REVIEW ARTICLE

DRUG THERAPY

Drug-Eluting Coronary-Artery Stents

Giulio G. Stefanini, M.D., and David R. Holmes, Jr., M.D.

From the Department of Cardiology, Bern University Hospital, Bern, Switzerland (G.G.S.); and the Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, MN (D.R.H.). Address reprint requests to Dr. Stefanini at the Department of Cardiology, Bern University Hospital, Freiburgstrasse 4, 3010 Bern, Switzerland, or at giulio.stefanini@insel.ch.

N Engl J Med 2013;368:254-65.
DOI: 10.1056/NEJMra1210816

Percutaneous coronary intervention, which was pioneered by Grüntzig in 1977, has become the most frequently performed therapeutic procedure in medicine.[1] The use of balloon angioplasty, which was limited by abrupt vessel closure owing to dissections and restenosis, prompted the development of stents to maintain lumen integrity.[2] Coronary stents improved procedural safety and efficacy and eliminated the need for surgical standby.[3] However, stent-mediated arterial injury elicited neointimal hyperplasia, leading to restenosis and the need for repeat revascularization in up to one third of patients.[4]

Drug-eluting stents with controlled local release of antiproliferative agents have consistently reduced the risk of repeat revascularization, as compared with bare-metal stents.[5-7] However, a number of reports presented at the European Society of Cardiology Congress in 2006 questioned the long-term safety of drug-eluting stents, leading to a reduction in their use, along with intense review by regulatory agencies and recommendations to extend dual antiplatelet therapy for at least 12 months.[8-10] In 2007, the *Journal* published evidence that stents releasing sirolimus or paclitaxel, as compared with bare-metal stents, were associated with similar risks of death and myocardial infarction but with an increased, albeit small, risk of stent thrombosis beyond 1 year after stent implantation.[8,11-14] Since then, new platforms for drug-eluting stents that are aimed at improving safety and efficacy have been developed. Drug-eluting stents are now implanted in more than 500,000 patients every year in the United States.[15] This review provides an overview of currently available devices, summarizes evidence from randomized trials, and outlines clinical indications for use.

Platforms for Drug-Eluting Stents

Drug-eluting stents have three components: a metallic stent platform, a polymer coating, and an antiproliferative agent (Fig. 1).

Stent Platforms

Available platforms are made of stainless steel, cobalt–chrome, or platinum–chrome. Cobalt–chrome alloys provide improved radial strength and increased radiopacity, as compared with stainless steel, allowing for engineering of thinner struts with greater deliverability. Platforms made with thinner struts may result in less arterial injury and reduce the risk of restenosis,[16] with lower thrombogenicity.[17] Platinum–chrome alloys are used in an effort to further improve radial strength and conformability.

Polymer Coatings

Polymer coatings that are applied to the stent surface serve as drug carriers and permit controlled drug release. Progress in polymer technology has been aimed at decreasing local inflammatory reactions and thrombosis by improving the biocom-

patibility of polymers.[17,18] Drug-eluting stents that have been approved by the Food and Drug Administration (FDA) have durable polymer coatings (Table 1). However, new platforms for drug-eluting stents feature polymers that biodegrade after drug elution, resulting in a stent surface similar to that of a bare-metal stent.[19] These new platforms have not yet been approved by the FDA but are commonly used in clinical practice outside the United States.

ANTIPROLIFERATIVE AGENTS

Antiproliferative agents that are used for the platforms of drug-eluting stents are highly lipophilic molecules that are distributed into the arterial wall and exert either immunosuppressive effects (inhibitors of mammalian target of rapamycin) or antiproliferative effects (paclitaxel) on smooth-muscle cells (Fig. 1).

FDA-APPROVED DRUG-ELUTING STENTS

Early-generation stents released sirolimus or paclitaxel and had stainless-steel platforms, whereas new-generation stents release everolimus or zotarolimus and feature cobalt–chrome or platinum–chrome platforms with thinner strut thickness and more biocompatible, durable polymer coatings. These new-generation stents have almost completely replaced paclitaxel-eluting stents in clinical practice, and sirolimus-eluting stents are no longer manufactured.

VASCULAR BIOLOGY

ARTERIAL HEALING AFTER STENT IMPLANTATION

While providing inhibition of neointimal hyperplasia, drug-eluting stents should permit physiological arterial healing with smooth and homogeneous endothelial coverage of all stent struts. This may be overbalanced by an excessive antiproliferative effect and persistence of stent components (e.g., polymer coatings), leading to chronic inflammation and impaired arterial healing, with the attendant risk of thrombotic events (Fig. 2).[20]

Early-generation sirolimus- and paclitaxel-eluting stents were associated with delayed arterial healing — manifested as incomplete endothelialization of stent struts, vessel remodeling, and persistent fibrin and platelet deposition[20,21] — and with premature neoatherosclerosis.[22] Improved endothelial coverage has been reported after implantation of everolimus- and zotarolimus-eluting stents in studies in animals[23] and in clinical studies with intracoronary imaging.[24]

