## DRUG THERAPY

# Coronary-Artery Stents

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THE USE OF PERCUTANEOUSLY INTRODUCED PROSTHETIC DEVICES TO maintain the luminal integrity of diseased blood vessels was proposed by Dotter and Judkins in 1964,[1] well before the introduction of coronary angioplasty by Grüntzig et al. in 1977.[2] Palmaz et al. introduced the use of balloon-mounted stents (as used in coronary arteries today) in peripheral arteries in 1985.[3] Schatz et al. subsequently modified the Palmaz stent, which led to the development of the first commercially successful stent, the Palmaz–Schatz stent.[4] Puel and Sigwart were the first to implant a stent in humans in March 1986; they used a self-expanding mesh device. Sigwart and colleagues were also the first to describe the use of this stent in 1987 for emergency vessel closure during balloon angioplasty,[5] on the basis of the ability of the device to act as a scaffold to move intimal and medial flaps away from the lumen and maintain radial support to offset elastic recoil.[6] Early observational trials highlighted problems associated with the use of stents, in particular, a high incidence of subacute occlusion, despite aggressive anticoagulation regimens that prolonged hospital stays and were also associated with bleeding complications that were difficult to control and occasionally led to serious events.[7] Subsequent reports involving larger numbers of patients confirmed the utility and efficacy of stenting as a means to avoid emergency bypass surgery.[8]

In 1993, two important randomized clinical trials compared the Palmaz–Schatz stent with balloon angioplasty, establishing the elective placement of coronary stents as a standard treatment. The 520-patient Belgium Netherlands Stent (BENESTENT) study[9] and the 410-patient North American Stent Restenosis Study (STRESS)[10] separately demonstrated that intracoronary stents significantly reduced the incidence of angiographic restenosis (defined as more than 50 percent narrowing of a previously stented site, as measured by quantitative coronary angiography) and repeated angioplasty in patients with discrete, new lesions in large target vessels, leading to the era of elective stent implantation. By 1999, stenting comprised 84.2 percent of percutaneous coronary interventions.[11] Although the implantation of an intracoronary stent prevents the acute recoil and postinjury arterial shrinkage (constrictive remodeling) associated with balloon angioplasty, it increases the risk of subacute thrombosis and, more important, replaces atherosclerotic coronary disease with the more severe iatrogenic condition of in-stent neointimal hyperplasia — that is, the growth of scar tissue inside the stent through the cell-cycle pathway and as a result of the proliferation and migration of vascular smooth-muscle cells (Fig. 1).

At the time of the STRESS and BENESTENT trials, despite the use of an intensive anticoagulation regimen, subacute occlusion occurred in 3.7 percent of patients, a value higher than that seen with balloon angioplasty alone. The use of high balloon pressures to optimize apposition of the stent strut to the vessel wall, together with dual antiplatelet therapy with aspirin and ticlopidine (a thienopyridine) rather than anticoagulation resulted in a dramatic reduction in the rates of stent thrombosis.[12] Currently, clopidogrel is the more popular thienopyridine, owing to its bet-
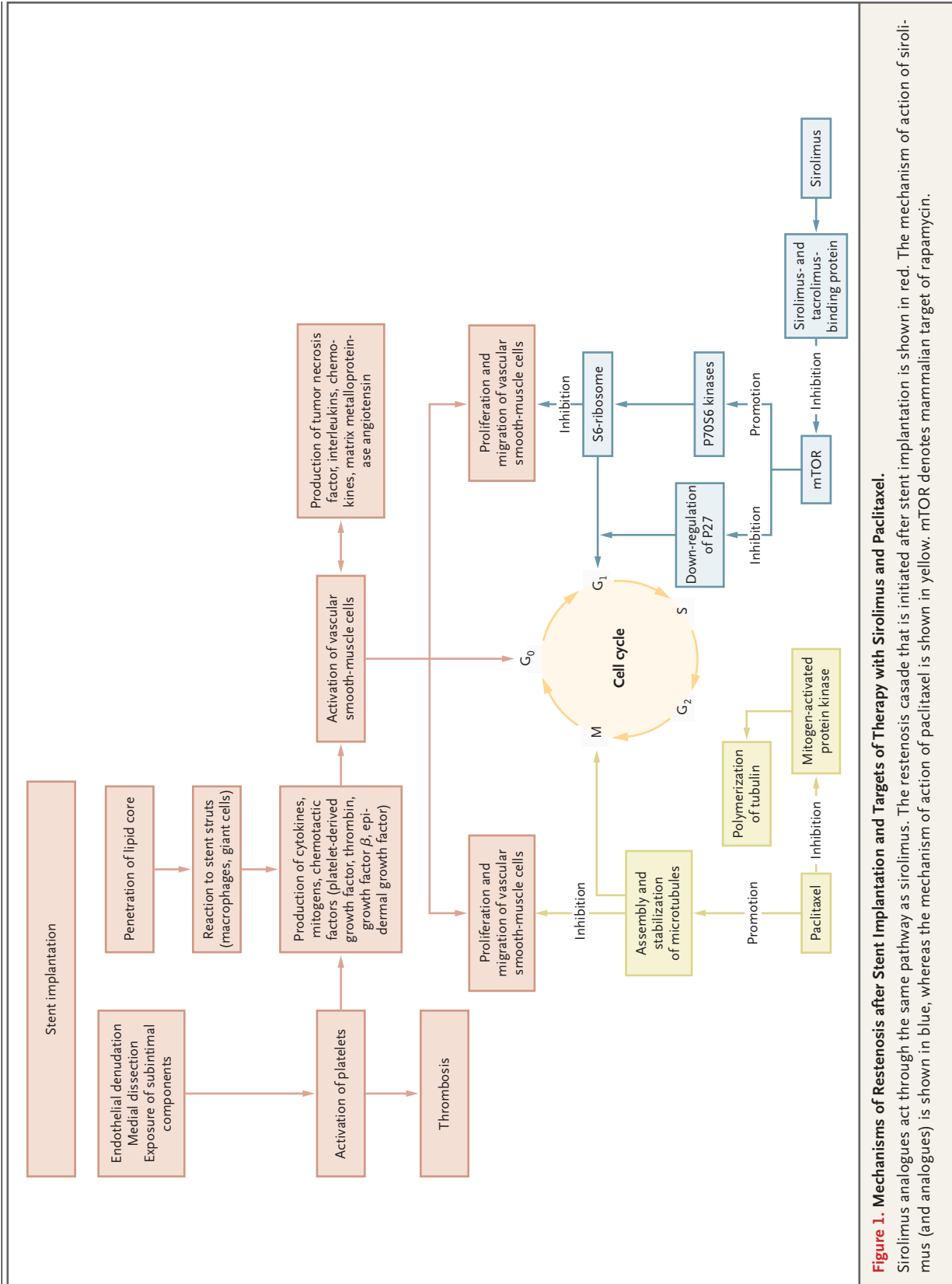
**Figure 1. Mechanisms of Restenosis after Stent Implantation and Targets of Therapy with Sirolimus and Paclitaxel.**

