Catheter-Based Treatment of Coronary Artery Disease
Past, Present, and Future

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Abstract—September 2007 marked the 30-year anniversary of the first human percutaneous coronary intervention, an index event that changed the course of modern-day cardiovascular care. Before that first procedure, adult invasive cardiology focused on diagnostic angiography as well as hemodynamic assessment of structural heart disease. Since that initial procedure, percutaneous coronary intervention has become the most frequently performed coronary revascularization procedure worldwide. Several factors have been responsible for this dramatic paradigm shift, the most prominent being identification of opportunities for technical improvement and the application of innovation and investigation in concert with colleagues, professional societies, and industry. These approaches will continue to be of paramount importance as new technologies are brought to bear on an increasingly broader group of patients with cardiovascular disease. (Circ Cardiovasc Intervent. 2008;1:60-73.)

Key Words: angioplasty ■ coronary disease ■ stents ■ balloon ■ catheters

The past 30 years witnessed a revolution in cardiovascular care with the introduction of percutaneous approaches for the treatment of patients with a variety of cardiovascular disorders.1-8 The nonsurgical, catheter-based treatment of heart disease began with Andreas Grünzig and coworkers in Zürich, Switzerland. The path they followed has served as the model for all subsequent iterations and innovations in this field. Dr Grünzig and colleagues began with a concept that evolved into a device, a balloon-tipped catheter, that could potentially widen the lumen of a narrowed, diseased artery. Proof of principle was confirmed by preclinical investigations in animal models. In September 1977, Dr Grünzig successfully relieved a severe stenosis in the proximal left anterior descending coronary artery of a 38-year-old man.3,5,8 The 30-year anniversary of this procedure, termed percutaneous transluminal coronary angioplasty (PTCA), was celebrated in Zürich in September 2007. The evolution from that index case to what has become the most commonly performed revascularization procedure worldwide has been characterized by continued development and investigation. Consideration of the driving forces in this process is important because they serve as a template for developing other new technologies. Identifying and applying these forces require an understanding of past experiences, present status, and future needs and opportunities.

Several factors have been key throughout the development of percutaneous coronary revascularization:

1. Identification of problems and solutions with the development of new technologies and approaches (with success typically earmarked by collaborative working relationships between physicians and industry)
2. Application of the new technology, after proof of principle, to broader patient and lesion groups
3. Performance of randomized clinical trials to characterize safety and effectiveness relative to conventional therapies
4. Development of a large body of evidence on which to base recommendations for usage indications and ancillary therapies
5. Creation of a broad range of educational initiatives, including local, regional, national, and international conferences; live case demonstration courses; extensive publications; and the use of simulation techniques
6. Implementation of training programs and certification and testing platforms such as Added Qualifications Certificates

Past

Procedural Technique and Results

Although rates of angiographic and clinical success were acceptable during the early application of PTCA, the equipment was rigid and awkward and used a fixed-wire system with very limited responsiveness and steerability1-8 (Figure 1A). These factors limited patient selection to groups such as those with single, straightforward proximal stenoses who were good candidates for bypass surgery and had significant but stable angina. With these stringent criteria, very few patients, <4%, would be eligible for the procedure.8

Even with these restricted selection criteria, initial results were suboptimal by today’s standards,7,10-12 with clinical success achieved in only about two thirds of patients. In

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addition, careful attention was paid to measurement of other indices of coronary obstruction, including translesional pressure gradients and even great cardiac vein flow and lactate extraction; some of these assessments formed part of the criteria for procedural success, such as improvement in translesional gradient.7 (Figure 1B).

The initial use of PTCA was associated with a significant incidence of procedural complications. At the first National Heart, Lung, and Blood Institute (NHLBI) Workshop on Percutaneous Transluminal Coronary Angioplasty, Grünzig presented an initial experience with 76 patients. He was able to pass the lesion with the dilatation balloon catheter in 63 of the patients (83%).7 In 55 of these 63 patients, he achieved anatomic and clinical success. Nevertheless, 3 of these 55 patients developed evidence of a myocardial infarction. In the 8 patients for whom the procedure was unsuccessful, there was either no improvement in the lesion (2 patients) or sudden reclosure of the lesion that required emergency surgery. In the initial 34 cases at Mayo Clinic,12 the success rate was 65%. In this series, 3 patients failed because of progression of the subtotal lesion to a total occlusion. Moreover, 2 patients with what were believed to be successful dilations developed subendocardial infarctions that were related to side-branch occlusion. These early experiences documented that PTCA was feasible and that success could be expected in about two thirds of patients. Nevertheless, there was a significant incidence of procedure-related myocardial infarction, and a substantial proportion of patients required emergency coronary artery bypass graft (CABG). Of the initial 1155 patients enrolled in the 1978–1981 NHLBI PTCA registry, 5.8% required emergency surgery and 4.9% had a nonfatal infarction.13

In 1981, the NHLBI convened a second workshop and presented data on 1500 patients from 73 centers. The overall success rate was still only 63%.6 An analysis of complications in the NHLBI PTCA registry, in the 1801 patients enrolled from 1985 to 1986, showed that nonfatal infarction still occurred in 4.3% of patients, and 3.5% required emergency surgery.13 In this experience, procedure-related infarction, emergency CABG, and in-hospital mortality rates were interrelated.13 Thus, although complications had improved by the mid-1980s compared with 1978–1981, they remained a significant issue.