STENT THROMBOSIS

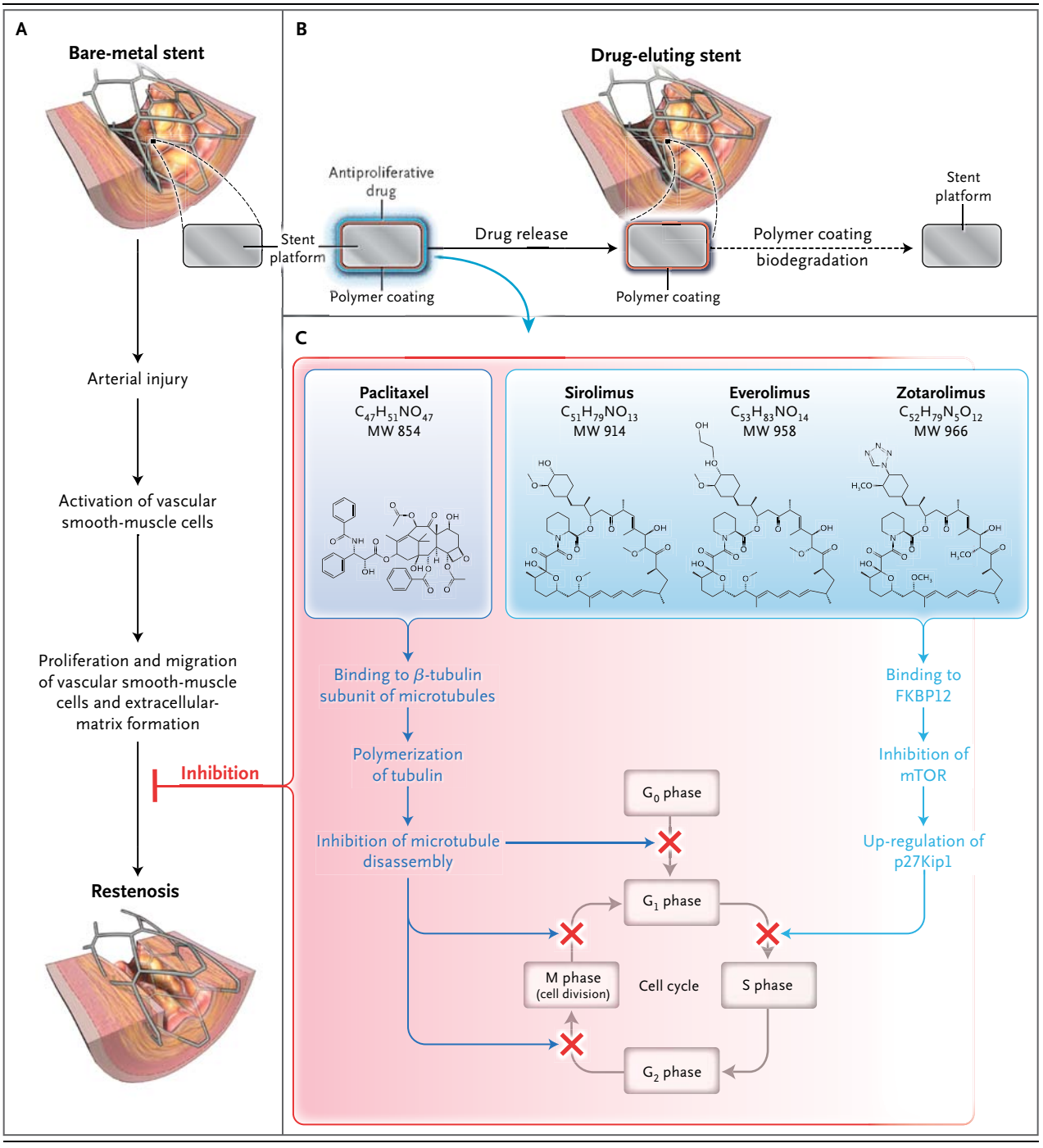
Stent thrombosis, which is a rare but serious complication of treatment with both bare-metal stents and drug-eluting stents,[25] has been related to procedural factors and inadequate platelet inhibition during the early postimplantation period, as well as to chronic inflammation and delayed arterial healing during late follow-up.[25] Early studies used different definitions of stent thrombosis, making comparisons across reports challenging. The Academic Research Consortium subsequently provided standardized criteria for the definition of stent thrombosis according to the time of occurrence (i.e., early, ≤1 month; late, >1 month to ≤1 year; or very late, >1 year) and the degree of diagnostic certainty (i.e., definite, probable, or possible).[26]

EFFICACY AND SAFETY OF DRUG-ELUTING STENTS

Pivotal trials investigating drug-eluting stents are summarized in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STENTS RELEASING SIROLIMUS OR PACLITAXEL

In a network meta-analysis[7] (an analysis of studies of multiple interventions that makes use of direct and indirect comparison) involving 38 trials and more than 18,000 patients, there was a marked reduction in the rate of repeat revascularization with both sirolimus-eluting stents and paclitaxel-eluting stents, as compared with bare-metal stents. On the basis of this analysis, 7 patients (95% confidence interval [CI], 6 to 8) would need to be treated with sirolimus-eluting stents and 8 patients (95% CI, 7 to 10) with paclitaxel-eluting stents in order to prevent one repeat revascularization, as compared with bare-metal stents. However, stents that release sirolimus or paclitaxel have been associated with an increased risk of very late stent thrombosis, as compared with bare-metal stents.[11,27] In contrast, the risks of death and myocardial infarction with sirolimus-eluting and paclitaxel-eluting stents were similar to the risks with bare-metal stents,[7] which may be explained by the low incidence of very late stent thrombosis (annual rate, 0.2 to 0.6%) and the compensatory effects of a reduced risk of re-



stenosis, which is manifested as myocardial infarction in 10 to 20% of patients.[28,29]

EVEROLIMUS-ELUTING STENTS

In randomized trials, everolimus-eluting stents improved clinical outcomes as compared with paclitaxel-eluting stents, reducing the risks of repeat revascularization, myocardial infarction, and stent thrombosis.[30,31] Randomized comparisons showed similar outcomes for stents releasing everolimus and those releasing sirolimus with respect to rates of death, myocardial infarction, and repeat revascularization.[32-34] A large trial showed lower rates of stent thrombosis with

Figure 1 (facing page). Components and Mechanisms of Action of Bare-Metal and Drug-Eluting Stents.