Sirolimus analogues act through the same pathway as sirolimus. The restenosis casade that is initiated after stent implantation is shown in red. The mechanism of action of siroli-mus (and analogues) is shown in blue, whereas the mechanism of action of paclitaxel is shown in yellow. mTOR denotes mammalian target of rapamycin.

ter safety profile, with a lower incidence of rash and neutropenia.[13] A recent meta-analysis of 29 published, randomized studies involving 9918 patients and comparing balloon angioplasty with routine coronary stenting with bare stents confirmed that stenting reduces restenosis and repeated intervention, but does not reduce mortality or myocardial infarction.[14] Once a role for elective stent implantation was established, the next goal was to overcome the complications of subacute stent thrombosis and neointimal hyperplasia through pharmacologic and physical means.

## BARRIER AND BIOACTIVE STENT COATINGS

### BARRIER STENT COATINGS

Stent implantation, inherently a thrombogenic procedure, initiates a complex interaction between the blood components and the metal surface of the stent, which includes the deposition of protein; the activation of platelets, the complement system, and coagulation factors; and the eventual propagation of thrombi over the surface of the stent[15] and the establishment of a confluent endothelial monolayer. 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 effectiveness of these strategies has not been proven in clinical trials. Indeed, gold coatings result in increased rates of restenosis.[16]

### ACTIVE STENT COATING TO PREVENT THROMBOSIS

In contrast to barrier laminates, heparin coatings provide a biologically active surface that interacts with circulating blood. The BENESTENT II randomized trial demonstrated that heparin-coated stents resulted in a lower rate of adverse events at one year than did balloon angioplasty (11 percent vs. 21 percent, P=0.004).[17] Analysis of data from a large, single-center registry demonstrated that, as compared with bare-metal stents, heparin-coated stents significantly reduced the rate of stent thrombosis.[18]

## DRUG-ELUTING STENTS

Considerable efforts have gone into the development of stents with an active coating to inhibit in-stent restenosis — the drug-eluting stent. The components of a drug-eluting stent 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 suitable for sterilization, allow time- and dose-controlled drug release, and not promote thrombogenesis and inflammation of the vessel wall and tissue.[19] Various coatings have been developed, including phosphorylcholine; biocompatible nonerodable, biodegradable, or bioabsorbable polymers; and ceramic layers.[20-25] Polymers are the most commonly used carriers. A drug that is successfully eluted should inhibit the complex cascade of events that leads to neointimal formation after stent implantation (Fig. 1). 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.

