spotlight expert roundtable »

Drug-Eluting Versus Bare-Metal Stents

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Moderated by **Gregg W. Stone, MD[1]**
Discussants: **Antonio Colombo, MD[2]; Dean Kereiakes, MD[3]; Ajay J. Kirtane, MD, SM[4]**

The following Expert Roundtable Discussion was held on September 11, 2012.

The discussion focused primarily on: (1) Advantages, disadvantages, and nuances of drug-eluting and bare-metal stents; (2) pathophysiology and clinical manifestations of coronary restenosis; (3) evolution from first-generation, drug-eluting stents to current generation devices; (4) current dual antiplatelet therapy (DAPT) recommendations (especially with regard to DAPT duration); (5) the appropriateness of drug-eluting vs bare-metal stents for particular patients; and (6) the future of stent technology. (*Med Roundtable Cardiovasc Ed*. 2014;3(4):208–217)

STUDIES DISCUSSED:
FAME study, ISCHEMIA trial, FAME II, COURAGE trial, OAT, PROTECT, large-scale DAPT trial, RESET trial, PRODIGY, EXCELLENT trial, ISAR-SAFE, HORIZONS-AMI trial, SYNTAX trial, FREEDOM trial

COMPOUNDS DISCUSSED:
dual antiplatelet therapy (DAPT; a combination of aspirin and an adenosine diphosphate receptor inhibitor)

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DR. STONE: Welcome to this roundtable discussion. Today, we'll be focusing on some of the advantages, disadvantages, and nuances of drug-eluting and bare-metal stents in the practice of interventional cardiology. My name is Gregg W. Stone; I'm an interventional cardiologist and Professor of Medicine at Columbia University Medical Center and the Cardiovascular Research Foundation in New York City. I'm very pleased to have a distinguished panel who will be leading us through this discussion; I'd like my colleagues to introduce themselves.

DR. COLOMBO: I'm Antonio Colombo, interventional cardiologist and Director of Interventions at San Raffaele Scientific Institute and Columbus Hospital in Milan, Italy.

DR. KEREIAKES: I'm Dean Kereiakes, an interventional cardiologist and Medical Director of The Christ Hospital Heart and Vascular Center and the Lindner Clinical Research Center at The Christ Hospital in Cincinnati, Ohio, and Clinical Professor of Medicine at Ohio State University.

DR. KIRTANE: I'm Ajay J. Kirtane, an interventional cardiologist and Chief Academic Officer of the Center for Interventional Vascular Therapy at Columbia University Medical Center/New York-Presbyterian Hospital in New York City, and I am also affiliated with the Cardiovascular Research Foundation.

DR. STONE: When I look back and think about the field of interventional cardiology, specifically percutaneous coronary intervention, I realize that we always describe its evolution in terms of 3 transformative or revolutionary phases. First, of course, was the introduction of balloon angioplasty by Andreas Gruentzig in 1977, followed by the bare-metal stent period beginning in the mid-1990s, and the current drug-eluting stent era (since 2003 in the US). Bare-metal stents were introduced to overcome some of the limitations of balloon angioplasty, specifically acute coronary occlusion that would occur during and shortly after the interventional procedure as well as late recoil and restenosis. Drug-eluting stents were then introduced principally to overcome the problem of late restenosis that was still occurring at an excessively high rate with bare-metal stents.

Today, stents (both drug-eluting and bare-metal) are the dominant revascularization modality for the treatment of most patients with obstructive coronary artery disease.

Drug-eluting stents are used in the majority of patients in most geographies, although bare-metal stents are still widely utilized in certain institutions in certain countries and for certain specific types of patients and indications, which we will be discussing today.

The principal reason why stents are so dominant (compared to balloon angioplasty) is that they prevent acute occlusion. However, today, we're going to focus mainly on restenosis. So, I would like to ask my panelists—I will start with Dr. Kirtane—to describe the pathophysiology and clinical manifestations of coronary restenosis.

DR. KIRTANE: When you put a foreign body such as a stent into the bloodstream, there's a normal response that involves not only healing but also a pathologic response. Smooth muscle cells undergo hyperplasia, which causes neointima formation within the stented area itself.

If the neointimal proliferation is severe, that essentially causes constriction of the lumen, which can then lead to an obstruction of flow beyond a certain point. If the growth of the tissue is such that it decreases flow, then patients can present with either angina in a stable form or even acute coronary syndromes if the neointimal proliferation becomes even more occlusive.