Shown are cross-sections and platforms of a bare-metal stent (Panel A) and a drug-eluting stent (Panel B). The implantation of a coronary-artery stent causes an arterial injury that activates vascular smooth-muscle cells and leads to their migration and proliferation, with extracellular-matrix formation resulting in the production of neointimal tissue. Excessive neointimal hyperplasia may lead to restenosis within the treated segment, with ischemia requiring repeat revascularization. Drug-eluting stents provide site-specific, controlled release of antiproliferative agents targeting the suppression of neointimal hyperplasia. These devices consist of three components: a metallic platform, a polymer coating that serves as drug carrier and permits controlled drug release, and an antiproliferative agent. The antiproliferative agent is released over time, whereas the stent platform and the durable polymer coating remain in the coronary artery. New platforms for drug-eluting stents — not yet approved by the Food and Drug Administration (FDA) but commonly used in clinical practice outside the United States — feature polymers that biodegrade after drug elution, resulting in a stent surface similar to that of a bare-metal stent. Antiproliferative agents used in FDA-approved drug-eluting stents and their mechanism of action are shown in Panel C. Most of the available drug-eluting stents use limus-family analogues: sirolimus, everolimus, and zotarolimus. These agents bind to the intracellular receptor FKBP12, inhibiting the mammalian target of rapamycin (mTOR), which results in up-regulation of cyclin-dependent kinase inhibitor p27Kip1. This blocks the proliferation of smooth-muscle cells in the gap 1 (G_1) phase of the cell cycle. Conversely, paclitaxel binds to the β-tubulin subunit of microtubules, inhibiting the disassembly of microtubules and thereby arresting cell replication in the G_0–G_1 and mitotic phases of the cycle of smooth-muscle cells. MW denotes molecular weight.

everolimus-eluting stents than with sirolimus-eluting stents at 2 years (0.2% vs. 0.9%, P=0.02).[33] A recent network meta-analysis showed that everolimus-eluting stents, as compared with sirolimus-eluting stents, may reduce the risk of stent thrombosis over the long term (relative risk, 0.37; 95% CI, 0.20 to 0.66) and myocardial infarction (relative risk, 0.77; 95% CI, 0.64 to 0.95).[35] However, the absence of differences with respect to ischemic outcomes in any of the individual trials allows no definitive conclusion regarding the comparative propensity for stent thrombosis with these two devices.

ZOTAROLIMUS-ELUTING STENTS

The Endeavor zotarolimus-eluting stent has been shown to reduce the risk of myocardial infarction

Table 1. Drug-Eluting Stents Approved by the Food and Drug Administration.*

Variable	Paclitaxel-Eluting Stents		Sirolimus-Eluting Stent	Everolimus-Eluting Stents			Zotarolimus-Eluting Stents	
	Type 1	Type 2		Type 1	Type 2	Type 3	Type 1	Type 2
Commercial name	Taxus Express	Taxus Liberté	Cypher	Xience	Promus	Promus Element	Endeavor	Resolute
Manufacturer	Boston Scientific	Boston Scientific	Cordis, Johnson & Johnson	Abbott Vascular	Boston Scientific	Boston Scientific	Medtronic	Medtronic
Platform material	Stainless steel	Stainless steel	Stainless steel	Cobalt–chrome	Cobalt–chrome	Platinum–chrome	Cobalt–chrome	Cobalt–chrome
Strut thickness (μm)	132	97	140	81	81	81	91	91
Polymer material	SIBS	SIBS	PEVA and PBMA	PBMA and PVDF-HFP	PBMA and PVDF-HFP	PBMA and PVDF-HFP	MPC, LMA, HPMA, and 3-MPMA	PBMA, PHMA, PVP, and PVA
Type of polymer	Durable	Durable	Durable	Durable	Durable	Durable	Durable	Durable
Drug concentration (μg/cm^2)	100	100	140	100	100	100	160	160
Drug release	10% during first 10 days†	10% during first 10 days†	80% during first 30 days	80% during first 30 days	80% during first 30 days	80% during first 30 days	80% during first 10 days	80% during first 60 days

* HPMA denotes hydroxypropyl methacrylate, LMA lauryl methacrylate, MPC methacryloyloxyethyl phosphorylcholine, 3-MPMA 3-(trimethoxysilyl)propyl methacrylate, PBMA poly(n-butyl methacrylate), PEVA poly(ethylene-co-vinyl acetate), PHMA poly(hexyl methacrylate), PVA polyvinyl acetate, PVDF-HFP copolymer of vinylidene fluoride and hexafluoropropylene, PVP polyvinylpyrrolidinone, and SIBS poly(styrene-b-isobutylene-b-styrene).
† The remaining 90% of the drug remains sequestered in the polymer indefinitely.

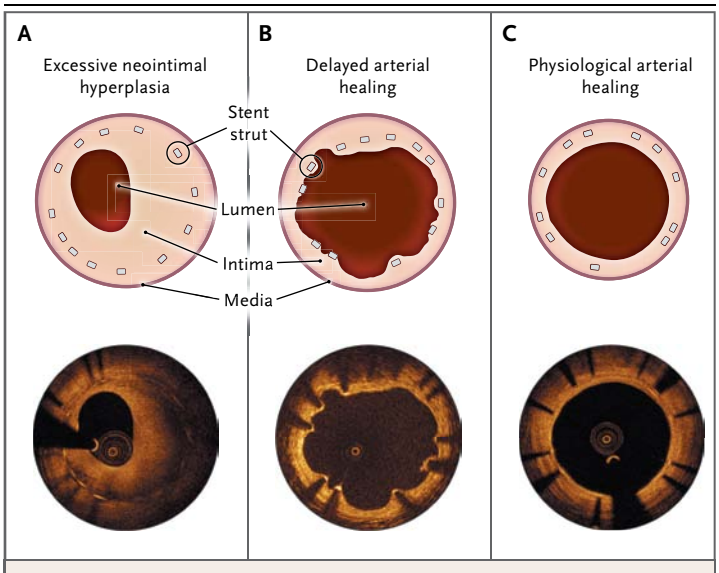


Figure 2. Patterns of Healing after Implantation of a Coronary-Artery Stent.
The implantation of a coronary-artery stent can trigger three possible arterial healing patterns, as shown in the schematic representations, with corresponding in vivo examples of images from intracoronary optical coherence tomography. Panel A shows excessive neointimal hyperplasia resulting in restenosis, observed in a patient 7 months after the implantation of a bare-metal stent. Panel B shows delayed arterial healing with vessel remodeling and protruding stent struts, observed in a patient 22 months after the implantation of a sirolimus-eluting stent. Panel C shows physiological arterial healing, observed in a patient 18 months after the implantation of a biolimus-eluting stent with a biodegradable polymer coating.