Durability of PTCA and the Development of Restenosis
A major concern about balloon angioplasty was the durability of the procedure. Successful PTCA typically was associated
with significant improvement in anginal symptoms and objective evidence of ischemia. In a substantial proportion of patients, however, symptoms recurred after the index procedure. Repeat angiography most commonly demonstrated restenosis or recurrent coronary narrowing >50% diameter reduction at the site of the originally treated lesion. The salient features of this new disease entity, described in 1984, included (1) recurrent ischemia identified by either functional testing or anginal symptoms and (2) timing typically within 3 to 6 months of the index procedure. In a classic study, Nobuyoshi et al performed serial angiograms in 229 patients after successful PTCA using quantitative measurements of coronary stenosis. As shown in Figure 2, the actuarial restenosis rate increased from 12.7% at 1 month to 52.5% at 1 year. Restenosis was usually readily treated by repeat PTCA. Repeat restenosis after this, however, was common.

Scientific Investigation of PTCA
Andreas Grünzig is credited for the rigorous scientific method used to evaluate the safety and effectiveness of PTCA. In addition, he championed the need for randomized trials of PTCA versus surgery to scientifically document the relative merits of each approach for coronary revascularization. After his original reports, the NHLBI established a registry for PTCA to further characterize the procedure. This registry continues to this day, albeit in a modified form. Borrowing from the data management and collection techniques used in randomized clinical trials, the registry gathers a vast amount of information to describe the types of patients treated, the techniques and strategies used, and early and late clinical outcomes. Multiple randomized trials have followed Grünzig’s work, and hundreds of thousands of patients have participated in clinical studies to advance our knowledge of interventional cardiology. This rapid but thorough approach to evaluating a new therapy has served as a model for other cardiovascular subspecialties.

Beyond Balloon Angioplasty
Understanding the early problems with PTCA led to improvements in equipment and procedural strategies to enhance effectiveness and safety of the procedure. Guiding catheters evolved radically to smaller diameters with enhanced steerability and greater back-up support. An enormous advance was the development of the over-the-wire balloon catheter, such that a wire could be advanced across a lesion and then followed by a more trackable balloon catheter. Using a guidewire with a shapeable but flexible tip allowed clinicians to gain access to almost any coronary segment no matter how distal. The combination of these advances in equipment and continued refinement of technique by operators changed PTCA from a niche approach to a mainline therapy for coronary artery disease.

Other efforts included development of catheter-based devices that could relieve coronary narrowing by a manner other than balloon dilatation. These included transluminal extraction catheters, directional coronary atherectomy, rotational atherectomy, and excimer laser. For each of these technologies, the initial goal was to make the percutaneous procedure safer by removing tissue, either plaque or calcium, on the premise that “bigger is better”—ie, the larger the lumen of the treated segment, the less likely the patient would experience restenosis. Reporting a series of 524 treated lesions, Kuntz et al found that apparent differences in subsequent restenosis with different devices were attributable solely to the postprocedural lumen diameter rather than the specific device used (Figure 3).

As might be expected, some of these new devices were associated with their own unique complications, such as coronary perforation. After the results of comparative trials, many of these devices disappeared from the market. Rotational atherectomy remains available for treatment of rigid, fibrotic, calcified lesions, although this approach is used very infrequently because of the availability of high-pressure noncompliant balloons, which can be used to treat these lesions.

Although a host of ablative devices have undergone intense development and analysis over the years, only stents, which are adjuncts to balloon angioplasty, have been proven to enhance the capabilities of percutaneous coronary interven-
tion (PCI) to decrease or prevent restenosis, whereas medical approaches typically have been unsuccessful.28,29 Coronary stents were first used in 1986,30 and the indication was for acute/threatened closure. This serious complication often resulted in emergency CABG surgery, myocardial infarction, and even death. In the 1985–1986 NHLBI PTCA registry (the pre-stent era), acute closure occurred in 4.9% of patients and coronary dissection in 4.8%.31 Initial observational studies quickly demonstrated the effectiveness of stents in treating abrupt coronary occlusion. Consequently, the incidence of periprocedural myocardial infarction and emergency CABG declined significantly.