The success of eluting devices is highly dependent on each component of the complex, as well as on the interactions among these elements. It is therefore unlikely that drug-eluting stents have a class effect, since there are myriad possible therapeutic combinations. Different drug-eluting stents vary in their ability to inhibit neointimal growth.[26] Finally, because the results of experiments in animal models cannot be directly translated to humans, specific clinical trials of safety and efficacy are required for each device.[27]

### SUCCESSFUL DRUG-ELUTING STENTS
*Sirolimus-Eluting Stents*
The first positive clinical data on drug-eluting stents came from trials examining sirolimus-coated stents. Sirolimus, a natural macrocyclic lactone with potent antiproliferative, antiinflammatory, and immunosuppressive effects, acts by inhibiting the activation of the mammalian target of rapamycin (mTOR), ultimately causing arrest of the cell cycle (Fig. 1).[28,29]

The Cypher sirolimus-eluting 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 in São Paulo, Brazil,[20] and Rotterdam, the Netherlands.[30] Four months after implantation, both types of stents were associated with minimal neointimal hyperplasia, as measured by intravascular ultrasonography and quantitative coronary angiography. The slow-release formulation was subsequently used. In the Brazilian study, intravascular ultrasonography at four 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 percent.[20]

The results of four randomized trials involving sirolimus-eluting stents have been published and are summarized in Figures 2 and 3 and in Table 1 of the Supplementary Appendix (available with the full text of this article at www.nejm.org). The Randomized Study with the Sirolimus-eluting Bx Velocity Balloon Expandable Stent (RAVEL) demonstrated a remarkable 0 percent rate of restenosis and complete inhibition of neointimal hyperplasia in the group that received a sirolimus-eluting stent, as measured by angiography, and led to the approval of the device in Europe.[31] Percutaneous revascularization of the treated lesion was required in 0 percent of the group that received a sirolimus-eluting stent group, as compared with 23 percent of the control group at one year. The results of the randomized, double-blind Sirolimus Eluting Stent in de Novo Coronary Lesions (SIRIUS) trial, involving 1055 patients, were used to gain approval of the device by the Food and Drug Administration (FDA) in the United States in 2003.[32] The SIRIUS trial confirmed the safety and efficacy of the sirolimus-eluting stent in single, previously untreated coronary artery lesions, with a lower rate of in-stent restenosis than found with otherwise identical bare-metal stents (3.2 percent vs. 35.4 percent, P<0.001). The smaller European and Latin American (E-SIRIUS)[33] and Canadian (C-SIRIUS)[34] multicenter SIRIUS trials confirmed the results of the SIRIUS trial. Most recently, the single-group Arterial Revascularization Therapies Study Part II (ARTS II), involving a cohort of patients with highly complex conditions who received an average of 3.7 sirolimus-eluting stents, reported low rates of repeated intervention rates — 8.5 percent — at one year, with an event-free survival rate of 89.5 percent.[35]

*Polymeric Paclitaxel–Eluting Stents*

Paclitaxel is a potent antiproliferative agent that inhibits the disassembly of microtubules (Fig. 1). A series of studies — the Randomized, Double-Blind Trial of a Slow-Release Paclitaxel-Eluting Stent for de Novo Coronary Lesions (TAXUS) studies — were conducted to collect data on two paclitaxel-eluting stents, the NIR stent and the Express stent (Boston Scientific). A copolymer coating (Translute, 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. Three randomized trials of this device have been published (Fig. 2 and 3, and Table 1 of the Supplementary Appendix). TAXUS-I evaluated the feasibility and safety of paclitaxel-eluting stents as compared with bare-metal stents and found similar six-month rates of restenosis of 0 and 10 percent, respectively.[21]

TAXUS-II investigated two formulations of paclitaxel-eluting stents: slow- and moderate-release.[36] Although both devices carry the same total dose of medication, drug release from the moderate-release device is eight times as high in the first 10 days. Excellent results were achieved with both formulations; only the slow-release formulation was readied for commercial use and received European approval partly on the basis of the results of this trial. The randomized, double-blind TAXUS-IV, 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.[37] Nine months after stenting, the need for a repeated procedure in the treated vessel was 4.7 percent in the group that received paclitaxel-eluting stents, as compared with 12.0 percent in the groups that received bare-metal stents (P<0.001). TAXUS-V and TAXUS-VI subsequently confirmed the efficacy of this stent in small vessels (less than 2.5 mm in diameter) and long lesions and the safety of procedures involving overlapping paclitaxel-eluting stents (Table 2 of the Supplementary Appendix).

