New Drugs and Technologies

New Frontiers in Interventional Cardiology

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The latest statistics from the American Heart Association are disturbing: In 2004, an estimated 865,000 Americans will develop a new acute coronary syndrome. Another 700,000 will have a stroke. Unfortunately, the contribution of percutaneous coronary intervention (PCI) to prevent such catastrophic outcomes has been limited. To date, intervention cardiologists have been constrained to the treatment of obstructive atherosclerosis disease in certain regions of the coronary tree. This approach has a clear benefit in reducing ischemia and symptoms but minimal direct impact on patients’ survival.

The coming decade in interventional cardiology will be characterized by continued advances and interplay between structural materials and biomaterials, as well as by erosion of the barriers between medical disciplines, including vascular medicine, heart failure and genetics. Advances in imaging technology are on the verge of a clinical debut, which will enhance our screening capabilities to detect subclinical yet hazardous atherosclerosis disease. An expansion of indications for PCI as well as the development and establishment of new therapeutic modalities also are expected in the coming years (Figure 1).

A comprehensive review of the entire field of intervention cardiology would be impractical. Progress in the areas of drug-eluting stents, detection of vulnerable plaques, percutaneous management of selected patients with stroke and valvular heart disease, angiogenesis and stem cell treatment of congestive heart failure, and increased use of the predictive capacity of genetic markers likely will be pivotal. The goal of this article is to provide an overview of recent achievements and upcoming technologies.

Drug-Eluting Stents

The BENESTENT (BElgian NEtherlands STENT) and STRESS (STent REStenosis Study) trials paved the way for the “stent era” in coronary revascularization.1,2 In-stent restenosis, however, persisted as a hindrance to stenting until recently. The incidence of restenosis after bare metal stents may vary from 8% to as high as 80% at 6 months depending on both anatomic and clinical risk factors.

The term drug-eluting stents (DES) derives from the ability of such metallic prosthesis to release single or multiple bioactive agents into the bloodstream and surrounding tissues. A detailed review on DES technologies and clinical trials was published previously.3,4 The present article reports on recent clinical trial results and emerging DES technologies.

Update on DES Clinical Studies

The 4-year angiographic follow-up of the First-In-Man study has just been completed and preliminary data showed sustained results late after treatment with a sirolimus-eluting stent (SES) (Figure 2). Three pivotal randomized clinical trials were reported recently. The TAXUS-IV trial randomized 1314 patients with de novo coronary lesions to be treated with a single slow-release polymeric paclitaxel-eluting stent (PES; n=662) or bare metal stent (n=652). Clopidogrel was prescribed for 6 months after the procedure. The incidence of subacute thrombosis (SAT) was 0.3% at 30 days and 0.6% at 6 months in the TAXUS arm. In-stent late loss was 0.39 mm and in-lesion restenosis was 7.9% in the TAXUS arm. After 12 months, 6.8% of the patients receiving the TAXUS stent (Boston Scientific Corp) underwent another target-vessel revascularization (TVR) as compared with 16.7% in the control group.

The other large studies reported less compelling results. In the DELIVER (Dexamethasone Loaded stents In small coronary VEssels to prevent Restenosis) trial (n=1043), late loss was 0.81 mm and 15% of patients underwent restenosis after nonpolymeric PES (3.0 μm/mm²) at their 9-month follow-up (W. O’Neill, MD, personal communication, November 2003). The ACTION (ACtinomycin eluting sTents Improve Outcomes by reducing Neointimal hyperplasia) study failed to show the efficacy of actionycin-eluting stents (P.W. Serruys, MD, personal communication, March 2003).

Upcoming DES Technologies

Many of the proposed DES technologies were supported by sound basic scientific data, but only a few have proven clinical viability (Table 1). Clinical investigations with the sirolimus analogues everolimus, biolimus A9, and ABT-578 (methyl rapamycin) are underway. Like sirolimus, these...
agents bind to FK506-binding protein 12 (FKBP12) and inhibit the cell cycle regulatory protein mTOR (mammalian target of rapamycin).

The ongoing HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) study is testing the R stents (Orbus Medical Technologies) coated with antibodies to CD34 receptors on progenitor cells. In the near future, stents eluting statins, trapidil, cytochalasin D, methotrexate, or the combination of multiple agents will be exposed to clinical testing.

Stents made of cobalt alloys became available recently. Cobalt alloy stents have thinner struts (<0.04-mm thick), a lower profile, and potentially enhanced deliverability as compared with stainless steel stents. Biodegradable stents, which “dissolve” slowly after implantation, would be ideal for DES. Theoretically, these devices provide the initial scaffold to prevent negative remodeling without the undesirable continuous vessel trauma caused by a permanent rigid foreign body. Vessel toxicity remains a major limitation for biodegradable stents, however. The Igaki-Tamai stent has been tested clinically.

The Conor MedSystems MedStent is customized for local drug delivery and has individual inlays to be loaded with medications. Pilot clinical investigations testing the Conor stent loaded with paclitaxel have been initiated.

How DES Are Changing PCI

The clinically approved SES (CYPHER, Cordis) and polymer-based PES (TAXUS) are now under intense scrutiny by “real-world” interventional cardiologists. Whether the excellent results observed in clinical trials, which involved selected populations, can be achieved in daily practice has been questioned.