With refinements in stent design and implantation technique, clinical investigators evaluated the ability of stents to reduce the incidence of restenosis after balloon angioplasty.31 Two landmark clinical trials, the Stent Restenosis Study (STRESS)32 and BENESTENT 1,33 demonstrated an approximately 30% reduction in restenosis rates compared with balloon angioplasty alone. Drawing on these and related studies, the 1998 American College of Cardiology Expert Consensus Document on Coronary Stents concluded that “stent implantation improves both short and long term outcome in selected patients. Multiple challenges still remain, including in-stent restenosis and the treatment of complex lesions.”34 Although stents have become the standard of care, they encountered several challenges on the road to achieve this status. An early concern was stent thrombosis and the related need for aggressive antithrombotic medical strategies that resulted in prolonged hospital stays and increased rates of significant bleeding. Subsequent studies documented that refinement of stent deployment techniques, such as high-pressure balloon inflations, and the routine addition of a thienopyridine to acetylsalicylic acid (dual-antiplatelet therapy) substantially minimized the chance for acute stent thrombosis.35 During this era, even the name of the procedure—PTCA (percutaneous transluminal coronary angioplasty)—changed to PCI (percutaneous coronary intervention). It became the preferred strategy for less invasive revascularization.36

Other devices were developed to make PCI safer, including filters and other devices for embolic protection36,37 that are now used routinely during the treatment of saphenous vein graft lesions and infarction. Coolong et al,38 using data from 5 randomized controlled trials and 1 registry of patients treated for degenerated saphenous vein graft disease, confirmed the benefit of embolic protection devices. However, even in vein graft lesions treated with a variety of embolic protection devices, 30-day major adverse cardiac event (MACE) rates remain close to 10%. Accordingly, the clinical problem remains and is specifically related to plaque volume and the extent and severity of vein graft degeneration.

In-Stent Restenosis: A New Disease

Although stents reduced the incidence of restenosis, they did not eliminate it, and a new disease was identified: restenosis developing within a previously implanted stent.38 In-stent restenosis was of particular concern because once it developed, subsequent recurrence rate was often >50%. Investigations of the pathophysiology of in-stent restenosis included basic and experimental animal studies and the use of intravascular ultrasound in patients. Trials of drug therapies failed to alleviate in-stent restenosis.28,29 In response, an entirely new field, intracoronary brachytherapy, was developed.39-40 Although vascular brachytherapy was demonstrated to be effective in the treatment of in-stent restenosis, its use was limited because of system delivery issues, such as the need for (1) involvement of radiation physics, (2) extra shielding, and (3) subsequent documentation of a late catch-up phenomenon.

On the basis of the concept that attenuation of the neointimal proliferative response could reduce the incidence of in-stent restenosis, unique stents were developed that incorporated an antiproliferative drug.41-45 These medicated drug-eluting stents (DES) had a marked impact in reducing the incidence of in-stent restenosis and the need for repeat revascularization procedures. After impressive results were obtained from multiple randomized clinical trials, DES became the standard of care and were selected in approximately 95% of all stent procedures shortly after their introduction. In addition, for patients who developed in-stent restenosis with bare metal stents (BMS), DES were found to be superior to vascular brachytherapy.46,47

In a recent meta-analysis, Dibra et al48 (Figure 4) analyzed 4 randomized trials comparing sirolimus- or paclitaxel-eluting stents versus either balloon angioplasty or vascular brachytherapy for the treatment of BMS restenosis. These authors found that the risks of target lesion revascularization (odds ratio [OR] 0.35; 95% confidence interval [CI], 0.25 to 0.49; P<0.001) and angiographic restenosis (OR 0.36; 95% CI, 0.27 to 0.49; P=0.001) were markedly better in patients treated with DES.

Development of Training Programs

As PCI expanded, the need for formal training programs and techniques for determining competence became apparent. Training programs in interventional cardiology that are approved by the Accreditation Council for Graduate Medical Education are now available. The American Board of Internal Medicine sponsors an examination of special qualifications. These training programs and approaches for development of added qualifications will be used as a template for the interventionalist and the interventional procedures of the future (eg, percutaneous valve replacement/repair).

Present

The appropriate use of DES is the focus of current-day PCI.41-45 These complex devices include a metallic backbone of variable design, a polymer coating, and a variety of drugs—initially single drugs approved for noncardiological applications, such as sirolimus or paclitaxel, and then so-called designer drugs, such as zotarolimus, developed specifically for vascular applications. Use of these stents has become the dominant revascularization strategy because of their well-documented efficacy in reducing the incidence of restenosis. Stettler et al42 performed a collaborative network meta-analysis of 38 trials and 18 023 patients treated with DES versus BMS and sirolimus- versus paclitaxel-eluting stents. The authors found a dramatic reduction in target lesion...
revascularization at 4 years of follow-up with DES but no significant difference in death or myocardial infarction (Figure 5). These stents have been studied in off-label and on-label settings. Marroquin et al documented decreased need for subsequent revascularization irrespective of whether DES were used for off-label or on-label indications (Figure 6). These authors also found no difference in the frequency of death or myocardial infarction when stents were used in off-label indications (Figure 8).