DR. STONE: Dr. Kereiakes, how common is restenosis with bare-metal stents? Here, we have to differentiate clinical from angiographic restenosis because not all patients with anatomic narrowing within the stent become symptomatic.

DR. KEREIAKES: Following bare-metal stent deployment, the development of restenosis is dependent on the substrate being treated. The major determinants are postprocedure minimum lumen diameter, which is the platform upon which restenosis occurs, and stent length. An additional important factor that shifts the curve for restenosis is the presence of diabetes. Diabetic patients have a more exuberant, more aggressive restenotic process. The incidence of clinical restenosis is about half that of angiographic restenosis, and following bare-metal stenting, it is not uncommon to see angiographic restenosis rates of 30% to 40% and clinical restenosis rates that are roughly half of that.

DR. STONE: The ability to differentiate complex from noncomplex anatomy is essential if we want to stratify the likelihood of restenosis, which is also modulated by increases in smooth muscle cell hyperplasia and extracellular matrix production that occur in diabetic patients. Therefore, to summarize, in the bare-metal stent era, restenosis rates varied anywhere from 10% to 50% depending on whether treatment was restricted to simple short lesions in large vessels (mostly seen in nondiabetic patients) or very complex lesions in diffusely diseased small vessels (often seen in diabetic patients). Dr. Colombo and all of us on this panel routinely treat these complex lesions at our referral centers. Typically, when using bare-metal stents in these complex cases, the initial result would be good; however, we would frequently be plagued by restenosis, for example, after opening up long chronic total occlusions or treating complex bifurcations, 4 to 6 lesions, small vessels, diffuse disease, etc.

> ***"We've reduced restenosis from as high as 50% or greater after balloon angioplasty down to approximately 10% or so after implantation of the best drug-eluting stents."***
>
> *~Gregg W. Stone, MD*

So Dr. Colombo, if drug-eluting stents reduce restenosis by approximately 50% to 60%, which is what most of the larger studies have shown, do all patients benefit from drug-eluting stents or bare-metal stents in terms of reduction in restenosis? Alternatively, should drug-eluting stents be reserved only for complex patients and lesions and bare-metal stents be reserved for short lesions in large vessels or perhaps thrombotic lesions?

DR. COLOMBO: The answer is yes and no. In general, I would say yes: all patients benefit from a drug-eluting stent in terms of reduction of restenosis. The difference is the number needed to treat. If you are dealing with high-risk subgroups, the benefit is more relevant and the number needed to treat is low. In vessels smaller than 3.5 mm, the benefit is clear. If you compare bare-metal stents placed on a short lesion in a vessel that is 3.5 mm or larger, the benefit is more limited. The difference is smaller, and that's why some centers reserve drug-eluting stent implantation for so-called "higher risk" lesions where the number needed to treat is relatively small.

DR. STONE: To summarize, a 50% or 60% reduction in restenosis is realized in essentially all patients and lesions; however, if your baseline clinical restenosis rate with bare-metal stents is 5%, then you're only going to see an advantage in 1 or 2 of 100 patients (1% to 2%), whereas if your baseline clinical restenosis rate is 20%, you would see a clinical benefit in more than 1 of 10 patients (~10%).

So, Dr. Kirtane, how do we factor the cost into clinical decision making? Some people believe that, as a society, we should primarily be making therapeutic decisions on a population basis. In this regard, there have been

papers describing theoretical models suggesting that if we treat only those patients who are at high risk for restenosis with drug-eluting stents, we could preserve substantial resources and not lose that much clinically in terms of greater rates of adverse outcomes. So, in addition to addressing your perspectives on the needs of the individual patient vs society, please also describe just how meaningful the clinical benefits of preventing angiographic restenosis are to the patient. Is this a major factor that substantially affects quality of life, freedom from angina, freedom from medication use, and freedom from subsequent revascularization procedures, or is this really a fairly minor endpoint?