without compromising effectiveness, as compared with paclitaxel-eluting stents.[36,37] A network meta-analysis showed a lower risk of myocardial infarction with Endeavor zotarolimus-eluting stents, as compared with paclitaxel-eluting stents, over the long term (relative risk, 0.66; 95% CI, 0.53 to 0.86) and a similar risk of target-lesion revascularization (relative risk, 1.14; 95% CI, 0.88 to 1.49).[35]

In the Patient-Related Outcomes with Endeavor versus Cypher Stenting Trial (PROTECT), involving 8791 patients, investigators comparing Endeavor zotarolimus-eluting stents with sirolimus-eluting stents observed no difference in the primary end point of definite or probable stent thrombosis at 3 years.[38] Similarly, the risk of death or myocardial infarction was similar with the two types of drug-eluting stents. Analyses of secondary outcomes showed a higher risk of repeat revascularization among patients treated with Endeavor zotarolimus-eluting stents than among those treated with sirolimus-eluting stents (5.6% vs. 3.5%, P<0.001), whereas patients treated with sirolimus-eluting stents had a higher risk of very late stent thrombosis (0.3% vs. 1.1%, P<0.001).[38] These findings are consistent with previous randomized evidence.[35]

The Resolute zotarolimus-eluting stent was compared with the everolimus-eluting stent in two large-scale trials, which showed similar risks of cardiac death, myocardial infarction, repeat revascularization, and stent thrombosis throughout a 2-year period.[39,40] Table 2 summarizes evidence from randomized trials of new-generation everolimus-eluting and zotarolimus-eluting stents.[30-42]

INDICATIONS FOR USE OF DRUG-ELUTING STENTS

Advantages and disadvantages of drug-eluting stents, bare-metal stents, and coronary-artery bypass surgery in various disorders are summarized in Table 3.

STABLE CORONARY ARTERY DISEASE

Drug-eluting stents appear to be effective and relatively safe in patients with stable coronary artery disease. The recent Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME-2) trial compared revascularization with the use of drug-eluting stents followed by optimal medical therapy with medical therapy alone in patients with stable coronary artery disease and evidence of ischemia, as assessed by fractional flow reserve. The trial was stopped early by the data and safety monitoring board because of a markedly reduced need for urgent revascularization in patients treated with drug-eluting stents, as compared with those who received optimal medical therapy alone (1.6% vs. 11.1%, P<0.001).[43] The risk of death or myocardial infarction did not differ significantly between groups. It is noteworthy that 50% of urgent revascularizations were triggered by myocardial infarction or unstable angina. According to the 2011 guidelines of the American College of Cardiology–American Heart Association for percutaneous coronary interventions, use of drug-eluting stents has a class IA recommendation for patients undergoing elective percutaneous revascularization who are able to adhere to a prolonged regimen of dual antiplatelet therapy.[44]

ACUTE MYOCARDIAL INFARCTION

Mechanical reperfusion with stent implantation represents the standard of care for patients with

Table 2. Summary of Evidence from Randomized Trials of the Efficacy and Safety of New-Generation Drug-Eluting Stents, as Compared with Other Types of Stents, According to Clinical Outcome.*

New-Generation Drug-Eluting Stent and Clinical Outcome	As Compared with Bare-Metal Stents	As Compared with Early-Generation Drug-Eluting Stents		As Compared with Other Stents
		Paclitaxel-Eluting Stents	Sirolimus-Eluting Stents	
Cardiac death and myocardial infarction				
Everolimus-eluting stent	Has a similar risk[32,41]	Reduces the risk of myocardial infarction by 30–40%[30,31]	Has a similar risk[32-34]	Has a risk similar to that of Resolute zotarolimus-eluting stent[39,40]
Zotarolimus-eluting stent				
Endeavor	Has a similar risk[35]	Might reduce the risk of myocardial infarction by 30–40%[35-37]	Has a similar risk[35,37,38]	NA
Resolute	No direct comparison available	No direct comparison available	No direct comparison available	Has a risk similar to that of everolimus-eluting stent[39,40]
Repeat revascularization				
Everolimus-eluting stent	Reduces the risk by 60–80%[32,41]	Reduces the risk by 40–50%[30,31]	Has a similar risk[32-34]	Has a risk similar to that of Resolute zotarolimus-eluting stent[39,40]
Zotarolimus-eluting stent				
Endeavor	Reduces the risk by 40–60%[35]	Has a similar risk[35-37]	Increases the risk by 30–50%[35,37,38]	NA
Resolute	No direct comparison available	No direct comparison available	No direct comparison available	Has a risk similar to that of everolimus-eluting stent[39,40]
Stent thrombosis				
Everolimus-eluting stent	Might reduce the risk by 50–60%[35,41,42]	Reduces the risk by 60–70%[32,33]	Might reduce the risk by 50–60%[33,35,42]	Has a risk similar to that of Resolute zotarolimus-eluting stent[39,40]
Zotarolimus-eluting stent				
Endeavor	Has a similar risk[35,42]	Might reduce the risk by 30–40%[35-37]	Might reduce the risk by 20–30%[35,38]	NA
Resolute	No direct comparison available	No direct comparison available	No direct comparison available	Has a risk similar to that of everolimus-eluting stent[39,40]

* For each clinical indication, comparisons are shown between the listed new-generation stent and other types of stents, as specified in the column headings. In cases in which it is stated that a certain type of stent reduces a risk, available data from randomized clinical trials have consistently shown a significant risk reduction. In cases in which it is stated that a certain type of stent might reduce a risk, meta-analyses of available randomized trials have shown a risk reduction, although such a reduction was not observed in individual randomized trials. NA denotes no additional comparisons available.