DES are not without controversy, much of which has centered around stent thrombosis, an issue that was the subject of a US Food and Drug Administration advisory panel in December 2006. The amount of interest in this clinical problem is in large part related to the recognition that stent thrombosis, even though very infrequent, is striking in its associated morbidity and mortality rates. In some series, stent thrombosis may be associated with myocardial infarction or death in 50% to 60% of patients. Because of the variable definitions used in the past, a standard nomenclature was established and embraced (Academic Research Consortium) that classified these events as definite, probable, or possible stent thrombosis and the timing as early, late, and very late stent thrombosis. This standardization has facilitated scientific evaluation of stent thrombosis, which has led to

### Table A

<table>
<thead>
<tr>
<th>Study</th>
<th>DES (no.)</th>
<th>Conventional (no.)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-DESIRE</td>
<td>27/200</td>
<td>33/100</td>
<td>0.32 (0.18-0.57)</td>
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<tr>
<td>RIBS II</td>
<td>8/76</td>
<td>22/74</td>
<td>0.28 (0.11-0.70)</td>
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<td>SISR</td>
<td>22/259</td>
<td>24/125</td>
<td>0.39 (0.21-0.73)</td>
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<tr>
<td>TAXUS-V ISR</td>
<td>12/195</td>
<td>27/201</td>
<td>0.42 (0.21-0.86)</td>
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<tr>
<td>Total</td>
<td>69/730</td>
<td>106/500</td>
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</tr>
<tr>
<td>Overall (fixed effects)</td>
<td></td>
<td></td>
<td>0.35 (0.25-0.49)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $X^2=0.76$ (df = 3) ($P=0.86$)
Test for overall effect: $z=0.04$, $P=0.96$

### Table B

<table>
<thead>
<tr>
<th>Study</th>
<th>DES (no.)</th>
<th>Conventional (no.)</th>
<th>Odds ratio (95% CI)</th>
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</thead>
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<td>ISAR-DESIRE</td>
<td>0/200</td>
<td>0/100</td>
<td>(Not estimable)</td>
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<tr>
<td>RIBS II</td>
<td>1/76</td>
<td>1/74</td>
<td>0.97 (0.06-15.85)</td>
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<tr>
<td>SISR</td>
<td>2/259</td>
<td>0/125</td>
<td>2.44 (0.12-51.14)</td>
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<tr>
<td>TAXUS-V ISR</td>
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<td>5/201</td>
<td>0.81 (0.14-2.60)</td>
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<tr>
<td>Total</td>
<td>6/730</td>
<td>6/500</td>
<td></td>
</tr>
<tr>
<td>Overall (fixed effects)</td>
<td></td>
<td></td>
<td>0.85 (0.28-2.64)</td>
</tr>
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</table>

Test for heterogeneity: $X^2=0.67$ (df = 2) ($P=0.72$)
Test for overall effect: $z=0.27$, $P=0.79$

### Table C

<table>
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<tr>
<th>Study</th>
<th>DES (no.)</th>
<th>Conventional (no.)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-DESIRE</td>
<td>6/200</td>
<td>3/100</td>
<td>1.00 (0.24-4.08)</td>
</tr>
<tr>
<td>RIBS II</td>
<td>3/76</td>
<td>3/74</td>
<td>0.97 (0.19-4.98)</td>
</tr>
<tr>
<td>SISR</td>
<td>6/259</td>
<td>0/125</td>
<td>6.44 (0.36-115.15)</td>
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<tr>
<td>TAXUS-V ISR</td>
<td>7/195</td>
<td>10/201</td>
<td>0.71 (0.27-1.91)</td>
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<tr>
<td>Total</td>
<td>22/730</td>
<td>16/500</td>
<td></td>
</tr>
<tr>
<td>Overall (fixed effects)</td>
<td></td>
<td></td>
<td>1.04 (0.54-2.03)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $X^2=2.12$ (df = 3) ($P=0.58$)
Test for overall effect: $z=0.13$, $P=0.90$

![Figure 4](image)

**Figure 4.** A, Meta-analysis of DES for in-stent restenosis of BMS. Treatment with DES improved target lesion revascularization. However, there were no significant differences in stent thrombosis (B) or the composite of death or infarction (C). Reproduced from Dibra et al with permission from the American College of Cardiology. Copyright 2007 American College of Cardiology.

![Figure 5](image)

**Figure 5.** Collaborative network meta-analysis of 38 trials. There was a dramatic reduction in target lesion revascularization with drug-eluting stents (A) but no significant decrease in death or myocardial infarction (B). PES indicates paclitaxel-eluting stent; SES, sirolimus-eluting stent; and HR, hazard ratio. Reproduced from Stettler et al with permission from Elsevier Ltd. Copyright 2007 Elsevier Ltd.

![Figure 6](image)

**Figure 6.** NHLBI Dynamic Registry of 6551 patients with off-label indications documenting no difference in adjusted risk of death or myocardial infarction in patients treated with DES but decreased target lesion revascularization. Reproduced from Marroquin et al with permission from The Massachusetts Medical Society. Copyright 2008 Massachusetts Medical Society. All rights reserved.