DR. KIRTANE: Not all patients will experience angiographic restenosis. Only a certain proportion of patients who have angiographic restenosis actually have clinical restenosis. If a patient has clinical restenosis, it usually results in another procedure—either a repeat angioplasty and stent procedure or, in some cases, bypass surgery. These things are clearly relevant to patients. You would want to avoid having these additional procedures, if possible. I think that brings us, ultimately, to the issue of making decisions with the individual patient in mind, because some of the modeling that you talked about occurs on the population level. These models are important in a cost-constrained environment; however, when you're looking at an individual patient, it is very difficult for a clinician to predict whether that patient is going to experience restenosis. So, if there is a way to avoid restenosis, or at least mitigate how frequently it occurs, and there's no disadvantage to using the drug-eluting stent, as a provider, you would always try to pick the more efficacious therapy for your patient. However, I'm curious to hear what the other panelists have to say about that.

DR. STONE: Dr. Kereiakes, you stated earlier that approximately 50% of patients with angiographic restenosis develop "clinical" restenosis. However, we tend to measure clinical restenosis in terms of the rate of ischemia-driven repeat revascularization procedures: either another percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery. This occurs 1 or more times in 50% of patients with angiographic restenosis. However, we haven't done a good job of characterizing what portion of the other 50% have actually developed recurrent angina or are limiting their lifestyle because of exertional dyspnea or other manifestations of ischemia. So, how essential are nonobstructive coronary arteries for quality of life, and conversely, how critical is the development of restenosis for quality of life impairment?

"Provided that we currently use only second- or, maybe in Europe, third-generation drug-eluting stents, I would prescribe a minimum of 6 months of DAPT, and I don't make a strong effort to prolong DAPT over 6 months."

~Antonio Colombo, MD

DR. KEREIAKES: I think you're touching upon an important topic now. The topic is not revascularization to improve survival or symptoms, but revascularization to improve ischemia and the use of ischemia guidance in revascularization. I don't think there's a more important topic right now, and whether it involves ischemia guidance with myocardial perfusion single-photon emission computed tomography as in the recent ASAN multivessel registry, which showed improved outcomes in patients who underwent multivessel revascularization following PCI compared to coronary artery bypass graft surgery, or the use of fractional flow reserve, as described in the Fractional Flow Reserve vs Angiography for Multivessel Evaluation (FAME) study,[1] where in-lab ischemia guidance using fractional flow reserve maximized the benefit relative to the risk of PCI revascularization. So, the more I think about criteria for coronary revascularization, the more I'm driven to allow the presence and magnitude of ischemia to dictate therapeutic strategy in my practice.

DR. STONE: Before we make a choice between drug-eluting and bare-metal stents, we should examine why we are performing PCI (or any revascularization procedure). Revascularization with stents improves survival and prevents myocardial infarction (MI) in patients with ST-segment elevation MI (STEMI) and most patients with non-STEMI. However, in patients with stable coronary artery disease, most studies suggest that revascularization (for most patients at least) does not prolong life or prevent future MIs. If this is true, then the rationale for PCI would be to improve quality of life, decrease the occurrence of angina, decrease the requirement for antianginal medications, and decrease the need for hospitalization for subsequent revascularization procedures.

On the other hand, emerging data suggest that PCI may prevent death and/or MI in some patients. Specifically, a strong relationship between ischemia and subsequent rates of death and MI have been reported in numerous studies, leading to the hypothesis that reducing ischemia by revascularization will prolong life and reduce MI rates. This is currently being tested in the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial (unpublished). Dr. Colombo,

acknowledging the fact that all 4 of us are interventional cardiologists, when you are treating somebody with severe double vessel or triple vessel disease including high-grade stenosis in the proximal left anterior descending (LAD) and/or left main coronary artery, do you believe that you are prolonging that patient's life or preventing MI (assuming it's stable coronary artery disease)? This is a difficult question without concrete data.

DR. COLOMBO: It is my opinion that it will be difficult to randomize many of the patients with high-risk lesions in studies such as Fractional Flow Reserve Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment Verses Optimal Medical Treatment (FAME II).[2] A referring cardiologist dealing with a patient, with a proximal LAD lesion with positive fractional flow reserve, will feel uncomfortable to suggest medical therapy and wait for more dramatic symptoms.

DR. STONE: You make an important point because it is very difficult to enroll adequate numbers of truly high-risk patients in clinical trials. For example, if you look at the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial,[3] you will note very low mortality rates and a low level of ischemia in most of the patients who were enrolled. Even though these patients had numerous cardiac risk factors, they were still a low risk cohort.