In the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) trial, investigators adopted a unique policy of using SES as the default strategy for all PCI procedures performed at the Thoraxcenter. Approximately 68% of patients would have been excluded from earlier clinical trials because of previous coronary surgery, in-stent restenosis, acute myocardial infarction, or need for multivessel stenting, among other risk factors. At 1 year, the risk of major cardiac events was reduced by 38% as compared with bare metal stents (9.7% versus 14.8%; \( P < 0.01 \)) mainly because of a 65% reduction in the risk of clinically driven repeat intervention after SES (3.7% versus 10.9%; \( P < 0.01 \) versus bare metal stent). Among the patients treated with SES, only 2 (0.4%) presented with SAT in the first month after the procedure versus a 1.6% SAT rate in the bare stent group. Historically, thrombosis rates with bare metal stents range from 0.4% to 2.8% (Table 2). The second phase of the RESEARCH registry, which tests PES as a default strategy for PCI, has been initiated, but long-term results are pending.
TABLE 1. DES Platforms Under Clinical Investigation

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Randomized</th>
<th>Drug/Agent</th>
<th>Stent</th>
<th>Late Loss* (Time of Follow-Up)</th>
<th>MACE Rates* (Time of Follow-Up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUTURE I (42)</td>
<td>Yes</td>
<td>Everolimus</td>
<td>Challenge</td>
<td>0.11 mm (6 mo)</td>
<td>7.7% (6 mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control=0.85 mm</td>
<td>Control=7.7%</td>
</tr>
<tr>
<td>FUTURE II (64)</td>
<td>Yes</td>
<td>Everolimus</td>
<td>Challenge</td>
<td>0.12 mm (6 mo)</td>
<td>4.8% (6 mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control=0.33 mm</td>
<td>Control=17.5%</td>
</tr>
<tr>
<td>ENDEAVOR (100)</td>
<td>No</td>
<td>ABT-578</td>
<td>Driver</td>
<td>(4 mo)</td>
<td>2% (4 mo)</td>
</tr>
<tr>
<td>STEALTH I (100)</td>
<td>No</td>
<td>Biolimus A9</td>
<td>Challenge</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>IMPACT (150)</td>
<td>Yes</td>
<td>Mycophenolic acid</td>
<td>Duraflex</td>
<td>Fast release=1.04 mm (6 mo)</td>
<td>Fast release=12% (6 mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Slow release=0.95 mm</td>
<td>Slow release=16.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control=0.91 mm</td>
<td>Control=18%</td>
</tr>
<tr>
<td>PRESENT (22)</td>
<td>No</td>
<td>Tacrolimus</td>
<td>Ceramic Coated Flex</td>
<td>0.81 mm (6 mo)</td>
<td>13.6% (6 mo)</td>
</tr>
<tr>
<td>EASTER (30)</td>
<td>No</td>
<td>Estradiol</td>
<td>Byodivysio</td>
<td>0.54 mm (6 mo)</td>
<td>3.3% (1 y)</td>
</tr>
<tr>
<td>NOBLESSE (45)</td>
<td>No</td>
<td>Oxygen free-radical scavenger</td>
<td>Genic Stent</td>
<td>0.69 mm (4 mo)</td>
<td>6.7% (4 mo)</td>
</tr>
<tr>
<td>HEALING (16)</td>
<td>No</td>
<td>Anti-CD34 antibodies</td>
<td>R Stent</td>
<td>Not available</td>
<td>Not available</td>
</tr>
</tbody>
</table>

*Data from control groups provided when available.

FUTURE indicates First Use To Underscore restenosis Reduction with Everolimus; STEALTH, Stent Eluting A9 Biolimus Trial in Humans; PRESENT, PREEminent Safety Evaluation of Nanoporous Tacrolimus eluting stents; IMPACT, Inhibition with MPA of Coronary restenosis Trial; EASTER, Estrogen And Stents To Eliminate Restenosis; NOBLESSE, Nitric Oxide through Bioabsorbable Layer Elective Study for Safety and Efficacy.

The SECURE (Compassionate Use of SES) trial enrolled 252 patients who had no acceptable alternative treatment available, including brachytherapy or CABG. Clopidogrel was maintained indefinitely for patients with previous brachytherapy failure (>60% of the study population). A higher incidence of TVR was observed in patients who had experienced previous brachytherapy failure (23.5%) versus patients without previous irradiation (8.5%). The SECURE registry certainly challenged this technology in extreme clinical and anatomic situations beyond the “real world,” yet the outcomes observed in this study have been favorable.

The e-CYPHER is an ongoing multinational postmarketing surveillance registry involving 275 sites worldwide. A total of 8763 patients were enrolled until November 2003. There were 1.4 stents implanted per patient. Stents were deployed at 14.2 atm; postdilation was performed in 22% and direct stenting in 31% of patients (G. Guagliumi, MD, personal communication, November 2003). The incidence of SAT was only 0.95% in the first 2056 patients, with complete 6-month follow-up data. The overall major adverse coronary event (MACE) rate was 5.86% (death=2.1%, myocardial infarction=1.45%, target-lesion revascularization=2.38%) at 6-month follow-up, which substantiates the findings of the RESEARCH study and allays any concerns about the safety of SES in actual clinical practice.