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Outcomes | Hazard ratio (95% CI) | Hazard ratio (95% CI) |
---------|-----------------------|-----------------------|
Safety   |                       |                       |
Standard use | 1.47 (0.87-2.48) |                       |
Myocardial infarction | 0.71 (0.47-1.05) | 0.69 (0.48-1.02) |
Death or myocardial infarction | 3.34 (1.04-10.56) |                       |
Off-label use |                       |                       |
Death | 0.84 (0.64-1.13) |                       |
Myocardial infarction | 0.71 (0.56-1.00) |                       |
Death or myocardial infarction | 0.78 (0.60-1.02) |                       |
Efficacy |                       |                       |
Standard Use |                       |                       |
Repeat PCI | 0.61 (0.46-0.81) |                       |
Revascularization | 0.53 (0.41-0.69) |                       |
Off-label use |                       |                       |
Repeat PCI | 0.75 (0.61-0.93) |                       |
Revascularization | 0.63 (0.53-0.77) |                       |

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**Drug-eluting stent better**...
increasing information on the epidemiology and pathophysiology of this problem and new treatment options.

Although the relationship between stent thrombosis and DES has been emphasized, stent thrombosis also occurs with BMS. Doyle et al. evaluated the long-term outcomes of 4503 patients with BMS placed between 1994 and 2000 who received dual-antiplatelet therapy. Stent thrombosis was defined as per the Academic Research Consortium definitions. During a mean follow-up of 7.9 years, stent thrombosis rates increased such that by 10 years, stent thrombosis had been documented in 2.0% of patients (Figure 7). Clinical and procedural characteristics associated with stent thrombosis included acute myocardial infarction at presentation or a history of myocardial infarction, CABG surgery, stroke, or peripheral vascular disease. In this series, the mortality risk associated with stent thrombosis was greatly increased. Clinical restenosis had occurred in approximately 16% of patients. Of great importance was the fact that unstable angina or acute myocardial infarction related to restenosis was identified in approximately 9% of patients at 10 years; in addition, restenosis was associated with increased mortality rate. Other smaller series confirmed these observations of stent thrombosis with BMS and the clinical price to be paid for restenosis of BMS.

Only recently have investigations compared the incidence and timing of stent thrombosis with DES versus BMS. It appears that up to 5 years after stent implantation, the overall frequency is similar between the 2 groups, but the timing is slightly earlier for BMS than DES. These findings appear to be true for patients regardless of whether initial indications were standard or off-label. Whether stent thrombosis will continue over longer-term follow-up with either BMS or DES is uncertain. Information regarding very late follow-up has implications for patients treated with stents at a young age.
For example, if DES are placed in a patient at 35 years of age and stent thrombosis continues to occur, even with a very low incremental yearly rate, the total stent thrombosis rate would be substantial after $\geq 30$ years.

Controversy also exists about the incidence of stent thrombosis between different types of DES. None of the head-to-head randomized trials have been powered to evaluate this important question. However, there has been some suggestion that paclitaxel-eluting stents may be more prone to stent thrombosis than those with a “limus” drug. Further reduction or elimination of stent thrombosis is a goal for future DES technology. This may be achieved by changing the stent design, eliminating or modifying the polymer, or changing the drug formulation.

It is hoped that a better understanding of the pathophysiology of stent thrombosis will provide insight into ways to reduce its incidence. Possible mechanisms include delayed endothelialization, toxic response from the drug or the polymer carrier, suboptimal initial deployment, and the presence of a side branch arising from the target lesion. Detailed histopathologic information regarding DES thrombosis is limited and can only be derived from autopsy series.

Several important questions remain unanswered, for example, whether delayed endothelialization occurs in patients who have not experienced any adverse events. Furthermore, for some DES, the active drug may be gone within 3 months; it is difficult to implicate drug toxicity for an event that may occur several years later. Alternatively, the polymer component of a DES may be responsible for stent thrombosis. Accordingly, new stent platforms are evaluating polymers that are biodegradable. If the issue of stent thrombosis is related to the long-term presence of a polymer, these stents with biodegradable polymers or even no polymer may have a unique advantage.

There is agreement that premature discontinuation of dual antiplatelet therapy is a key factor associated with stent thrombosis. This finding has led to intense emphasis on patient education and to a change in suggested guidelines of care whereby dual-antiplatelet therapy is recommended for 1 year after placement of a DES. This finding has also led to careful evaluation of the patient’s ability to undergo dual-antiplatelet therapy and the need for noncardiac surgery.

Incorporation of New DES Into Practice

Several DES are commercially available worldwide. In the United States, expanding DES options will raise important considerations of how, when, and whether to incorporate DES into the catheterization laboratory inventory and how to decide which DES will be used for a specific patient or lesion. This process is complex and driven by multiple factors, including physician preference, vendor contracts, and head-to-head data from randomized clinical trials. Theoretical concerns about physiological properties such as late loss for a specific stent may not result in different clinical outcomes. It must also be remembered that the results of DES are probably not class effects.

Concerns About Dual-Antiplatelet Therapy

Awareness of the critical role of dual-antiplatelet therapy has focused attention on the concept of drug resistance and on testing the magnitude of inhibition of platelet aggregation according to the type and dose of drug and individual patient responsiveness. Measuring platelet function involves many considerations, including the type of test, the complexity of performing the test, variability in the test results, the definition of resistance, and the timing of measurements, among others.

If resistance to clopidogrel is suspected, then ticlopidine may be effective because cross-resistance is uncommon. Another approach to clopidogrel resistance is the empirical doubling of dosage to 150 mg/d, although data on this approach are very limited. Alternatively, cilostazol can be substituted, although again data on this are very limited. Newer, more potent agents that may be available in the future, such as prasugrel, may be more effective in selected patients.