DR. COLOMBO: If I may interrupt, Dr. Stone. The results of those trials are important, but they don't give a complete picture of the reality. Many of the patients we just described will have difficulties entering those trials.

DR. STONE: Dr. Kereiakes, do you have complementary or differing views? Do you believe that we are reducing death and/or MI in select patients with stable coronary disease and a certain type of coronary anatomy? This is a critical question because we have to take care of these patients today without the benefit of the perfect clinical trial for every scenario.

DR. KEREIAKES: Over time, in populations, ischemia relief causes reductions in death and MI. If you look at Leslie Shaw's nuclear substudy of COURAGE,[4] there's a direct linear relationship between ischemia, even at quantitatively low levels, and death or MI over a follow-up period of 5 years. So, I really believe that a drug-eluting stent is an improvement over a bare-metal stent, as shown in both the BAsel Stent Kosten Effektivitäts Trial (BASKET) Nuclear Substudy[5] and in the Occluded Artery Trial (OAT),[6] and provides more durable relief of ischemia than do bare-metal stents or medical therapy.

DR. STONE: The antirestenotic benefits of drug-eluting stents (due to inhibition of smooth muscle cell proliferation) are concurrent with increased inhibition of endothelial cells and thus stent strut coverage. Everyone is aware of the grave concerns regarding increased rates of stent thrombosis in patients with first-generation, drug-eluting stents, especially the increased rates of very-late stent thrombosis after 1 year, leading to increased requirements for prolonged dual antiplatelet therapy (DAPT), ie, aspirin and an adenosine diphosphate receptor inhibitor. Dr. Kirtane, can you talk to us about the evolution from first-generation, drug-eluting stents to current generation devices and the risk of stent thrombosis compared to bare-metal stents.

DR. KIRTANE: I think that was the real caveat. As physicians, we will opt to treat patients with an effective therapy, provided it has no downside, and one of the limiting factors restricting the more widespread use of drug-eluting stents compared to bare-metal stents was a concern over stent thrombosis. One thing that has been clear is when you look at the randomized trial data with drug-eluting stents and bare-metal stents—and we have good follow-up of 5 years now—there appears to be no difference in the overall stent thrombosis rates over time. We can argue about definitions of stent thrombosis, but that's beyond the scope of this discussion. I think it's clear that there's no excess. The issue, though, is that there appears to be a late accrual of events, particularly with first-generation drug-eluting stents. Moving into the present with the types of stents we have currently, we see a flattening of the event curves beyond 1 year not only with durable polymer designs but also with bioabsorbable polymer designs. There are new data suggesting that there may be a stent thrombosis advantage with certain current generation platforms compared with first-generation platforms and even bare-metal stents. We don't know if extended DAPT duration makes a difference (Dr. Kereiakes and others are studying this extensively), but stent thrombosis is probably lesser of an issue than we thought in 2006.

DR. STONE: Dr. Colombo, you were the first person who clearly demonstrated that we are able to reduce both stent thrombosis and restenosis using excellent technique. Your work in this regard was initially with bare-metal stents, but the same holds true (perhaps, even more so) with drug-eluting stents. Technique and drug-eluting stent technology continue to improve over time, and stent thrombosis rates are declining. So, what is your current practice with DAPT? How long is DAPT required, and do you treat different types differently in this regard?

DR. COLOMBO: Provided that we currently use only second- or, maybe in Europe, third-generation drug-eluting

stents, I would prescribe a minimum of 6 months of DAPT, and I don't make a strong effort to prolong DAPT over 6 months. Nevertheless, I routinely prescribe DAPT for 1 year. If the patient asks me to stop DAPT after 6 months, I do not disagree. The only exceptions are in the cases of diabetics; very long stents; and unprotected left main, complex bifurcations. In these settings, I usually try to extend DAPT over 1 year. Of course, all of this is done on a personal basis. The bottom line is that 6 months is probably acceptable, and over 6 months is probably useful in some situations. Unfortunately the words "probably" and "acceptable" are used too frequently.

But let me ask you a question, Dr. Stone. Recently, I had a debate with a cardiac surgeon regarding first- and second-generation stents: the issue of stent thrombosis has been raised. There is no question that recent data show that second-generation drug-eluting stents have a lower thrombosis rate than do first-generation stents. I was surprised that the surgeon had an opposing view.