The WISDOM (Web-based taxa Intercontinental obServational Data transitiOnal registry prograM) registry is an ongoing multinational registry, which enrolled ~1000 patients treated with PES at 26 sites (A. Abizaid, MD, personal communication, September 2003). Clopidogrel was prescribed for 6 months. At 30 days, only 0.4% of patients had stent thrombosis. Long-term data are pending.

Stent Deployment Technique

The ongoing Prospective Evaluation of the Impact of Stent Deployment Technique on Clinical Outcomes of Patients Treated With the Cypher Sirolimus-Eluting Stent (STLLR) trial will enroll 1500 patients treated with SES in 50 US clinical sites to address the important issue of optimal deployment technique. Operators will follow specific criteria for stent deployment, particularly stent sizing. An independent core laboratory will determine whether there was inadequate stent deployment (geographical miss) or not. Patients will be followed for 12 months to define whether SES deployment technique affects clinical outcomes.

In the RESEARCH registry, the number of stents (2.1 stents per patient), the total stent length (38.7 mm), and the use of longer stents were higher in the SES group than in the bare stent group, which reflects an attempt by the operators to cover the diseased and injured segments with the DES (ie, “from normal to normal vessel”; the “longer is better” philosophy). The use of longer stent lengths and a high incidence of direct stenting (∼30%) also were noted in large multinational registries.

Expanding PCI Indications

Despite the economic and inventory constraints that certainly hindered a more prompt adoption of DES, this technology is likely to replace bare metal stents in the catheterization laboratory. The postmarket multinational registries provide a glimpse at what indications for PCI may be in the impending DES world. The trend of frequent off-label use of DES in daily practice was confirmed in e-CYPHER. It seems that operators worldwide have been encouraged to treat more complex anatomic and clinical situations. A large number of complex lesions including left main (2%), chronic total occlusion (9.4%), bifurcation (8.6%), long lesions >30 mm (12.2%), restenosis (14.5%), and vein grafts (2.1%) have been treated in e-CYPHER. A similar high-risk population profile was observed in the WISDOM registry. Before sweeping changes are made in clinical practice, intervention cardiologists should be aware of the lack of controlled, randomized scientific data for most of the indications described.
What is the therapy for vulnerable plaque?
What is the percentage of coronary plaques that rupture?
What is the relative contribution of blood coagulability to coronary events?
Why are specific vascular beds more prone to thrombotic events than others?
Is C-reactive protein a marker or a trigger?
How is plaque erosion identified?
Inflammation also is present in nonruptured, stable plaques. The histological features of eroded plaques involves abundant smooth muscle cells and proteoglycans, with minimal or no lipid necrotic core, but the mechanisms of erosion remain an enigma.

Whether plaque instability is a systemic versus a focal phenomenon remains debatable. The combination of both hypotheses (ie, it is a systemic process with focal or multifocal manifestation) will likely prevail. Local factors such as shear stress and high tensile mechanical stress may explain why plaque rupture usually is confined to specific locations of the circulation and not diffusely distributed to all arterial beds. A number of potential pitfalls are associated with above. Until these results become available, operators should use caution when applying DES off-label.

### New Diagnostic Modalities

Further expansion of the PCI world will occur only after the development of new diagnostic modalities capable of detecting subclinical yet high-risk atherosclerosis disease. Current standard technology such as coronary angiography is unable to predict the likelihood of a thrombotic clinical event because it provides no information about vessel wall structures, including the atherosclerotic plaque itself.

Plaque rupture often is not highly stenotic and may be undetected by coronary angiography because of positive vascular remodeling. The transition to plaque rupture has been characterized by the presence of active inflammation (monocyte/macrophage infiltration), thinning fibrous cap (<30 μm), development of a large lipid necrotic core, endothelial denudation with superficial platelet aggregation, and intraplaque hemorrhage. Plaque erosion, although less frequently observed in overall autopsy studies, seems to be associated with most of the coronary events in premenopausal women. The histological features of eroded plaques involves abundant smooth muscle cells and proteoglycans, with minimal or no lipid necrotic core, but the mechanisms of erosion remain an enigma.