### REAL-WORLD EXPERIENCE

Concern that the results of the clinical trials might not translate into daily practice were addressed in the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) sequential registry.[38] A total of 508 consecutive patients with previously untreated coronary lesions exclu-
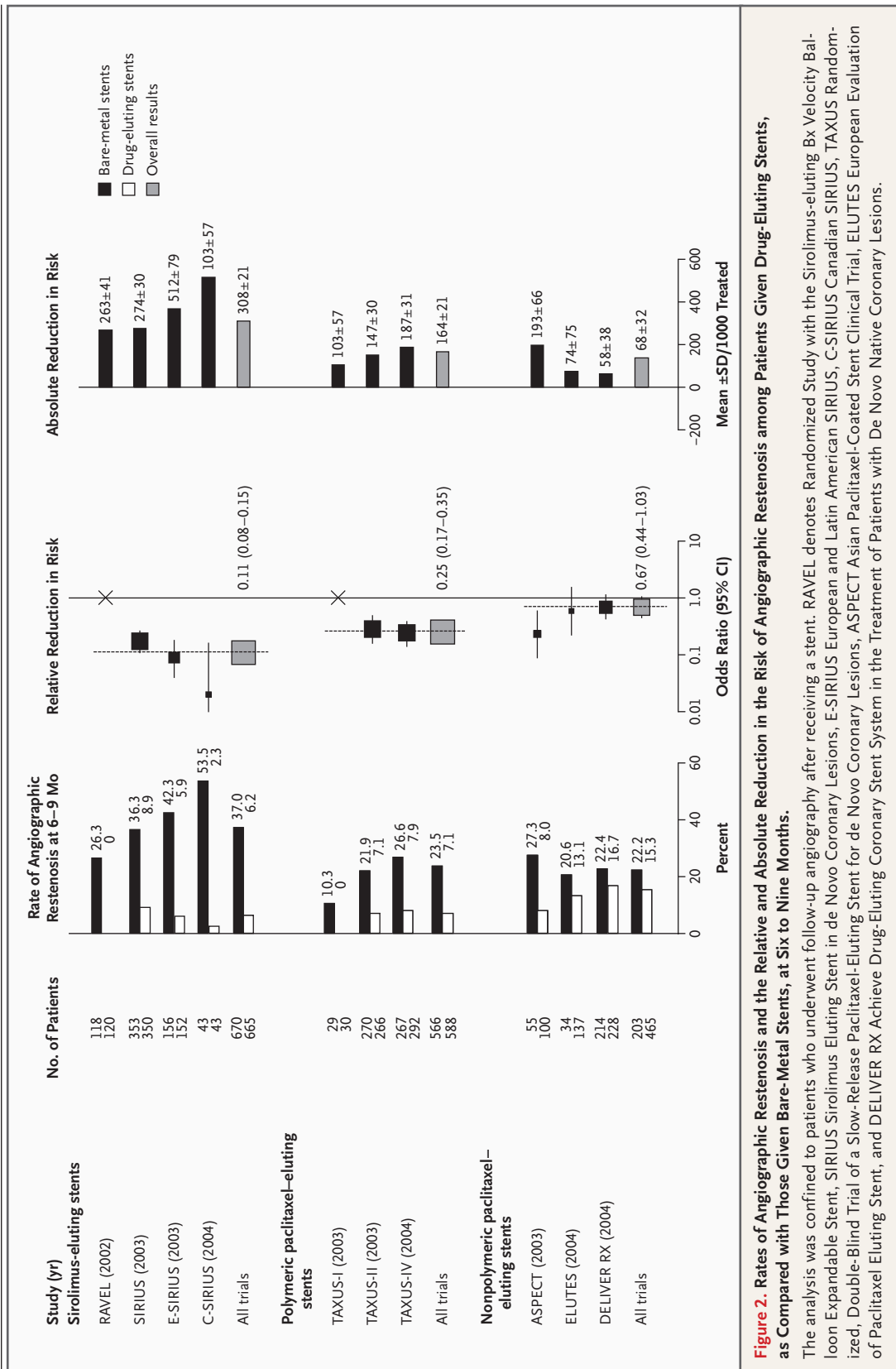
**Figure 2. Rates of Angiographic Restenosis and the Relative and Absolute Reduction in the Risk of Angiographic Restenosis among Patients Given Drug-Eluting Stents, as Compared with Those Given Bare-Metal Stents, at Six to Nine Months.**