DR. STONE: Yes, that's true. In general, the major differences that we've seen between first- and second-generation, drug-eluting stents have been (1) improved deliverability and user friendliness due to thinner struts and enhanced stent and delivery system designs; (2) some reduction in restenosis; and (3) a clear reduction in stent thrombosis, especially with the durable fluoropolymer-based, everolimus-eluting stents (EES). We have not seen observable differences in death or cardiac death in any randomized or registry studies. Of course, the causes of death are multifactorial, and the frequency of stent-related cardiac death is low, so it may be hard to delineate such a difference in studies, if indeed one exists. Dr. Kirtane, would you like comment on this issue?

DR. KIRTANE: I think the hard endpoints are obviously very important, and some of these data can be used to generate a hypothesis because they are derived from studies in different eras. I think it's nice that we now have some head-to-head data from adequately powered studies. For instance, at the European Society of Cardiology (ESC) Congress, we had data from the Patient Related OuTcomes With Endeavor Versus Cypher Stenting Trial (PROTECT),[7] which aimed to examine stent thrombosis between first- and second-generation, drug-eluting stents.

DR. STONE: It is worth stating, however, that data from large network meta-analyses, such as the recently published work by Bangalore and colleagues,[8,9] suggest that there may actually be a reduction in hard endpoints such as MI with certain current-generation, drug-eluting stents. This is also consistent with the meta-analysis by Palmerini[10] showing a clear reduction in stent thrombosis. Although network meta-analyses are not definitive and don't provide the same level of evidence as a definitive, large-scale, randomized trial, accumulating evidence indicates that patient event-free survival is improving over time with improvements in our devices, drugs, and technique.

> ***"We need to look at landmark analyses in late follow-up to prove that a bioresorbable scaffold indeed provides material benefit with respect to reduction in death, MI, and repeat revascularization."***
>
> *~Dean Kereiakes, MD*

DR. STONE: Dr. Kereiakes, you are the coprincipal investigator of the large-scale DAPT trial, which is examining the benefits of 1 year vs 2.5 years of DAPT after drug-eluting stent implantation. Other trials have studied shorter-term DAPT (less than 1 year), and 3 of these have already been published—the Restoration of Chronotropic Competence in Heart Failure Patients with Normal Ejection Fraction (RESET) trial,[11] the Prolonging Dual Antiplatelet Treatment after Grading Stent-induced Intimal Hyperplasia Study (PRODIGY),[12] and the Efficacy of Xience/Promus Versus Cypher in rEducing Late Loss After stENTing (EXCELLENT) trial[13]—all of which have suggested that 3 to 6 months of clopidogrel therapy may be more acceptable than 12 months of this therapy. Additionally, most of these studies involved first-generation, drug-eluting stents; early DAPT discontinuation is more likely to be safe with second-generation, drug-eluting stents. So, what are your views on the current evidence base regarding the duration of DAPT treatment for patients with current-generation, drug-eluting stents, and what do you tell your patients?

DR. KEREIAKES: What I would say about Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events (REAL-LATE)/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), PRODIGY, and EXCELLENT, the studies you have referenced, is that (1) they're underpowered, (2) they're not blinded, and (3) they're somewhat confused by factorial design and multiple tiered randomizations. I believe that smaller trials are best when they focus on and answer a single question, rather than multiple questions.

That being said, none of those trials show a difference in ischemic endpoints—either the primary or key secondary ischemic endpoints—stratified by duration of therapy. In fact, REAL-LATE / ZEST-LATE shows a trend in the opposite direction for increased ischemic events with longer duration DAPT. However, less than 25% of the patients enrolled into this trial reached the 2-year time point for evaluation. If the trial is underpowered at 2700 patients, it is extremely underpowered at 600, which is exactly how many patients were counted at 2 years. There are also other methodological flaws in this trial, including the fact that approximately 12% of the subjects were not even randomized until 18-24 months after their PCI procedure. Recall that the hypothesis being tested was 1 vs 2 years of DAPT. In addition, TIMI major bleeding was observed in only 0.1% of subjects at 1 year and 0.2% at 2 years in stark contrast to the 0.6% at 1 year in EXCELLENT and 1.6% at 2 years in PRODIGY. This raises serious question as to the accuracy of endpoint assessment as a quality measure in REAL-LATE/ZEST-LATE.