### TABLE 3. Challenges to the Concept of Vulnerable Plaque

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Drug Regimen (mo)</th>
<th>Population, n</th>
<th>Clinical Setting</th>
<th>Stent Thrombosis, % Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antithrombotic studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STARS</td>
<td>A (1)</td>
<td>557</td>
<td>&gt;60% CSA</td>
<td>3.6 30 d</td>
</tr>
<tr>
<td></td>
<td>A+OAC (1)</td>
<td>550</td>
<td>&gt;62% CSA</td>
<td>2.7 30 d</td>
</tr>
<tr>
<td></td>
<td>A+T (1)</td>
<td>546</td>
<td>&gt;59% CSA</td>
<td>0.5 30 d</td>
</tr>
<tr>
<td>ISAR I</td>
<td>A+T (1)</td>
<td>273</td>
<td>70% UA</td>
<td>0.8 30 d</td>
</tr>
<tr>
<td></td>
<td>A+OAC (1)</td>
<td>281</td>
<td>67% UA</td>
<td>5.4 30 d</td>
</tr>
<tr>
<td>FANTASTIC</td>
<td>A+T</td>
<td>249</td>
<td>49% CSA</td>
<td>2.8 6 wk</td>
</tr>
<tr>
<td></td>
<td>A+OAC</td>
<td>236</td>
<td>50% CSA</td>
<td>3.9 6 wk</td>
</tr>
<tr>
<td><strong>Stent studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BENESTENT II (heparin-coated stent)</td>
<td>A+T (1)</td>
<td>414</td>
<td>45% UA, single stent</td>
<td>0.2 30 d</td>
</tr>
<tr>
<td>ARTS (stent group)</td>
<td></td>
<td>600</td>
<td>Multivessel stent</td>
<td>2.8 30 d</td>
</tr>
<tr>
<td>SICCO (stent group)</td>
<td></td>
<td>58</td>
<td>CTO</td>
<td>6.9 2 wk</td>
</tr>
<tr>
<td>TAXUS (PES-slow release)</td>
<td>A+C (6)</td>
<td>131</td>
<td>Single PES, 35% UA</td>
<td>1.5 1 y</td>
</tr>
<tr>
<td>TAXUS II (PES-moderate release)</td>
<td>A+C (6)</td>
<td>135</td>
<td>Single PES, 30% UA</td>
<td>0.7 1 y</td>
</tr>
<tr>
<td>TAXUS IV (PES)</td>
<td>A+C (6)</td>
<td>662</td>
<td>Single PES, 36% UA</td>
<td>0.6 1 y</td>
</tr>
<tr>
<td>TAXUS IV (BMS)</td>
<td>A+C (6)</td>
<td>652</td>
<td>33% UA</td>
<td>0.8 1 y</td>
</tr>
<tr>
<td>RAVEL (SES)</td>
<td>A+C; A+T (2)</td>
<td>238</td>
<td>39% CSA, single SES</td>
<td>0 1 y</td>
</tr>
<tr>
<td>SIRIUS (SES)</td>
<td>A+C (3)</td>
<td>533</td>
<td>Multi-SES, 53% UA</td>
<td>0.4 1 y</td>
</tr>
<tr>
<td>SIRIUS (BMS)</td>
<td>A+C (3)</td>
<td>525</td>
<td>54% UA</td>
<td>0.8 1 y</td>
</tr>
<tr>
<td>RESEARCH (SES)</td>
<td>A+C (3–6)</td>
<td>508</td>
<td>Unselected, 37% UA, 18% MI</td>
<td>0.4 30 d</td>
</tr>
<tr>
<td>RESEARCH (BMS)</td>
<td>A+C (1)</td>
<td>450</td>
<td>35% UA, 18% MI</td>
<td>1.6 30 d</td>
</tr>
<tr>
<td>e-CYPHER (preliminary data)</td>
<td>A+C (27.8% = 2)</td>
<td>4131</td>
<td>34% UA, 9.4% CTO, 8.6% Bif, 25% multi-SES</td>
<td>0.95 30 d</td>
</tr>
</tbody>
</table>

STARS indicates St. Thomas Atherosclerosis Regression Study; A, aspirin; CSA, chronic stable angina; OAC, oral anticoagulation; T, ticlopidine; ISAR, Intraocular Stenting and Antithrombogenic Regimen; UA, unstable angina; FANTASTIC, Full Anticoagulation Versus Aspirin and Ticlopidine; ARTS, Arterial Revascularization Therapy Study; SICCO, Stenting in Chronic Coronary Occlusion; D, dipyridamole; CTO, chronic total occlusion; C, clopidogrel; RAVEL, Randomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary Lesions trial; SIRIUS, SIRolImUS-coated Bx velocity balloon-expandable stent in the treatment of patients with de novo native coronary lesions trial; Bif, bifurcation. Other abbreviations as in text.
proposed strategies to predict thrombotic events based on the current paradigm of “vulnerable plaque” (Table 3).11,12 Nevertheless, several imaging and functional techniques to detect vulnerable plaques have been proposed (Table 4).13–18 Despite much enthusiasm, we still need to unravel the underlying mechanisms and natural history of this paradigm. The debate on the most appropriate therapeutic strategy for vulnerable plaque has already started.

Noninvasive Coronary Imaging

The ideal method for screening subclinical atherosclerosis disease and potentially vulnerable plaque and vulnerable patients should be noninvasive, applicable to asymptomatic patients, and provide assessment of multiple vascular beds. For detection of coronary obstructive disease, a spatial resolution in all 3 dimensions of at least 1 mm is needed. Much higher resolutions, not yet available, are required for plaque characterization. Data processing should be quick and operator independent. The diagnostic procedure should be harmless (ie, radiation and contrast free) and costless. Unfortunately, no current technology fulfills all these criteria and no one should expect such an ideal screening tool in the foreseeable future.

Electron beam computed tomography has been used for 3D visualization of coronary anatomy and quantification of coronary calcium, which has been associated with long-term coronary events.19 Electron beam computed tomography applies a stationary source with a rotational field for the production of x-rays, which allows rapid image acquisition (100 milliseconds/slice). Continuous intravenous contrast injection (100 to 200 mL) at 4 to 6 mL/s is required.