Application of PCI for Patients With Mild Symptoms/Ischemia and Stable Angina

The value of PCI for patients with disabling or unstable angina or myocardial infarction is well recognized. Controversial, however, is the role of PCI for patients who are either asymptomatic or minimally symptomatic. This issue intensified after the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, which randomized 2287 patients who had stable coronary artery disease to either optimal medical therapy plus PCI or optimal medical therapy alone. The primary end point was death from any cause and nonfatal myocardial infarction during a follow-up period of 2.5 to 7 years with a median of 4.6 years.

A group of relatively low-risk patients were randomized: 12% to 13% were asymptomatic, whereas 30% had Canadian Cardiovascular Society class 1 angina; approximately 70% had 1- or 2-vessel disease; and the ejection fraction was 61%. During the trial, 33% of the medical group crossed over to PCI, whereas only 21% of the PCI group required repeat revascularization ($P<0.001$). However, the primary end points were initially almost identical: 19% for PCI and 18.5% for optimal medical therapy.

Important were observations from COURAGE regarding relief of ischemia. In the nuclear ischemia substudy, the importance of treatment of ischemia was underscored. The findings of this prespecified substudy indicated that PCI accompanied by optimal medical therapy resulted in less residual ischemia than optimal medical therapy alone. Furthermore, the more severe was the residual ischemia, the higher were the rates of subsequent mortality and morbidity. In the COURAGE trial, if there was no residual ischemia, then at 4.6 years there was no death or myocardial infarction. Accordingly, the principle that remains in patients who are minimally symptomatic or have only very minor ischemia is that PCI does not improve mortality rate or subsequent myocardial infarction but is associated with decreased subsequent revascularization, whereas in those patients with significant ischemia, the target should be relief of ischemia, which will improve not only symptoms but the hard end points of death and infarction.
Future
Exciting opportunities for interventional cardiology lie ahead. There are several major opportunities in the treatment of ever-more-complex disease. As optimal treatment strategies for high-risk patients and lesions are identified, the number of patients who can benefit from PCI will increase.

Chronic Total Occlusion
From the earliest days of percutaneous intervention, the ability to treat chronic total occlusion has been limited. The presence of a chronic total occlusion has been one of the most common reasons to refer patients for CABG surgery rather than the less invasive percutaneous approach. The major shortcoming in the treatment of chronic total occlusion has been the inability to cross the occlusion with a guidewire and access the distal vessel. Unsuccessful attempts may compromise ipsilateral collaterals to the distal bed and result in complications even though the vessel was already completely occluded.71-74

In a recent experience, Prasad et al73 evaluated a 25-year experience of 1262 patients with chronic total occlusion from a single institution. In the most recent period, 2003–2005, success was only achieved in 70% of cases, which was not different than rates achieved in patients treated from the early to mid-1990s. However, emergency surgical rates decreased substantially to 0.7% in the most recent period, and MACE rates decreased by almost 50%, down to 4%. In addition, the 1-year target-vessel revascularization (TVR) rates declined by approximately 50% with the use of DES. Of note, several series have documented a survival benefit when successful PCI of a chronic total occlusion is achieved.71,74

Several innovative approaches to enhance our ability to cross total occlusion have been developed, particularly by Japanese and Korean interventional cardiologists. These include a variety of guidewire techniques, such as anchoring a balloon in a side branch, using parallel wires, performing subintimal dissection, and using the retrograde approach, which involves the use of collateral channels that arise from a contralateral coronary artery. These techniques have not been widely adopted in many areas for several reasons, including long procedure times, excessive radiation exposure, lack of familiarity with the techniques, and limited availability of new guidewire systems. Unconventional approaches, perhaps with magnetic guidance, forward-looking ultrasound, or local dissolution of plaque and thrombus material, are being evaluated. Solution of this problem could dramatically increase the number of patients in whom PCI is a reasonable option.

Bifurcation Lesions
Bifurcation lesions continue to present challenges, with side-branch occlusions resulting in myocardial necrosis as well as increased restenosis.75–77 Plaque shift and failure to adequately cover the carina may result in increased acute closure with periprocedural infarction as well as long-term increased restenosis.

Although a number of strategies have been tested and are used clinically, including V-stenting, T-stenting, crush, and cullotte techniques, among others, the majority of studies indicate that a simpler approach with stenting of the main branch and provisional stenting of the side branch is the least complicated and is associated with equivalent outcomes as multiple-stent techniques.75 With this approach, the side branch stenosis is only dilated and then the major target vessel is stented; if the side branch stenosis does not worsen significantly, a stent is not placed in the side branch.

The future will likely involve dedicated bifurcation stent systems, several of which are under investigation.77 Designing an optimal treatment for bifurcation lesions has great implications for patients with left main coronary artery stenosis (vide infra). In approximately 50% of patients with left main coronary artery disease, the stenosis involves the distal left main coronary artery, and therefore treatment requires a bifurcation approach or even a trifurcation approach if a large intermediate vessel is present.