Finally, specific subgroups of patients may derive differential benefit from longer duration DAPT. For example, in 749 consecutive diabetic patients described by Brar who were treated with either drug-eluting stents or bare-metal stents and then stratified by DAPT duration (<6 months, 6 to 9 months, and >9 months), a stepwise reduction in death or MI in follow-up was observed with longer duration DAPT therapy. Similarly, in EXCELLENT, there is a highly significant interaction observed among the diabetic cohort for a reduction in target vessel failure with longer duration (12 months) DAPT vs shorter duration (6 months).

I believe that patient substrate matters and specific subsets such as diabetics may derive differential or preferential benefit from longer duration DAPT therapy. I also think that stent platform matters. For example, the EES polyvinylidene fluoride fluoro co-polymer has a lower rate of stent thrombosis than do non-EES drug-eluting stents or bare-metal stents. In recent network meta-analyses of multiple stent randomized trials, EES have the lowest incidence of stent thrombosis over a 2-year follow-up period.

DR. STONE: We certainly need to wait for the results of the large-scale DAPT study to fully understand whether DAPT has late benefits—not only with respect to preventing stent thrombosis but also systemically for secondary prevention. There are also large trials of early DAPT discontinuation that are ongoing, such as Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE)[14] and others that are in the planning phase. Dr. Colombo's opinion was to aim for 1 year for everybody, but 6 months is acceptable. Dr. Kirtane, what do you do for your patients in terms of DAPT duration?

DR. KIRTANE: I try to screen patients for their ability to adhere to DAPT in advance, and I go through a variety of factors that might affect that decision. If we implant a bare-metal stent, I'll use DAPT for a minimum of 4 to 6 weeks. If the clinical scenario is an acute coronary syndrome, I'll extend therapy for a year. If we implant a drug-eluting stent, I'll do pretty much what Dr. Colombo said. If they can take DAPT for a year, that would be ideal, particularly if they have an acute coronary syndrome. If not, then it's 3 to 6 months, in general.

DR. STONE: It seems as if we're all pretty much on the same page: on the basis of the current evidence, 1 year should still be the goal, although 3 to 6 months might be safe with the best current technology.

In what percentage of your patients are you implanting bare-metal stents today? Additionally, in whom are you implanting these stents? For example, you may be dealing with a patient with an acute coronary syndrome or a lesion with thrombus, a noncompliant patient who you're not confident will take at least 6 months of DAPT, or a patient requiring surgery in the short term who will have to discontinue DAPT. Alternatively, do you use drug-eluting stents in 100% of patients (as reported in certain regions in Asia)?

DR. COLOMBO: I use drug-eluting stents in over 90% of stable patients; I use bare-metal stents in at least 60% of patients with STEMI and in some patients with acute coronary syndrome. I would summarize that I use drug-eluting stents in at least 80% of all patients undergoing PCI.

DR. KEREIAKES: I use drug-eluting stents in more than 90% of stable patients. I would consider putting a bare-metal stent in somebody who needs major surgery within 3 months, and if the referring cardiologist is demanding implantation of a bare-metal stent. With regard to STEMI, I differ from Dr. Colombo. I think 90% of the time I would use a drug-eluting stent because all of the multiple randomized trials and meta-analyses that have been done, with follow-up periods of up to 3 to 5 years, demonstrate a highly significant reduction in target vessel revascularization with no penalty. By that I mean there is no increase in stent thrombosis or MI with drug-eluting stents vs bare-metal stents.

DR. KIRTANE: I also use drug-eluting stents for the great majority of our patients. Our patient mix (in Washington Heights, New York) is a little different, so I'd say for electives, it's probably 70% to 80% drug-eluting stents,

but the decision-making hinges on adherence and then, as Dr. Kereiakes said, surgery. This typically only applies to upcoming surgery within the next 3 months, because I think if you can delay the surgery for 3 months, with some of the early discontinuation data, you may still be able to implant the drug-eluting stent.

DR. COLOMBO: There is no question about the benefit of drug-eluting stents in some patients with STEMI. These patients are diabetics or any patient with a lesion on a vessel smaller than 3 mm in diameter or requiring a stent longer than 15/20 mm.