Multislice computed tomography (MSCT) currently uses up to 16 detector rows each with submillimeter slice width to acquire data simultaneously.20,21 MSCT scanners provide a scan range of nearly 1 cm/s. A breath-hold of <20 seconds is long enough to scan the entire heart. Pharmacological heart rate control for patients with rates >65 bpm (metoprolol 100 mg given 1 hour before the examination) is required to enhance the image quality of MSCT. Pilot studies have shown good correlation between MSCT and coronary angiography in assessing stenosis severity, with a sensitivity between 75% and 90%, specificity of 90% to 95%, positive predictive value of 0.7 to 0.9, and a negative predictive value of 0.8 to 0.9 for the detection of hemodynamically significant stenosis22 (Figure 3). Currently, MSCT imaging does not provide enough clinical reliability or resolution to replace angiography or intravascular ultrasound. Severe calcification or motion artifacts in patients with fast heart rates or irregular rhythm remain important limitations for MSCT. New scanners with up to 128 detectors may overcome some of these limitations and place MSCT as the screening tool for coronary artery stenoses, particularly in patients with chest pain but relatively low likelihood of disease. Other applications include the analysis of bypass and post-PCI patency and the evaluation of coronary anomalies.

MRI provides imaging without the need for ionizing radiation or iodine contrast injection. Good accuracy (72%) of cardiac MRI to define lesion severity in proximal coronary segments has been reported23; however, coronary imaging poses considerable technical difficulties for MRI because of the relative small size and tortuous course of coronary arteries, cardiac and respiratory motion artifact, and poor spatial resolution (0.39 × 0.39 × 2 mm³ maximum). The use of contrast agents to target specific components of atherosclerotic plaques was proposed recently and holds promise.24 The assessment of plaque progression, particularly in the aorta and carotid arteries, represents a potential application of MRI imaging. The feasibility of magnetic resonance–guided intervention in pigs has been shown,25 but magnetic resonance–guided PCI remains a remote goal in humans. Finally, MRI may be used to monitor angiogenesis and myogenesis therapy,26 perhaps the most intriguing new frontier in cardiology.

Angiogenesis and Myogenesis

Despite—and perhaps because of—decreases in mortality associated with myocardial infarction during the past 2
decades, morbidity and mortality from congestive heart failure (CHF) continues to increase. Recent advances in the pharmacological and nonpharmacological therapies of CHF, including costly procedures such as surgical cardiomyoplasty, heart transplantation, biventricular pacing, implantable cardioverter defibrillators, and left ventricle assist devices, have been unable to produce major survival benefits for patients with CHF (Figure 4).

In recent years, angiogenesis, which refers to the formation of new arteriolas lacking developed media from preexisting vessels, has been proposed as an alternative treatment for patients with CHF and poor candidates for current revascularization strategies. Furthermore, angiogenesis may become an adjunctive strategy to other revascularization strategies, such as PCI and CABG, in patients with severe coronary artery disease.

The major physiological stimuli to angiogenesis include tissue hypoxia and inflammation. Initial attempts to promote angiogenesis have used laser or other mechanical means to create multiple small holes in the endocardium. The use of growth factor proteins such as vascular endothelium growth factor (VEGF) and fibroblast growth factors or genes encoding these proteins to promote angiogenesis has been under study for the last decade. Gene transfer has the advantage of sustained production of growth factors by specific targeted host cells, but experience with this complex therapy is limited. Cell transplantation also has been proposed as a...
strategy to promote both neovascularization and tissue replacement. The plasticity of precursor stem cells has led to the hope that the ravages of CHF may be ameliorated by cell transplantation therapy.

Our understanding of stem cell biology has advanced considerably in recent years. The existence of both resident and circulating stem cells committed to cardiac cell lines has been demonstrated. The bone marrow appears to be an important source of these cells, but their precise origin is uncertain. Evidence is increasing that cell transplantation may improve perfusion and contractile function of the ischemic myocardium, yet the potential for transdifferentiation of stem cells remains controversial.

The most appropriate route for delivery of angiogenic promoters remains debatable. Geographic accuracy and delivery of high concentrations of cells, angiogenic proteins, or genes within the target myocardium are desirable. Direct epicardial injection via surgical thoracotomy was used in early studies. Other researchers have proposed intravenous and, more recently, catheter-based intracoronary injections of genes and cells. These approaches have been associated with relatively low uptake in the target tissue and potential homing of transplanted cells into other organs. Percutaneous approaches also involve direct intramyocardial injection guided by fluoroscopy with dedicated catheters or nonfluoroscopic electromechanical mapping (NOGA, Biosense Webster). The latter offers the advantage of assessing the viability of target sites before each injection and ensuring intramyocardial delivery. Areas supplied by totally occluded epicardial vascular beds can be targeted. Another innovative strategy is a transvenous cell delivery approach via the coronary sinus.

Despite our limited understanding of several issues involving angiogenesis, data on autologous bone marrow stem cells, skeletal myoblasts, and endothelial progenitor cell transplantation are accumulating. The myocardial microenvironment may supply proper signals for the cardiomyogenic differentiation of transplanted cells. Whether the mechanism of action involves myocardium repopulation, neovascularization, or ideally both remains to be determined. Transplanted cells may also stimulate the resident myocytes to improve their contractility via the release of cytokines and improvement in blood flow.