The analysis was confined to patients who underwent follow-up angiography after receiving a stent. RAVEL denotes Randomized Study with the Sirolimus-eluting Bx Velocity Balloon Expandable Stent, SIRIUS Sirolimus Eluting Stent in de Novo Coronary Lesions, E-SIRIUS European and Latin American SIRIUS, C-SIRIUS Canadian SIRIUS, TAXUS Randomized, Double-Blind Trial of a Slow-Release Paclitaxel-Eluting Stent for de Novo Coronary Lesions, ASPECT Asian Paclitaxel-Coated Stent Clinical Trial, ELUTES European Evaluation of Paclitaxel Eluting Stent, and DELIVER RX Achieve Drug-Eluting Coronary Stent System in the Treatment of Patients with De Novo Native Coronary Lesions.
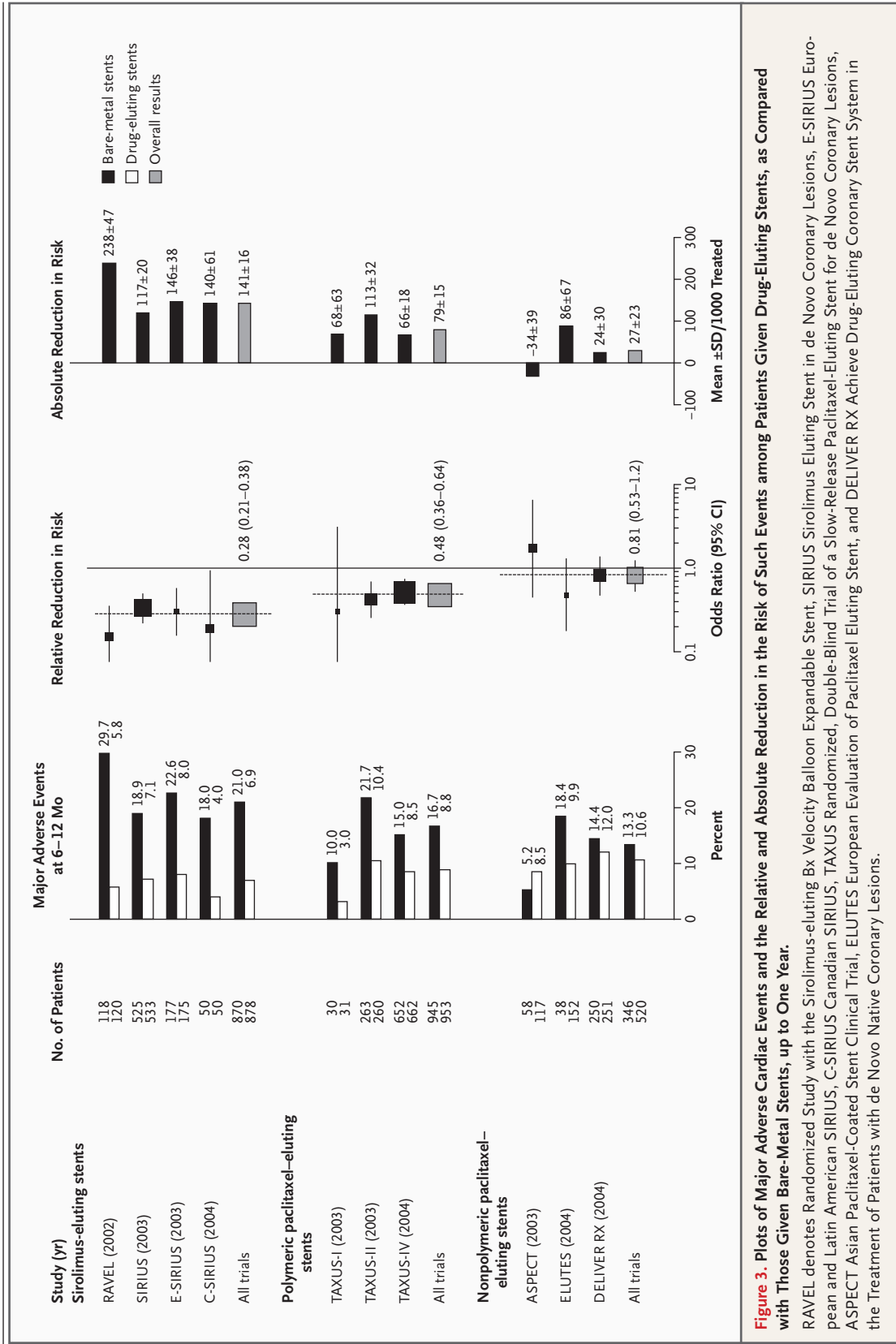
**Figure 3. Plots of Major Adverse Cardiac Events and the Relative and Absolute Reduction in the Risk of Such Events among Patients Given Drug-Eluting Stents, as Compared with Those Given Bare-Metal Stents, up to One Year.**

RAVEL denotes Randomized Study with the Sirolimus-eluting Bx Velocity Balloon Expandable Stent, SIRIUS Sirolimus Eluting Stent in de Novo Coronary Lesions, E-SIRIUS European and Latin American SIRIUS, C-SIRIUS Canadian SIRIUS, TAXUS Randomized, Double-Blind Trial of a Slow-Release Paclitaxel-Eluting Stent for de Novo Coronary Lesions, ASPECT Asian Paclitaxel-Coated Stent Clinical Trial, ELUTES European Evaluation of Paclitaxel Eluting Stent, and DELIVER RX Achieve Drug-Eluting Coronary Stent System in the Treatment of Patients with de Novo Native Coronary Lesions.

sively treated with sirolimus-eluting stents were compared with a control group of 450 patients who had received bare-metal stents in the period immediately preceding the introduction of drug-eluting stents. Patients who received sirolimus-eluting stents had a lower rate of adverse events at one year (9.7 percent vs. 14.8 percent, P=0.008), with the difference largely accounted for by a reduction in the rate of clinically driven reinterventions (3.7 percent vs. 10.9 percent, P<0.001). The two-year results of this study confirmed the durability of this device, with rates of adverse events of 15.4 percent in the group given sirolimus-eluting stents, as compared with 22.0 percent in the group given bare-metal stents (P<0.01).[39] The randomized Basel Stent Kosten Effektivitäts Trial (BASKET) confirmed the superiority of drug-eluting stents over bare-metal stents at six months.[40]