Table 3. Efficacy and Safety of Drug-Eluting Stents, Bare-Metal Stents, and Coronary-Artery Bypass Grafting (CABG), According to Clinical Indication.*

Outcome and Intervention	Stable Coronary Artery Disease	Acute Myocardial Infarction	Diabetes	Multivessel Disease	Left Main Coronary Artery Disease
Restenosis					
Implantation of bare-metal stent	+	+	+	+	+
Implantation of drug-eluting stent					
Early-generation	++	++	++	++	++
New-generation	+++	+++	++	++ [+]	++ [+]
CABG	+++	–	+++	+++	+++
Cardiac death, myocardial infarction, or stent thrombosis					
Implantation of bare-metal stent	+	+	+	+	+
Implantation of drug-eluting stent					
Early-generation	+	+/–	+	+	+
New-generation	+ [+]	+ [+]	+	+ [+]	++ [+]
CABG	+	–	++	++	++

* Data are based on available findings from randomized clinical trials, with the use of bare-metal stents as the reference. (Results of these trials are summarized in Table S2 in the Supplementary Appendix.) For each listed clinical indication, the recommendation for the use of each type of stent or CABG is indicated by a symbol, with a minus sign (–) indicating a disadvantage; a plus sign indicating an advantage, with the number of plus signs (+, ++, or +++) indicating the degree of advantage; and a plus sign in brackets ([+]) indicating a potential advantage that is currently being tested in randomized, controlled trials.

acute infarction. Drug-eluting stents have been compared with bare-metal stents in several trials, which have shown similar risks of death and reinfarction and a reduction in the risk of repeat revascularization. Fifteen patients (95% CI, 11 to 27) would need to be treated with drug-eluting stents in order to prevent one repeat revascularization, as compared with bare-metal stents (Table S2 in the Supplementary Appendix).[45] However, the use of sirolimus-eluting and paclitaxel-eluting stents was associated with an increased risk of very late stent thrombosis.[45] It has been speculated that the large amount of intracoronary thrombus in patients with acute infarction may predispose them to stent malapposition — because of stent undersizing or thrombus resolution — and subsequently increased thrombogenicity.[46] In addition, implantation of drug-eluting stents in ruptured plaques in patients with acute infarction has been associated with delayed arterial healing.[47]

Recently, in the Evaluation of Xience-V Stent in Acute Myocardial Infarction (EXAMINATION) trial,[41] everolimus-eluting stents were found not to be superior to bare-metal stents with respect to the composite end point of death, myocardial infarction, or any further revascularization among patients with acute infarction. However, everolimus-eluting stents reduced the risk of target-lesion revascularization as well as stent thrombosis, as compared with bare-metal stents.[41] Long-term follow-up and larger trials that are powered for assessment of ischemic events will shed more light on the use of drug-eluting stents in patients with acute infarction. In such patients, the use of drug-eluting stents has a class IA recommendation if patients are able to comply with a prolonged regimen of dual antiplatelet therapy.[44]

DIABETES

Patients with diabetes have a higher burden of atherosclerosis, smaller coronary arteries, and a higher risk of repeat revascularization after implantation of a bare-metal stent than do patients without diabetes.[48] Drug-eluting stents have been widely tested in patients with diabetes and have consistently reduced the rate of restenosis, as compared with bare-metal stents (Table S2 in the Supplementary Appendix). A network meta-analysis[49] involving 3852 patients with diabetes and 10,947 patients without diabetes showed that drug-eluting stents were as safe as bare-metal stents in patients with diabetes when dual antiplatelet therapy was prescribed for 6 months or more. In

addition, the reduction in the risk of repeat revascularization with the use of drug-eluting stents in patients with diabetes was similar to the risk reduction in patients without diabetes. According to current guidelines, diabetes is a condition in which the use of drug-eluting stents is preferable to the use of bare-metal stents.[44] The selection of a specific type of drug-eluting stent in patients with diabetes is controversial.[49-51]

MULTIVESSEL DISEASE

Patients with complex multivessel coronary artery disease represent a high-risk subgroup. Angioplasty and implantation of bare-metal stents have been compared with bypass surgery in numerous randomized studies, as summarized in a systematic review that included 22 trials and in a pooled analysis involving 7812 patients from 10 trials.[52,53] Both analyses led to the conclusion that percutaneous and surgical revascularization strategies have similar outcomes with respect to rates of death and myocardial infarction. However, recurrent angina and repeat revascularization were more common among patients treated percutaneously, whereas stroke was more frequent among patients treated surgically.[52,53]

Three randomized trials have compared drug-eluting stents with bypass surgery in patients with multivessel disease: the Coronary Artery Revascularization in Diabetes (CARDia) study,[54] the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial,[55] and the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) study[56] (Table S2 in the Supplementary Appendix). In the CARDia trial, the use of percutaneous coronary intervention (with drug-eluting stents used in 69% of procedures) was not shown to be noninferior to bypass surgery in patients with multivessel disease and diabetes, with respect to the composite end point of death, myocardial infarction, or stroke for a period of up to 5 years.[54] The larger FREEDOM trial showed that revascularization with drug-eluting stents (predominantly stents releasing sirolimus or paclitaxel) was inferior to bypass surgery in patients with multivessel disease and diabetes, with respect to the composite end point of death, myocardial infarction, or stroke. Bypass surgery was associated with significantly reduced risks of death and myocardial infarction but a higher risk of stroke during the 5-year study.