Different clinical indications are likely to require specific cell lines. Intramyocardial injection of autologous skeletal myoblasts have shown improvement in ventricular function late after myocardial infarction; however, recent data suggested the arrhythmogenic potential of transplanted skeletal cells, and new studies testing this approach have recommended the prophylactic use of implantable cardioverter defibrillators. Whether arrhythmia is caused by the lack of electromechanical coupling properties of newly formed myotubes or a mismatch between blood supply and demand in the repopulated myocardium remains to be determined. To improve blood supply to grafted cells, the use of skeletal myoblasts transfected with human angiogenic factor (VEGF165) gene has been proposed.

Bone marrow stromal cells (BMCs) comprise multiple cell lines and are characterized by considerable functional plasticity. Perin et al injected autologous BMCs intramyocardium guided by NOGA in patients with severe ischemic heart failure and no further options for revascularization. Increased perfusion and ejection fraction was observed at 4-month follow-up and no patient developed arrhythmia. As a result, the first US trial testing the feasibility of intramyocardial injection of BMCs in patients with CHF was initiated at the Texas Heart Institute, Houston. Patients will be studied with cardiac MRI to assess segmental and global improvement in wall motion and myocardial perfusion, among other traditional end point measures. The BOOST (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration) trial randomized 60 patients with acute ST-elevation infarction to receive stent implantation followed by optimal medical treatment or stent implantation plus BMC transfer. BMC transfer improved heart function as compared with controls, as assessed by MRI (K.C. Wollert, MD, personal communication, November 2003).

Progenitor endothelial cells (PEC), which express CD34 and CD133 (AC133) antigens, remain high on the list of candidate cells for promoting angiogenesis. These cells have the potential to differentiate into vascular endothelial cells and blood cells and ultimately promote vasculogenesis, a phenomenon not yet demonstrated in adult human hearts. PECs can be identified in adult peripheral blood, bone marrow, and human umbilical cord blood; however, PECs represent only a minute fraction of the BMCs, and ex vivo culture and expansion of blood-derived PEC may be required. The precise signal and homing mechanism of the PECs remains to be defined. The TOPCARE-AMI (Transplantation of Progenitor Cells And Regeneration Enhancement in Acute Myocardial Infarction) investigators have shown that intramyocardial injection of expanded blood-derived PECs is feasible and may attenuate the remodeling process in 20 postinfarction patients who underwent revascularization, without the occurrence of malignant arrhythmias.

Although some investigators hope to use basic cellular homing mechanisms to direct simple replacement cells to acutely or chronically ischemic myocardium, the attenuation of homing factors shortly after acute infarction and the low survival rate of transplanted cells make it likely that successful stem cell therapy will require modification of cells via extracorporeal transfection with survival factors such as Akt. It is also likely that homing factor(s) or the cells themselves will be injected into appropriate targets, giving catheter-based technologies a key role in this developing field.

**Percutaneous Methods to Prevent Stroke**

Stroke kills or disables 700,000 Americans every year. Separation from carotid and cerebrovascular artery disease, cardiovascular abnormalities account for one fifth of all strokes. Interventional cardiologists have joined the fight to reduce first-time and recurrent stroke by developing percutaneous techniques to treat obstructive carotid atherosclerosis and atrial fibrillation and to prevent paradoxical embolism resulting from patent foramen ovale (PFO) and systemic embolization of left atrial appendage (LAA) thrombus. Despite rapid technical advances, the effectiveness of these strategies in stroke prevention is largely unproved, with the exception of carotid artery stenting. Further
clinical investigation is required before the full impact of these techniques is realized.

**Percutaneous Carotid Intervention**

Percutaneous carotid intervention has progressed rapidly with the advent of nitinol stents and emboli-protection devices and the accrual of some randomized multicenter data. The first randomized study was CAVATAS (Carotid and Vertebral Artery Treatment with Angioplasty Study), which compared angioplasty to endarterectomy in symptomatic patients \((n = 450)\). Bailout stenting was allowed and performed in 25% of patients, but emboli-protection devices were not used.\(^5\) The 30-day end point of death or any stroke was identical in both groups at 10%. Cranial nerve palsies, myocardial infarction, and major hematoma were less frequent in the angioplasty group. At 3 years, death and disabling stroke rates were 14.2% with surgery and 14.3% with angioplasty. In addition, extensive neuropsychological testing in 2 large subgroups did not show any difference between the angioplasty and endarterectomy groups. Repeated procedures were rare in the 2 groups.

The first randomized trial that used stenting and emboli-protection devices was SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy), which enrolled 750 patients with comorbid conditions and increased risk for endarterectomy. Patients \((n = 334)\) were randomized to either endarterectomy or stenting; 409 patients were entered into a stent registry, and 7 patients were entered into a surgical registry. Decisions about the feasibility of randomization were made by a team at each center composed of a neurologist, a surgeon, and an interventionalist. The stenting with emboli-protection arm was not inferior to surgery for the 30-day and 1-year end points, and the final results of this trial will be published in the near future.

Nonrandomized multicenter registries also became available in 2004. The ARChER (Acculink for Revascularization of Carotids in High-Risk Patients) study was a single-arm study that evaluated high-risk, symptomatic, and asymptomatic patients being treated with carotid stenting. The 30-day MACE (death, stroke, or myocardial infarction) rate was 7.8% (M.H. Wholey, MD, unpublished data, March 2003). The Registry Study to Evaluate the Neuroshield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy (SECURITY) was another single-arm study with 305 high-risk patients showing a 30-day MACE rate of 7.2% (P. Whitlow, unpublished data, 2003). These multicenter studies demonstrate the safety of treating high-risk patients with carotid stenting in a variety of hospitals. In addition, carotid stenting with emboli protection appears to be safer than carotid endarterectomy in this group of patients. Studies in lower-risk patients are ongoing.