DR. STONE: We actually demonstrated this in a substudy of the Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial.[15] We found that the 2-year rates of target-lesion revascularization with bare-metal stents and drug-eluting stents were similar in nondiabetic MI patients with a large reference vessel diameter and a short culprit lesion. However, the target-lesion revascularization rates with bare-metal stents were increased significantly in patients with 1 or more of these 3 risk factors, and such patients had an incrementally greater benefit with drug-eluting stents in terms of absolute reduction of target lesion revascularization. This holds true in patients with non-STEMI and stable coronary artery disease as well. So, this is a very reasonable approach for all patients, especially those with STEMI in whom target lesion revascularization rates tend to be lower because of an infarcted myocardium that is less likely to produce symptoms of angina if restenosis occurs.

Dr. Kirtane, clearly the current-generation, drug-eluting stents have improved outcomes for patients, have reduced stent thrombosis rates, may have reduced MI rates, conferred long-term freedom from ischemia, etc. Most of the trials that we're founding our clinical decisions on, such as the COURAGE trial comparing PCI to medical therapy in stable coronary artery disease and the SYNergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX)[16] and Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trials[17] comparing PCI to surgery in complex coronary disease, were performed with either bare-metal stents or first-generation, drug-eluting stents. How would the availability of the current-generation, drug-eluting stents have affected the outcomes of these trials and therefore our decision making?

"It is difficult to deal with the fact that technology advances faster than the trials can enroll patients and subsequently be published, so it seems as though we're always communicating or commenting on trials that have been performed in a different era."

~Ajay J. Kirtane, MD, SM

DR. KIRTANE: I think that's a critically important question. Particularly regarding COURAGE, SYNTAX, and even the FREEDOM trial, this is very relevant. In terms of the safety endpoints, in the SYNTAX trial with a first-generation, drug-eluting stent, there was a stent thrombosis rate of over 10% at 5 years. Similarly, the PCI-related durability of symptom relief and quality-of-life benefits were called into question in COURAGE, but the use of drug-eluting stents in COURAGE would have likely changed those findings dramatically. It is difficult to deal with the fact that technology advances faster than the trials can enroll patients and subsequently be published, so it seems as though we're always communicating or commenting on trials that have been performed in a different era. I personally think that this is important for all of us to realize, but it's more important to communicate this to noninterventionalists. As interventionalists, we all know these data because we're exposed to it every day, but for noninterventionalists, these may be novel concepts.

DR. STONE: Finally, I would like to hear some future perspectives from both Drs. Kereiakes and Colombo. Do you anticipate a fourth revolution in drug-eluting stent technology as we move from durable polymers to bioresorbable polymers to truly polymer-free, metallic, drug-eluting stents and finally to fully bioresorbable vascular scaffolds? Alternatively, are the changes likely to be small and iterative or even difficult to demonstrate given the excellent outcomes with today's devices?

DR. COLOMBO: Stents without polymer have a rationale. Dr. Kereiakes, very correctly, said that we need to prove that no polymer is superior to a fluorinated polymer in terms of thrombosis. This is an open field. I will not be surprised to see no clear advantage between no polymer vs "special polymer." But let's be optimistic and believe that we can go lower in terms of thrombosis. To move forward, I would like to say that bioabsorbable vascular scaffolds are a very exciting concept. I will vote for "no more metal in the coronary arteries."

DR. STONE: In support of your belief, even with our best metallic drug-eluting stents, our patients still experience a 1.5% to 2.5% annual rate of adverse ischemic events related to the target

lesion that keep occurring after 1 year, when healing is supposed to be stable, all the way up through (at least) 5 years. Dr. Kereiakes, you and I are leading one of the first US initiatives for a fully bioresorbable vascular scaffold (with Steve Ellis). How optimistic are you that we may further improve long-term outcomes for patients with coronary disease by using this novel device?