### COMPARATIVE TRIALS

The Prospective, Randomized, Multi-Center Comparison Study of the Cypher Sirolimus-Eluting and TAXUS Paclitaxel-Eluting Stent Systems (REALITY) compared sirolimus-eluting stents and paclitaxel-eluting stents.[26] The rate of late loss (a measure of neointimal hyperplasia assessed by means of quantitative coronary angiography) was lower with sirolimus-eluting stents than with paclitaxel-eluting stents, but the rates of angiographic restenosis and, more important, the need for reintervention in the treated lesion did not differ significantly between groups (5.0 percent vs. 5.4 percent, P=0.8). The two-center Randomized Comparison of Sirolimus with Paclitaxel Eluting Stents for Coronary Revascularization of All Comers (SIRTAX)[41] reported better outcomes with sirolimus-eluting stents than with paclitaxel-eluting stents. The single-center Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) study, a sequential monocentric registry of patients who received drug-eluting stents without any restrictions, reported no significant difference in the incidence of adverse cardiac events between the two devices.[42] Two smaller randomized trials demonstrated that sirolimus-eluting stents were more efficacious than paclitaxel-eluting stents in specific types of patients: those with restenosis in bare-metal stents (the Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis [ISAR-DESIRE] study) and those with diabetes (the ISAR: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting

and Sirolimus-Eluting Stents [ISAR-DIABETES] study).[43,44]

### INVESTIGATIVE AGENTS

#### Zotarolimus

Zotarolimus is a sirolimus analogue that blocks the function of mTOR and is currently being investigated (Fig. 1, and Table 2 of the Supplementary Appendix). A series of clinical trials — Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in de Novo Native Coronary Artery Lesions (ENDEAVOR) — have been designed to examine the safety and efficacy of zotarolimus released from a phosphorylcholine-delivery matrix on the cobalt-based alloy Driver stent (Medtronic).[22] The single-group ENDEAVOR-I safety study was followed by the randomized, multicenter ENDEAVOR-II trial, involving 1197 patients, which confirmed the efficacy of this device, with restenosis rates of 9.5 percent, as compared with 32.7 percent for bare-metal stents (P<0.001).[45] The implications of a mean in-stent late loss of 0.62 mm, which was consistently seen in both trials and is higher than that reported in trials of sirolimus-eluting and paclitaxel-eluting stents, are unknown.

The Zomaxx stent (Abbott) contains zotarolimus on a low-profile, trilayer stent composed of tantalum and stainless steel (TriMaxx), with a modified phosphorylcholine coating to allow slower drug release than afforded by the Medtronic device. The first of Abbott's clinical trials has completed enrollment, and a second is under way (Table 2 of the Supplementary Appendix).

#### Everolimus

As a sirolimus analogue, everolimus inhibits mTOR (Fig. 1). Trials involving everolimus-coated stents are split into two: the First Use to Underscore Restenosis Reduction with Everolimus (FUTURE) and A Randomized Comparison of a Durable Polymer Everolimus-Eluting Stent with a Bare-Metal Coronary Stent (SPIRIT) studies (Tables 1 and 2 of the Supplementary Appendix). The small FUTURE-I study was a prospective, randomized, single-blind trial that evaluated the safety of an everolimus-eluting stent with an ultrathin coating of a polyhydroxyacid bioabsorbable polymer used for drug delivery (Biosensors International). As compared with bare-metal stents in previously untreated lesions, everolimus-eluting stents sig-

nificantly reduced the extent of late loss (0.11 mm vs. 0.85 mm, P<0.001).[23] The results of the FUTURE-II trial have yet to be published. The SPIRIT FIRST trial confirmed the safety and efficacy of everolimus coupled with a durable polymer on a chromium–cobalt stent and has led to the initiation of SPIRIT-II outside and SPIRIT-III within the United States.[24]

### Other Agents

Other agents that appear promising and are currently undergoing safety and efficacy trials include biolimus A9 (a sirolimus analogue),[25] tacrolimus (a sirolimus analogue), and paclitaxel contained in reservoirs within the stent. If shown to be successful, they will then undergo larger comparative trials, most likely with one or more of the established devices used as a benchmark.

## INDICATIONS FOR THE USE OF CORONARY STENTS

Currently, better equipment and drug-eluting stents have changed percutaneous coronary intervention so that 90 to 95 percent involve stent implantation. However, most published data originated in the era of bare-metal stents. Given the lack of long-term follow-up with drug-eluting stents, careful scrutiny of the literature is necessary before convincing recommendations can be made.

### PRIMARY REVASCULARIZATION AFTER MYOCARDIAL INFARCTION INVOLVING ST-SEGMENT ELEVATION

Randomized trials have compared stent implantation with balloon angioplasty as the primary revascularization strategy for myocardial infarction involving ST-segment elevation,[46-48] with meta-analyses reporting the superiority of stenting, as reflected by a reduced need for reintervention in the treated vessel for up to 12 months.[49] More recently, two major studies, Danish Multicenter Randomized Study of Fibrinolytic Therapy vs. Acute Coronary Angioplasty in Acute Myocardial Infarction 2 (DANAMI-2)[50] and Primary Angioplasty in Patients Transferred from General Community Hospitals to Specialized Percutaneous Transluminal Coronary Angioplasty (PTCA) Units with or without Emergency Thrombolysis 2 (PRAGUE-2),[51] have indicated the superiority of stenting over thrombolytic therapy, primarily as a result of the ability of stenting to reduce re-infarction rates. Drug-eluting stents are superior to bare-metal stents because they further reduce the need for reintervention in the treated vessel.[52]

### Focal Lesions in Vessels 3.0 mm or More in Diameter

The trials comparing balloon angioplasty with stent implantation have been confined to patients with vessels with diameters of 3.0 mm or greater on visual assessment (smaller-diameter stents were not available in the past). Results of such trials have consistently shown a reduction in adverse events with the use of stenting.[9,10,17] A notable finding is that a sizable number of patients who received stents had vessel diameters smaller than 3.0 mm when later measured with the use of quantitative coronary angiography.