**Patent Foramen Ovale Closure**

In 30% to 40% of ischemic stroke patients, no identifiable cause is found.\(^5\) Such strokes are called cryptogenic. The presence of a PFO has been implicated as the potential culprit in half of these patients, particularly in those <55 years old.\(^5\)\(^4\)\(^5\) It is uncertain whether this is a causative association, and if it is, why only a small minority of people with PFO have a stroke. Published studies are only observational and fraught with a number of methodological problems contributing to this uncertainty, including selection bias, inconsistencies in the proper diagnosis and characterization of the morphology of the septum, size of PFO, and right-to-left shunting. The underlying pathophysiology of PFO-related stroke also is unclear. Proposed mechanisms include paradoxical embolism from the venous circulation and thrombus formation on the surface of the septum. Paroxysmal atrial fibrillation and increased thrombogenicity associated with the atrial pathology cannot be excluded.

Transesophageal echocardiography (TEE) is the most sensitive tool available to identify the anatomic characteristics of PFO, such as the size of the opening, length of the tunnel, and degree of mobility. PFO and right-to-left shunt, particularly those that become manifest only after the Valsalva maneuver, may be difficult to demonstrate, however, because of inadequate patient effort, the patient’s position during examination, or the dose and route of contrast administration. The size of the PFO and amount of right-to-left shunt have been correlated with embolization risk.\(^5\) The presence of atrial septal aneurysm, commonly defined as a minimum excursion of the septum into the right and left atria exceeding 10 to 15 mm, has been suggested to represent an incremental risk factor.\(^5\)

Procedural and long-term complications of the percutaneous approach should be compared with the problems associated with lifelong medical therapy, including difficulties maintaining therapeutic anticoagulation and bleeding. The prevalence of recurrent stroke or transient ischemic attack (TIA) 1 year after a first ischemic stroke in 895 patients who were treated medically ranged from 3.8% to 12%.\(^9\) The data are limited with regard to the comparative efficacy and risks of antiplatelet agents (mainly aspirin) versus anticoagulation with warfarin. The risk of recurrent TIA or stroke at 1 year in 1355 patients treated with transcatheter septal closure ranged between 0% and 4.9%. Acknowledging the paucity of data and methodological difficulties in ascertaining the benefit of closure devices when anticoagulation therapy is continued, how should patients who present with cryptogenic stroke and PFO be treated? Patients with recurrent stroke on medical therapy and patients who cannot tolerate or do not want to continue medical therapy are reasonable candidates for percutaneous PFO closure.\(^6\) Younger patients who have high-risk anatomic or functional (or both) characteristics also may be considered for PFO closure.

Several ongoing randomized trials will improve our ability to appropriately assess therapy. The hypothesis of the 300-patient multicenter randomized RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial is that transcatheter closure with the Amplatzer PFO occluder (AGA Medical Corp) is not inferior to medical therapy. The 1600-patient Evaluation of the STARFlex Septal Closure System in Patients With A Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale (CLOSURE I) trial is designed to determine whether closure by STARFlex device (NMT Medical, Inc) is superior to medical therapy. Both PFO closure devices sized by ultrasound, fluoroscopy, or both examinations are implanted via a sheath placed into the left atrium through the PFO from the femoral vein. Many operators use TEE or intracardiac echocardiography\(^6\) to
adjust their technique according to anatomic variations and to accurately assess the results of device placement. Complete closure of the interatrial communication should be the goal of any closure procedure because postprocedural shunt has been correlated with increased risk of recurrent embolic events. Discontinuing medical therapy after complete closure of the PFO may expose patients to the risk of recurrent embolic events.

We should not embrace a technology before establishing the evidence-based indications. Cryptogenic stroke by definition is a diagnosis of elimination that is limited by the thoroughness of investigation. Our inability to differentiate between the culprit PFO and the bystander PFO likely results in unnecessary implantation of closure devices in some patients. At the same time, efforts to develop safer and more effective closure devices are under way. These devices include those with little or no metal component and those with biodegradable discs. Ideally, we should be able to identify at-risk patients before they sustain a stroke and to prevent stroke by closing the PFO with a device that should result in complete closure, be made of material that conforms to both sides of the septum, and have no risk of erosion, infection, arrhythmia, or thrombogenicity.

Percutaneous Closure of LAA
Thromboembolism from atrial fibrillation is responsible for ≈15% of all strokes. Anticoagulation with warfarin limits the risk of thromboembolism, but it is limited by inconsistencies of anticoagulation and the risk of bleeding. Necropsy and TEE studies demonstrate that >90% of left atrial thrombi are located in the appendage. LAA exclusions have been performed surgically for decades. Although the concept of LAA exclusion is appealing, the data proving the efficacy of LAA occlusion are based on small patient series with limited follow-up. Moreover, surgical LAA closure may be incomplete in up to 36% of patients.

