recently been studied with similar rigor. Although pooled analyses of randomized trials of the two approved DES platforms to 4 years of follow-up have not shown significant differences in risk of thrombosis between DES and BMS, the confidence intervals of these estimates are wide, suggesting that up to a 1.4% absolute risk difference at 4 years cannot be excluded.

In other terms, on the basis of a decision analytic model incorporating the best data currently available, the authors found that even a small (<1%) incremental risk in thrombosis with DES was sufficient to outweigh the benefit of restenosis prevention and favors BMS use for the overall PCI population. This analysis argues against the systematic use of first-generation DES in all cases; instead DES should be preferentially used in patient/lesion subsets with a high likelihood of restenosis when treated with BMS.

Silvio Berlusconi is sworn in as the Italian Prime Minister for his fourth term in office; a pro-Europe coalition wins the Serbian parliamentary election; and a magnitude 7.9 earthquake hits China’s Sichuan province, with at least 22 000 casualties.
### Drug-Eluting Stents in Angina

**Bibliography of One Hundred Key Papers**

selected by William Wijns*, MD, PhD, FESC and Marco Valgimigli†, MD

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**Bibliography of One Hundred Key Papers**


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