In the SYNTAX trial, the use of paclitaxel-eluting stents was not shown to be noninferior to bypass surgery with respect to the composite end point of death, myocardial infarction, stroke, or repeat revascularization at 1 year in patients with multivessel and left main coronary artery disease.[56] The rate of the primary end point at 1 year was higher among patients treated with paclitaxel-eluting stents than among those treated with bypass surgery, mainly because of higher rates of repeat revascularization in the stent group. Conversely, stroke was more frequent among patients treated with bypass surgery. Five years of follow-up suggested that the rate of the primary end point continued to be higher among patients treated with paclitaxel-eluting stents than among those treated with bypass surgery (37.3% vs. 26.9%, P<0.001).[57] Patients were stratified into three groups on the basis of the complexity of disease as seen on angiography according to a prespecified algorithm that assigned a SYNTAX score, ranging from 0 to 84, with higher scores indicating a greater complexity of disease. At 5 years, the rate of the primary end point in the stent group was similar to that in the surgery group among patients with a low complexity of disease (SYNTAX score, ≤22; 32.1% and 28.6%, respectively; P=0.43), whereas the benefit of bypass surgery emerged among patients with either intermediate disease complexity (SYNTAX score, 23 to 32; 36.0% vs. 25.8%; P=0.008) or high disease complexity (SYNTAX score, ≥33; 44.0% vs. 26.8%; P<0.001).[57] These findings are hypothesis generating, and whether outcomes may be improved with the use of new-generation drug-eluting stents is a matter of debate. However, bypass surgery remains the treatment of choice for patients with the most extensive, complex multivessel disease.[44] A discussion by a multidisciplinary heart team composed of an interventionalist and a surgeon is recommended for such patients (class IC).[44]

LEFT MAIN CORONARY ARTERY DISEASE

In the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial, sirolimus-eluting stents were shown to be noninferior to bypass surgery in patients with left main coronary artery disease with respect to the composite end point of death, myocardial infarction, stroke, or target-vessel revascularization at 1 year (Table

S2 in the Supplementary Appendix).[58] However, the trial was small and had a wide noninferiority margin, which precluded definitive conclusions. In the SYNTAX trial, randomization was stratified according to the presence or absence of left main coronary artery disease. Among 705 patients with left main coronary artery disease, the risk of the primary end point, as well as the risk of cardiac death or myocardial infarction, at 3 years in the group that received paclitaxel-eluting stents was similar to the risk in the group that underwent bypass surgery.[59] Stroke occurred more frequently among patients treated with bypass surgery, whereas repeat revascularization occurred more frequently among patients treated with paclitaxel-eluting stents. Everolimus-eluting stents are being compared with bypass surgery in the Evaluation of Xience Everolimus-Eluting Stent System versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial (ClinicalTrials.gov number, NCT01205776) in patients with left main coronary artery disease. According to guidelines, percutaneous revascularization is a reasonable alternative to bypass surgery in selected patients with left main coronary artery disease (class IIaB).[44]

ANTIPLATELET THERAPY

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor reduces the risk of ischemic events after stent placement; however, the duration of therapy remains a matter of debate. Clopidogrel in addition to aspirin for at least 12 months has been shown to reduce the composite end point of death, myocardial infarction, or stroke, as compared with aspirin alone, among patients with acute coronary syndromes.[60] The more potent drugs prasugrel and ticagrelor have been shown to be superior to clopidogrel in patients presenting with acute coronary syndromes.[61,62] However, long-term dual antiplatelet therapy significantly increases the risk of bleeding.[60-62] Moreover, only a few patients included in these trials were treated with drug-eluting stents, and data providing guidance on the duration of therapy in patients undergoing elective coronary stenting are sparse. Current guidelines support a 12-month regimen of dual antiplatelet therapy in patients treated with drug-eluting stents (class IB)[44] on the basis of observational data pointing to the risk of stent thrombosis after premature discontinuation of clopidogrel.[10] A combined analysis of data from two trials, the Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation — Late Coronary Arterial Thrombotic Events (REAL-LATE) study and the Evaluation of the Long-Term Safety after Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions — Late Coronary Arterial Thrombotic Events (ZEST-LATE) trial, suggests that a prolongation of dual antiplatelet therapy beyond 12 months after implantation of drug-eluting stents does not reduce the risk of death or myocardial infarction, as compared with the use of aspirin alone.[63] In the Prolonging Dual Antiplatelet Treatment after Grading Stent-Induced Intimal Hyperplasia (PRODIGY) trial, among patients who were treated with 6 months of dual antiplatelet therapy, the risk of the composite end point of death, myocardial infarction, or stroke was similar to that among patients receiving 24 months of therapy, but those receiving 6 months of therapy had a markedly reduced risk of bleeding.[64] Moreover, a few observational studies have suggested that early discontinuation of dual antiplatelet therapy might be safe after the implantation of stents releasing either zotarolimus or everolimus.[65,66] Overall, the available evidence is inconclusive, and large-scale comparisons of different durations of dual antiplatelet therapy are ongoing (NCT00977938, NCT00661206, and NCT00822536).

The antiplatelet-therapy regimen after implantation of drug-eluting stents in patients taking oral anticoagulants is also debated because of the increased risk of bleeding in such patients. In the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) trial,[67] patients who received only clopidogrel in addition to oral anticoagulants had a reduced risk of bleeding at 1 year, as compared with those receiving triple therapy with aspirin, clopidogrel, and oral anticoagulants, and the study suggested that the less intensive therapy might provide adequate protection against thrombotic complications. However, larger studies are needed for definite conclusions.