Two devices specifically designed for LAA occlusion are under investigation. The PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device (Appriva Medical, Inc) has a nitinol framework and an ePTFE covering. It is deployed into the orifice of the LAA via transseptal access. In the European PLAATO feasibility trial, the device was successfully deployed in 101 of 103 patients. Adverse outcomes included 8 pericardial effusions that required treatment, 3 non-procedural deaths, 2 strokes, and 2 TIs at a mean follow-up of 10 months. A percutaneous filter device (Atriatech) conforms to both sides of the septum, and have no risk of erosion, infection, arrhythmia, or thrombogenicity.

Valvular Heart Disease
Percutaneous treatment with balloon dilatation is the treatment of choice for most patients with mitral stenosis, pulmonary stenosis, and congenital aortic stenosis; however, these valvular lesions constitute a small portion of the valvular heart disease spectrum that cardiologists confront every day. Technological advances may allow percutaneous treatment of common valvular lesions such as mitral regurgitation and calcific aortic stenosis.

Percutaneous Mitral Valve Repair
Mitral regurgitation is caused by ≥1 structural abnormalities of the valve itself and its supporting structures (ie, chordae, papillary muscles) or by functional alterations resulting from geometric changes of the annulus and left ventricle.

Several groups have exploited the proximity of the coronary sinus (CS) to the posterior mitral annulus to perform percutaneous annuloplasty. In animal studies, a novel nitinol mitral annular constraint device was inserted into the CS via the right internal jugular vein. After stabilization distally and proximally with an anchoring mechanism, controlled tension was applied. Significant reduction in the mitral annular dimensions and extent of mitral regurgitation was accompanied by favorable changes in the cardiac output and pulmonary capillary pressure. The potential risks of this technique include CS erosion or thrombosis and trauma to circumflex coronary artery.

In the first published study of percutaneous edge-to-edge repair, a specially designed implantable clip was inserted through a transseptal guiding catheter into the left atrium of pigs. The clip was advanced across the mitral valve, and the edges of the anterior and posterior leaflets grasped at their mid-portions. In 12 of the 14 pigs, the successfully deployed clip created a double orifice without any evidence of mitral stenosis or regurgitation. Preliminary results from the ongoing phase II trial suggest that this is a feasible and effective procedure that can be carried out with a high degree of safety.

Given the excellent results after surgical repair, it is likely that these techniques will be applied initially in patients who are deemed to be too high risk for open-heart surgery. Further applications may be found in the 15% of CHF patients with moderate mitral regurgitation. The ability to offer a low-risk percutaneous treatment option may represent an important advance in the treatment of these patients.

Percutaneous Aortic Valve Replacement
As our population ages, the prevalence of acquired calcific aortic stenosis increases. In the 1980s, balloon aortic valvuloplasty was thought to be a viable alternative to surgery in high-risk patients; the initial enthusiasm was dampened, however, by subsequent reports demonstrating unacceptable rates of restenosis.

The first human percutaneous aortic valve replacement for the treatment of calcific stenosis in an inoperable patient was reported recently. The valve–balloon combination was advanced across the transseptal puncture site and placed across the calcific stenotic valve over the previously placed stent wire. This technique resulted in a functional valve without clinically significant stenosis or regurgitation. Similar successful results were
obtained in other end-stage heart failure patients. This exciting technique provides new hope for patients with high operative risk. Some serious challenges lay ahead: The presence of the heavily calcified native valve may impede complete apposition of the new valve prosthesis to the aortic wall. Malapposition may lead to fixation problems and paravalvular leaks. The risk of obstructing the coronary ostia also requires the development of a reliable technique for positioning and deploying the prosthesis.

Interventional cardiologists must develop the skills necessary to apply these emerging techniques for noncoronary cardiac interventions such as transseptal catheterization and work in the left atrium. They also need an in-depth understanding of echocardiographic imaging of the atrial structures and valves. Initially, these procedures will be concentrated in a limited number of centers. As their efficacy and safety are established, training standards will be established.

Other Areas

Nearly obeying a biotechnological variant of Moore’s law71 (which, loosely speaking, guarantees a doubling in computer power every 18 months), our capacity to rapidly and inex- pensively identify genetic differences that modify risk and response to therapy is growing exponentially. It is not at all unreasonable to expect this sea change to affect interventional cardiology by allowing specialists to better predict future events (plaque rupture, vessel thrombosis, graft or stent failure, antithrombotic therapy failure) and to deter them via patient-specific interventions short of gene therapy itself. Large-scale association studies, albeit straining conventional resources, may pavesely identify genetic differences that modify risk and response to therapy is growing exponentially. It is not at all unreasonable to expect this sea change to affect interventional cardiology by allowing specialists to better predict future events (plaque rupture, vessel thrombosis, graft or stent failure, antithrombotic therapy failure) and to deter them via patient-specific interventions short of gene therapy itself. Large-scale association studies, albeit straining conventional statistical methodology, are under way to detect these influences. The major impact of personalized medicine may well not be understood until after 2010, however.


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In the article by Sousa et al, “New Frontiers in Interventional Cardiology,” which appeared in the February 8, 2005, issue of the journal (Circulation. 2005;111:671–681), an error appears on page 671. Please note that the name of the trial incorrectly appeared as “DExamethasone Loaded stents In small coronary VEssels to prevent Restenosis.” The correct name of the trial is “Non–Polymer-Based Paclitaxel-Coated Coronary Stents for the Treatment of Patients With De Novo Coronary Lesions.”

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