Left Main Coronary Artery Stenosis
During the early phases of PTCA, the left main coronary artery was an attractive target because it was readily accessible even with the rigid, inflexible, and poorly steerable equipment. However, it was recognized that restenosis of the left main artery could be fatal, and subsequently the procedure was used only in patients with a protected left main coronary artery stenosis and those for whom surgery was either contraindicated or not possible. With the introduction of stent implantation, there was a rebirth of interest in a percutaneous approach. Of interest is the great worldwide regional variability in the use of PCI for left main coronary artery stenosis. In Japan and Korea, for example, left main coronary artery lesions are routinely treated with stent implantation; in the North America, surgery is typically considered the treatment of choice.78–80

Information regarding PCI treatment of left main lesions is nearly completely based on observational reports rather than randomized, comparative trials. A recent collaborative systematic review and meta-analysis of patients undergoing DES placement for unprotected left main coronary artery disease identified 16 studies with 1278 patients followed for a median of 10 months.80 DES was superior to BMS for improving follow-up MACE and TVR (OR 0.34; 95% CI, 0.16 to 0.71; P=0.004 for MACE, and OR 0.34; 95% CI, 0.12 to 0.94; P=0.04 for TVR). Information on DES versus CABG has been limited. Seung et al81 reported on a matched cohort of Korean patients. In patients with unprotected left main coronary artery disease, the investigators found no difference in death or the composite end point of death, Q-wave infarction, or stroke between patients receiving stents and those undergoing CABG. Even with DES, however, higher rates of TVR were required than seen in patients treated surgically (9.3% versus 1.6%, P<0.001) (Figure 8).

With appropriately sized DES and ostial or midshaft lesions, stent placement is an excellent option. Results are less favorable if the distal left main coronary artery is diseased. The long-term results are in large measure dependent on whether the patient is a good surgical candidate (a surrogate for the absence or presence of severe comorbidity). In patients who are good surgical candidates, stent implantation results in excellent long-term outcomes; if the patients...
are high risk or inoperable, the results are less favorable but still reasonable if significant ischemia is present. The multicenter SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trial,70,82 to be reported on later this year, will include approximately 750 patients with left main coronary artery stenosis randomized to either CABG surgery or the TAXUS (Boston Scientific Corp, Boston, Mass) DES. The results of this trial will greatly affect the field of left main coronary artery intervention.

Multivessel Disease

The application of PCI in patients with multivessel disease remains controversial, particularly in the setting of diabetes mellitus.83-90 In clinical practice, patients with severe multivessel disease, particularly those with abnormal left ventricular function, are usually referred for surgery, whereas patients with less severe multivessel disease may be treated with PCI. Multiple randomized trials have compared either PTCA alone or PTCA in conjunction with BMS to CABG surgery in selected patients with multivessel coronary artery disease, and rates of survival free from myocardial infarction have been similar. Typically, patients treated with PCI require a greater number of subsequent revascularization procedures related to restenosis or incomplete revascularization. A common element in these trials has been that a small proportion of screened patients are enrolled and randomized. This substantial discrepancy between those screened and proportion of screened patients are enrolled and randomized has implications for the generalizability of the results.

Studies have evaluated use of DES in patients with multivessel disease. These trials have not been randomized, and results have been discordant. Recently, Hannan et al83 evaluated the New York State PCI registry experience of patients with multivessel disease who either received a DES or underwent CABG surgery between October 2003 and December 2004. The investigators’ analysis of 17,400 patients was complicated in that it included both adjusted and unadjusted outcomes. Unadjusted curves documented no difference in long-term survival and survival free from myocardial infarction for both 2- and 3-vessel disease. After adjustment for differences in baseline characteristics, however, there were minor shifts in the differences in percentage of events (Figure 9). Given the number of patients involved, these small shifts resulted in identification of a significant difference in results, with CABG surgery patients having improved outcomes. As the authors pointed out, selection bias cannot be completely eliminated; from the standpoint of clinical practice for the individual patient, it is not possible to adjust patient characteristics.

The Arterial Revascularization Therapies Study (ARTS) II89,90 approached the issues in a different way. Patient and lesion criteria that had been used in the randomized trial of BMS versus CABG surgery (ARTS I) were used to select patients to be treated with DES, and then the outcomes were assessed. Patients treated with DES had outcomes similar to those of patients treated with CABG surgery, but the difference in the need for repeat revascularization procedures previously seen in those patients treated with BMS versus CABG surgery had narrowed considerably. This was not a randomized trial; instead, it compared new stent approaches with somewhat older surgery, which reduced the generalizability of the trial.

Bravata et al88 systematically reviewed 23 randomized clinical trials of 5019 PCI and 4944 CABG patients. The investigators found a difference of <1% in survival over 10 years of follow-up between the 2 groups and no significant differences in diabetic patients. However, the investigators found that procedure-related strokes were more common after CABG (1.2% versus 0.6%, P=0.002) (Figure 10). Finally, Bravata et al documented the repeated observation that patients treated with PCI require more repeat revascularization than surgical patients.