COST-EFFECTIVENESS

A reduction in the rate of restenosis with the use of drug-eluting stents comes at the expense of increased device cost, as compared with bare-metal stents. Several studies have recommended

restricting the use of drug-eluting stents to patients at increased risk for restenosis in order to balance the risk–benefit assessment with cost-effectiveness.[68,69] Reducing the use of drug-eluting stents among patients at low risk for restenosis may result in cost savings with a small effect on the rate of repeat revascularization.[69,70] However, reimbursement systems vary widely, rendering cost-effectiveness analyses rarely applicable to different health care systems. In the United States, a reduction in the use of drug-eluting stents in 2007, as compared with a more liberal use of such stents in the period from 2004 through 2006 (in 68% and 92% of procedures, respectively), was associated with a small increase in the risk of repeat revascularization (4.1 to 5.1%) and a modest reduction in costs ($400 per patient) over a period of 1 year.[70] Nevertheless, a recent analysis of stent use in routine clinical practice in the United States showed that the higher cost of drug-eluting stents, as compared with bare-metal stents, was offset by lower costs of repeat revascularization procedures over a period of 3 years.[71] Whether drug-eluting stents should be used with or without restriction remains a subject of debate, particularly in light of uncertainty regarding the optimal duration of dual antiplatelet therapy, which has a substantial effect on health care costs.[71] Moreover, a reduction in costs with the use of everolimus-eluting stents, as compared with paclitaxel-eluting stents, has recently been documented.[72]

OPEN ISSUES AND FUTURE DIRECTIONS

SAFETY OF NEW DRUG-ELUTING STENTS VERSUS BARE-METAL STENTS

Network meta-analyses of randomized studies indicate a lower risk of stent thrombosis with everolimus-eluting stents than with bare-metal stents.[35,42] This potential benefit needs to be addressed in appropriately designed studies. However, the feasibility and cost-effectiveness of such trials is questionable owing to the exceedingly low incidence of stent thrombosis.

BIODEGRADABLE POLYMER STENTS

The use of drug-eluting stents that have been coated with biodegradable polymers, which are commonly used in clinical practice outside the United States, has been shown to improve long-term safety and efficacy, as compared with the use of sirolimus-eluting stents.[19,73] In two recent trials, drug-eluting stents with biodegradable-polymer coatings improved safety, as compared with bare-metal stents, in patients with acute infarction,[74] and provided outcomes similar to those with everolimus-eluting stents in patients with coronary artery disease at 1 year.[75] Additional studies and longer-term follow-up are needed to address possible differences between these two technologies.

FULLY BIORESORBABLE SCAFFOLDS

Fully bioresorbable drug-eluting vascular scaffolds will soon be available for clinical use.[76] Although the concept is attractive, it remains to be determined whether these devices can outperform available drug-eluting stents with respect to safety and efficacy.

CONCLUSIONS

Drug-eluting stents mitigate the risk of restenosis and thus represent an important advance in the percutaneous treatment of coronary artery disease. New drug-eluting stents with thin struts releasing limus-family analogues from durable polymers have further improved clinical outcomes, as compared with early-generation stents releasing sirolimus or paclitaxel. The risk of stent thrombosis has become exceedingly low and no longer represents a limitation of the use of drug-eluting stents. Notably, the improved safety profile of new drug-eluting stents comes without compromising their effectiveness. Available evidence supports the use of drug-eluting stents in most clinical settings without safety concerns, unless patients have contraindications to the use of dual antiplatelet therapy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. N Engl J Med 2012;366:54-63. [Erratum, N Engl J Med 2012;366:970.]
2. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316:701-6.
3. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489-95.
4. Serruys PW, Unger F, Sousa JE, et al.

Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001; 344:1117-24.
5. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.
6. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221-31.
7. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370: 937-48.
8. Lagerqvist B, James SK, Stenestrand U, Lindbäck J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356:1009-19.
9. Daemen J, Wenaweser P, Tsuchida K, et al. 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;369:667-78.
10. Grines CL, Bonow RO, Casey DE Jr, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. J Am Coll Cardiol 2007;49:734-9.
11. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998-1008.
12. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989-97.
13. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030-9.
14. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020-9.
15. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics — 2012 update: a report from the American Heart Association. Circulation 2012; 125(1):e2-e220. [Erratum, Circulation 2012;125(22):e1002.]
16. Kastrati A, Mehilli J, Dirschinger J, et al. Intracoronary Stenting and Angiographic Results: Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO) trial. Circulation 2001;103:2816-21.
17. Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation 2011;123:1400-9.
18. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation 1996; 94:1690-7.
19. Stefanini GG, Kalesan B, Serruys PW, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. Lancet 2011;378:1940-8.
20. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193-202.
21. Räber L, Baumgartner S, Garcia HM, et al. Long-term vascular healing in response to sirolimus- and paclitaxel-eluting stents: an optical coherence tomography study. JACC Cardiovasc Interv 2012; 5:946-57.
22. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol 2011;57:1314-22.
23. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333-42.
24. Kim JS, Kim BK, Jang IK, et al. ComparisOn of neointimal coVerage betwEen zotaRolimus-eluting stent and everolimus-eluting stent using Optical Coherence Tomography (COVER OCT). Am Heart J 2012;163:601-7.
25. Holmes DR Jr, Kereiakes DJ, Garg S, et al. Stent thrombosis. J Am Coll Cardiol 2010;56:1357-65.
26. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
27. Räber L, Magro M, Stefanini GG, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation 2012;125:1110-21.
28. Stone GW, Ellis SG, Colombo A, et al. Offsetting impact of thrombosis and restenosis on the occurrence of death and myocardial infarction after paclitaxel-eluting and bare metal stent implantation. Circulation 2007;115:2842-7.
29. Doyle B, Rihal CS, O'Sullivan CJ, et al. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. Circulation 2007;116:2391-8.
30. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201-9.
31. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663-74.
32. Kaiser C, Galatius S, Erne P, et al. Drug-eluting versus bare-metal stents in large coronary arteries. N Engl J Med 2010; 363:2310-9.
33. Jensen LO, Thayssen P, Hansen HS, et al. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation 2012;125:1246-55.
34. Kimura T, Morimoto T, Natsuaki M, et al. Comparison of everolimus-eluting and sirolimus-eluting coronary stents: 1-year outcomes from the Randomized Evaluation of Sirolimus-Eluting versus Everolimus-Eluting Stent Trial (RESET). Circulation 2012;126:1225-36.
35. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;125:2873-91.
36. Leon MB, Nikolsky E, Cutlip DE, et al. Improved late clinical safety with zotarolimus-eluting stents compared with paclitaxel-eluting stents in patients with de novo coronary lesions: 3-year follow-up from the ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) trial. JACC Cardiovasc Interv 2010;3:1043-50.
37. Park DW, Kim YH, Yun SC, et al. Comparison of zotarolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for coronary revascularization: the ZEST (comparison of the efficacy and safety of zotarolimus-eluting stent with sirolimus-eluting and paclitaxel-eluting stent for coronary lesions) randomized trial. J Am Coll Cardiol 2010;56:1187-95.
38. Camenzind EW, Wijns W, Mauri L, et al. Stent thrombosis and major clinical events at 3 years after zotarolimus-eluting or sirolimus-eluting coronary stent implantation: a randomised, multicentre, open-label, controlled trial. Lancet 2012; 380:1396-405.
39. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136-46.
40. von Birgelen C, Basalus MW, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol 2012;59:1350-61.
41. Sabate M, Cequier A, Iñiguez A, et al. Everolimus-eluting stent versus bare-met-

al stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. Lancet 2012;380:1482-90.
42. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393-402.
43. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve–guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991-1001.
44. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58(24):e44-e122.
45. Kalesan B, Pilgrim T, Heinimann K, et al. Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction. Eur Heart J 2012;33:977-87.
46. Guo N, Maehara A, Mintz GS, et al. Incidence, mechanisms, predictors, and clinical impact of acute and late stent malapposition after primary intervention in patients with acute myocardial infarction: an intravascular ultrasound substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. Circulation 2010;122:1077-84.
47. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138-45.
48. Berry C, Tardif JC, Bourassa MG. Coronary heart disease in patients with diabetes: part II: recent advances in coronary revascularization. J Am Coll Cardiol 2007;49:643-56.
49. Stettler C, Allemann S, Wandel S, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. BMJ 2008;337:a1331.
50. Stone GW, Kedhi E, Kereiakes DJ, et al. Differential clinical responses to everolimus-eluting and paclitaxel-eluting coronary stents in patients with and without diabetes mellitus. Circulation 2011;124:893-900.
51. Bangalore S, Kumar S, Fusaro M, et al. Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. BMJ 2012;345:e5170.
52. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007;147:703-16.
53. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190-7.
54. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 2010;55:432-40.
55. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375-84.
56. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
57. Mohr F. Final five-year follow-up of the SYNTAX Trial. Presented at the European Society of Cardiology (ESC) Congress, Munich, Germany, August 25–29, 2012.
58. Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med 2011;364:1718-27.
59. Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;32:2125-34.
60. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502. [Errata, N Engl J Med 2001;345:1506, 1716.]
61. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
62. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
63. Park S-J, Park D-W, Kim Y-H, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med 2010;362:1374-82.
64. Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012;125:2015-26.
65. Kandzari DE, Barker CS, Leon MB, et al. Dual antiplatelet therapy duration and clinical outcomes following treatment with zotarolimus-eluting stents. JACC Cardiovasc Interv 2011;4:1119-28.
66. Kedhi E, Stone GW, Kereiakes DJ, et al. Stent thrombosis: insights on outcomes, predictors and impact of dual antiplatelet therapy interruption from the SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE trials. EuroIntervention 2012;8:599-606.
67. Dewilde W. WOEST: first randomised trial that compares two different regimens with and without aspirin in patients on oral anticoagulant therapy (OAC) undergoing coronary stent placement (PCI). Presented at the European Society of Cardiology (ESC) Congress, Munich, Germany, August 25–29, 2012.
68. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med 2007;357:1393-402.
69. Amin AP, Spertus JA, Cohen DJ, et al. Use of drug-eluting stents as a function of predicted benefit: clinical and economic implications of current practice. Arch Intern Med 2012;172:1145-52.
70. Venkitachalam L, Lei Y, Stolker JM, et al. Clinical and economic outcomes of liberal versus selective drug-eluting stent use: insights from temporal analysis of the multicenter Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry. Circulation 2011;124:1028-37.
71. Schafer PE, Sacrinty MT, Cohen DJ, et al. Cost-effectiveness of drug-eluting stents versus bare metal stents in clinical practice. Circ Cardiovasc Qual Outcomes 2011;4:408-15.
72. Amin AP, Reynolds MR, Lei Y, et al. Cost-effectiveness of everolimus- versus paclitaxel-eluting stents for patients undergoing percutaneous coronary revascularization (from the SPIRIT-IV Trial). Am J Cardiol 2012;110:765-70.
73. Stefanini GG, Byrne RA, Serruys PW, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J 2012;33:1214-22.
74. Räber L, Kelbaek H, Ostoijc M, et al. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. JAMA 2012;308:777-87.
75. Smits PC. COMPARE II trial: a large scale, multicenter, prospective randomized comparison between the durable polymer everolimus-eluting stent and the abluminal biodegradable polymer biolimus-eluting stent in a real life setting. Presented at the European Society of Cardiology (ESC) Congress, Munich, Germany, August 25–29, 2012.
76. Serruys PW, Onuma Y, Dudek D, et al. Evaluation of the second generation of a bioresorbable everolimus-eluting vascular scaffold for the treatment of de novo coronary artery stenosis: 12-month clinical and imaging outcomes. J Am Coll Cardiol 2011;58:1578-88.