### Focal Lesions in Saphenous-Vein Grafts

Both observational and randomized trials have indicated a high rate of procedural success with vein-graft stenting, improved clinical outcomes during hospitalization, and improved long-term graft patency.[53] The Randomized Evaluation of Polytetrafluoroethylene Covered Stents in Saphenous Vein Grafts (RECOVERS) study[54] demonstrated that stents covered with a polytetrafluoroethylene membrane conferred no advantage over bare-metal stents for the treatment of vein-graft disease. Distal embolization is a major problem in old and friable vein grafts, and the use of devices placed downstream of the treated area to catch vascular debris has improved the safety of vein-graft interventions.[55,56]

### Treatment of Chronic Total Occlusions

Various trials comparing stenting with balloon angioplasty for coronary-artery occlusions have reported that stenting reduces the rate of angiographic and clinical restenosis and reocclusion.[57] More recently, registry series comparing drug-eluting stents with bare-metal stents have confirmed the superior efficacy of the former.[58]

### Treatment of Restenosis after Balloon Angioplasty

The randomized Restenosis Stent Trial (REST) demonstrated that in patients with restenosis after balloon angioplasty, the implantation of a stent was associated with a lower rate of angiographic restenosis and repeated intervention than was balloon angioplasty.[59]

## SEGMENTAL LESIONS FOR WHICH CORONARY STENTING IS PROBABLY BENEFICIAL

Although stents are used for long lesions, vessels that are less than 3.0 mm in diameter, and lesions at bifurcations, there is less evidence to support their use.

### Long Lesions

The length of the stented segment is a recognized independent risk factor for restenosis.[60] In a nonrandomized comparison, balloon angioplasty with intravascular-ultrasound–guided placement of multiple small stents to cover stenoses along vessel lesions ("spot" stenting) had a better long-term outcome than stenting the entire portion of a diseased vessel.[61] One randomized trial compared the use of stents with balloon angioplasty for long lesions and found lower rates of angiographic restenosis in the stent group than in the angioplasty group at six months (27 percent vs. 42 percent, $P<0.05$) but no significant difference in clinical benefit at nine months.[62] Placing sequential overlapping stents in long lesions increases the length of the stented area within the vessel and is associated with increased rates of restenosis. Evidence to date indicates that drug-eluting stents may be safely used in this manner and are seemingly associated with markedly reduced rates of restenosis. Thus, drug-eluting stents appear to be associated with a substantially smaller risk of restenosis than bare-metal stents, especially in long lesions.[63]

### Small Vessels

The benefit of stenting vessels smaller than 3.0 mm in diameter is unclear; a meta-analysis indicated that stenting significantly reduced the rates of repeated revascularization, as compared with balloon angioplasty, with similar rates of adverse events.[64] The recent subgroup analyses of TAXUS-V and TAXUS-VI suggest that drug-eluting stents reduce the rate of restenosis in small vessels, without associated side effects.

### Lesions at Bifurcations

Different stenting techniques, each with their own advantages and indications, have been used to treat lesions at bifurcations.[65] Observational studies have suggested that stenting both branches of bifurcated lesions confers no advantage over stenting one branch and performing balloon angioplasty on the other.[66] Currently, the most appropriate technique for treating lesions at bifurcations remains to be determined. As compared with historical results with bare-metal stents, drug-eluting stents are associated with a lower overall rate of restenosis, although the rates remain higher in side branches than in the main vessel.[67]

## UNRESOLVED ISSUES

### Stenosis of an Unprotected Left Main Coronary Artery

Safety studies and early efficacy studies have shown that stenting of a previously ungrafted stenosis in the left main stem may be a promising alternative to bypass surgery in selected patients.[68,69] Analysis of recent registries suggests a potential role for drug-eluting stents in left main lesions,[70,71] with the ongoing Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) Study designed to address the role of drug-eluting stents as compared with bypass surgery in a randomized manner.[72]

### Multivessel Disease

Long-term follow-up of patients with multivessel disease in the ARTS trial found no significant difference in mortality rates between patients treated with bare-metal stents and those treated with bypass surgery, but the former group had a higher rate of repeated procedures.[73] The SYNTAX study will address the role of drug-eluting stents, as compared with bypass surgery, in three-vessel disease.[72]

### Diabetes Mellitus

Diabetes has repeatedly been shown to confer an independent risk of restenosis and adverse clinical events after stent implantation in multiple trials of bare-metal and drug-eluting stents.[32,37] Although as compared with bare-metal stents, drug-eluting stents appear to reduce the reintervention rate by up to two thirds among patients with diabetes with bare stents, the reintervention rate in this subgroup remains up to twice as frequent as that among patients without diabetes who receive stents.[35] A randomized trial is under way — the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) study — that specifically compares drug-eluting stents with bypass surgery in patients with diabetes who have multivessel disease.