The controversy continues, and it is hoped that the ongoing SYNTAX70,82 and Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease (FREEDOM)91 trials of patients with multivessel disease randomized to either surgery or PCI will shed important light on the field. However, the individual physician caring for the patient and helping to define the patient’s expectations is in the best position to render an opinion about the optimal treatment strategy. There are important related issues, including the issue of complete versus incomplete revascularization.85 One of the reasons that CABG may improve long-term outcome is that complete revascularization is achieved more frequently. As previously mentioned, this is usually attributable to a chronic total occlusion. Researchers in interventional cardiology need to develop approaches to maximize the chance of complete revascularization.

Vein Graft Disease

Treatment of patients with vein graft disease continues to be a major problem. Percutaneous treatment of vein graft disease can be complicated by distal embolization of the friable atherothrombotic debris, cessation of coronary flow, and myocardial infarction or death. In the long term, patients undergoing vein graft PCI may experience rapid disease
A Procedural Stroke Risk

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<th>Procedure</th>
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<th>Risk differences (95% CI)</th>
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<td>PCI</td>
<td>3,640/3,660</td>
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<td>CABG</td>
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Figure 10. Systemic review of effectiveness of PCI and CABG using a total of 23 randomized clinical trials and a total of 9963 patients. Adapted from Bravata et al88 with permission from the American College of Physicians. Copyright 2007 American College of Physicians.

future Advances in Adjunctive Medical Therapy

Adjunctive medical therapy will continue to advance. Interventionalists must continue to learn about new drugs and ensure that patients receive optimal medical management. Among the new drugs to be available are more potent inhibitors of platelet aggregation. A recent report describes the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) of 13,608 patients with acute coronary syndromes who underwent PCI. Prasugrel was studied as 1 limb of the trial and was dramatically successful in reducing the primary end point. From the standpoint of interventional cardiology, an important finding was a dramatic decrease of stent thrombosis, which was reduced from 2.4% to 1.1%. This was seen with both DES and BMS. The price paid for this reduction was an increase in major bleeding, which was documented at 2.4% with prasugrel and aspirin compared with 1.8% with aspirin and clopidogrel bisulfate. Other new antiplatelet drugs are currently being evaluated, including cangrelor.93,94 These new drugs appear to be more effective in modifying platelet function than older drugs and have a different and improved onset of action. In addition, cangrelor is administered intravenously and has a very short half-life. This drug may be particularly useful in bridging patients requiring noncardiac surgery who are taking clopidogrel bisulfate. In this setting, cangrelor can be given intravenously up to approximately 1 hour before surgery and then discontinued; after surgery, the drug can be restarted and bridged back to oral clopidogrel bisulfate. New research will focus, in part, on improving dual antiplatelet strategies and minimizing bleeding.

Interventionalists of the Future

Interventionalists of the future will face several new challenges. They will require experience with and knowledge of multiple specialties, including cardiovascular surgery, interventional cardiology, vascular radiology, neurosurgery, and neuroradiology, each of which will provide different but complementary skill sets. Team approaches will be the best solution but will require careful planning and training as well as reengineering of traditional organizational structure. Targets of intense interest will include percutaneous treatment of valvular heart disease with replacement of valves or repair of valves. Other areas will be carotid artery stenosis and intracerebral disease with the development of acute stroke centers. The treatment of peripheral arterial disease will continue to evolve as screening procedures become more specific, sensitive, and widely used. All of these approaches will involve the use of equipment that was originally developed for the treatment of coronary artery disease but now will be used in multiple different noncoronary vascular beds.

Interventionalists will also need to better understand vascular and cell biology. Coronary artery disease is a manifestation of a systemic illness. Accordingly, some of the triggers of plaque rupture and myocardial infarction might not be localized to the affected plaque. Responsible mechanisms may include inflammation and degradation of the matrix metallic proteins as well as abnormalities of the endothelial cells. Interventionalists will need to identify plaques that are
By guest on June 29, 2017

Dr. Williams has served as a consultant to Cordis Corporation. Dr. Williams has performed revascularization procedures in the world for the past 30 years, and industries to develop technological and pharmacological approaches that promote public education and early warning systems.

Another crucial area will be development of systems of care. PCI has become established as the treatment of choice for patients with ST-segment–elevation myocardial infarction. As such, interventional cardiology should be the doorway through which all patients with acute infarction enter. It is crucial that we develop systems of care, such as improving door-to-balloon time, and work with emergency room physicians, transport services, clinical cardiologists, and organizations that promote public education and early warning systems.

Conclusion
Since the inception of interventional cardiology 30 years ago, percutaneous procedures have become the most commonly performed revascularization procedures in the world for the treatment of coronary artery disease. This shift in therapeutic approaches has been brought about by defining clinical and technical problems, working in concert with many individuals and industries to develop technological and pharmacological treatments, carefully conducting robust scientific study of the results of treatment, and using innovative approaches to select patients for treatment. The future of interventional cardiology will be limited only by our ability to imagine and create.

Disclosures
Dr. Williams has served as a consultant to Cordis Corporation. Dr. Holmes reports no potential conflicts of interest.

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