Clinical Implications

- Stents (both drug-eluting and bare-metal) are currently the dominant revascularization modality for the treatment of most patients with obstructive coronary artery disease.
- Drug-eluting stents are used in the majority of patients in most geographies, although bare-metal stents are still widely utilized in certain institutions, in certain countries, and for certain specific types of patients and indications.
- Revascularization with stents improves survival and prevents MIs in patients with ST-segment elevation myocardial infarction (STEMI) and most patients with non-STEMI. However, in patients with stable coronary artery disease, most studies suggest that revascularization does not prolong life or prevent future MIs, but observational and small randomized trials have demonstrated improved survival with revascularization in patients with at least moderate amounts of ischemia, and a large-scale trial is underway to verify this finding.
- Drug-eluting stents provide more durable relief of ischemia than bare-metal stents, which are in turn, better than medical therapy.
- Diabetics benefit more from 12 months of DAPT vs 6 months. Currently, 1 year of DAPT is recommended in most patients who have received drug-eluting stents, with trials ongoing to determine whether a shorter or longer duration is preferred.
- Even with the best metallic drug-eluting stents, patients still experience a 1.5% to 2.5% annual rate of adverse ischemic events related to the target lesion that keep occurring after 1 year. Novel drug-eluting stent technologies and fully bioresorbable vascular scaffolds are being evaluated to determine whether long-term event-free survival may be further enhanced.

DR. KEREIAKES: I think we both share the optimism. Most of the trial designs for evaluating novel stent designs are going to demonstrate non-inferiority when compared to the "best-in-class" EES at 1 year. Beyond that point in time, the potential benefits of a completely bioresorbable platform, including the capacity for adaptive remodeling, the ability to accommodate atherosclerosis, the maintenance of autoregulation and normal microvascular endothelial function, and the potential to eliminate any nidus for neo-atherosclerosis, will be greater than either metal platform drug-eluting stents or bare-metal stents. This is the promise, Dr. Stone, but the real challenge will be to prove it. We need to look at landmark analyses in late follow-up to prove that a bioresorbable scaffold indeed provides material benefit with respect to reduction in death, MI, and repeat revascularization. Wouldn't you agree?

DR. STONE: I would agree with you fully. We're just beginning a 5-year clinical trial program with thousands of patients (the ABSORB clinical trials) to hopefully demonstrate whether this is true.

This has been an extraordinary discussion from 3 real experts in this field. If I were to summarize for the reader, I would say we've come a long way since 1977, when balloon angioplasty was introduced for the treatment of discrete proximal coronary stenosis, to the takeover of bare-metal stents, to the widespread adoption of first-generation and now second- and third-generation, drug-eluting stents. This evolution has translated into dramatic improvements in event-free survival for our patients. We've gone from stent thrombosis rates of >10% within the first 30 days to <0.5% within 30 days in most series with a very small incremental increase in stent thrombosis over time thereafter. We've reduced restenosis from as high as 50% or greater

after balloon angioplasty down to approximately 10% or so after implantation of the best drug-eluting stents. These changes have translated into marked improvements in freedom from angina, exertional dyspnea, requirement for medications, rehospitalization, and repeat procedures. The link between ischemia and death/MI suggests that freedom from restenosis may translate into improved survival and MI-free survival. A large ongoing trial is now underway in an attempt to prove this within the framework of a randomized investigation.

Nonetheless, even with the best drug-eluting stents, there are still concerns regarding increased risk of late stent thrombosis compared with bare-metal stents, which does necessitate a prolonged duration of DAPT. Taking both benefits and risks into account, the appropriate duration of DAPT, whether that is 3, 6, or ≥12 months, is the subject of current ongoing large-scale randomized trials. One must consider the excellent outcomes with current drug-eluting stent technology when making clinical decisions regarding how to treat patients with obstructive coronary disease while also considering the alternatives of medical therapy or surgery. In this regard, many of the best clinical trials we have are already out of date.

Finally, all 4 of us are extremely optimistic about the future. We are in the midst of an unparalleled era of improving biotechnology, and drug-eluting stents are evolving. Metallic stent designs continue to improve, the amount of polymer (whether durable or bioresorbable) will continue to diminish or disappear, and we are well on the way toward demonstrating real clinical benefits of a fully bioresorbable vascular scaffold that can restore the native coronary artery back to its pristine state once the obstructive lesion has been treated. Adjunct pharmacology with enhanced efficacy and safety is being developed as well, and we are learning which patients need more or less potent antiplatelet and antithrombotic agents. We are entering the era of personalized medicine, and it is possible that genetic profiling may lead the way to smarter decision making. All of this is occurring on the background of more effective "optimal" medical therapy and risk-factor modification for primary and secondary prevention.

With those closing comments I'd like to thank Drs. Colombo, Kereiakes and Kirtane, who are truly 3 of the great physicians in this field. Thank you very much.

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