*In-Stent Restenosis*

Both sirolimus-eluting stents[74] and paclitaxel-eluting stents[75] have been examined as treatments for restenosis. Although definitively better than balloon angioplasty in reducing the rate of recurrent restenosis,[43] they appear similar to conventional intracoronary brachytherapy (radiation delivered intravascularly through a catheter within the stent borders).[76] The TAXUS-V–In-Stent Restenosis randomized trial is comparing drug-eluting stents with brachytherapy for in-stent restenosis to confirm these results.

*Biodegradable Stents*

The development of biodegradable stents has been hampered by difficulties in replicating the properties of stainless-steel stents. There has been a revival of interest in developing a fully biodegradable stent that has pharmacologically active agents incorporated into the polymeric matrix. An effective drug-releasing, biodegradable stent must not cause an inflammatory reaction or release toxic breakdown products. The release of the drug from the stent must be safe and reliable, and the stent must have high radial strength similar to that of metal. Biodegradation should occur within a reasonable period (12 to 24 months). The Duke biodegradable stent[77] and the Igaki–Tamai biodegradable stent[78] are made from a special form of poly-L-lactide and are capable of incorporating pharmacologically active agents. The Igaki–Tamai stent has been successfully loaded with tranilast, a drug that inhibits the migration and proliferation of vascular smooth-muscle cells.[79] This type of stent has also been loaded with paclitaxel, and although effective in reducing the rate of restenosis in an animal model, it incites a considerable inflammatory response.[80] Another promising degradable stent undergoing clinical evaluation is made from magnesium alloy.[81]

## CAVEATS AND CONCLUSIONS

The three major milestones in the evolution of interventional cardiology were the development of the angioplasty balloon by Andreas Grüntzig, the introduction of the coronary-artery stent, and most recently, the development of drug-eluting stents. In the past three years, the use of drug-eluting stents has had an unprecedented effect on the practice of interventional cardiology. The acceptance of drug-eluting stents has followed the same course as all newly introduced techniques, with the initial period of overblown enthusiasm quickly followed by a period of intellectual reproach.

Recent results of longer-term studies in broader patient populations have highlighted troubling clinical issues. In studies in animals, the presence of fibrin, inflammatory cells, and incomplete endothelialization has been noted and at three months, when the drug has been completely eluted from the stent, neointimal growth at levels similar to those for bare-metal stents,[27] arousing concern about the possibility of late restenosis.[82] Delayed endothelialization has been seen in human arteries treated with drug-eluting stents[83]; this complete inhibition of healing may prevent encapsulation of the stent but, in one study, did not translate into adverse events at one year.[84] There have been rare instances of hypersensitivity reactions to the polymer, which can be fatal.[85]

The consequences of these findings have been clinically observed as stent thrombosis, a potentially fatal complication of stent implantation. Thrombosis within the stent may occur early, within the first 30 days after implantation, or late, if after this period, with differing causes. The most common cause of early stent thrombosis is mechanical (unrecognized dissection or underexpansion of the stent), whereas late stent thrombosis is potentially due to a mismatch between the stent and the vessel (stent malapposition), hypersensitivity,[85] or abnormal re-endothelialization. A recently recognized potential predisposing factor for stent thrombosis is resistance to aspirin and clopidogrel; this association requires more investigation. The rates of early stent thrombosis probably do not differ significantly between drug-eluting and bare-metal stents, occurring in 1.0 to 1.5 percent of patients.[86,87] Whether this is also true for late stent thrombosis is unclear; however, caution must be exercised, given the lack of comparative data and the difference in the duration of dual antiplatelet therapy between devices (one month for bare-metal stents and three to six months for drug-eluting stents).[88]

Most important, after the implantation of a drug-eluting stent, patients must strictly adhere to their regimen of dual antiplatelet therapy and, on completion, take aspirin monotherapy.[89] Patients with drug-eluting stents who require surgery, elective or otherwise, irrespective of the time since implantation, must continue to take aspirin

perioperatively unless it is absolutely contraindicated, since cessation of antiplatelet therapy, even if it occurs long after the implantation of the stent, may precipitate stent thrombosis, which carries a high risk of death or myocardial infarction.

As a solution, coatings that are more biologically friendly and promote rather than inhibit natural healing processes are rapidly being developed.[90,91] One example is the use of immobilized antibodies against circulating endothelial progenitor cells as a means of "self-seeding" intravascular devices.[90] Such techniques show promise for use in combination with drug-eluting stents and may provide a more physiologic alternative. With the development of better devices, uniquely engineered to be specific for each subgroup of lesions, the treatment of coronary artery disease will improve.

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