Cardiovascular Innovations: The Future Is Now

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Nanomaterials are materials in which 50% or more of the contained particles are in the range of 1 nm to 100 nm. They have several potential clinical applications, including antithrombotic therapy, cell therapy, treatment of atherosclerosis, drug delivery, and nanorods for induction of angiogenesis. Sanjay Misra, MD, Mayo Clinic, Rochester, Minnesota, USA, discussed the targets and therapies of nanotechnology.

Karagkiozaki et al. [*Int J Nanomedicine* 2010] found that the surface nanotopography of stent nanocoating influences the behavior of platelets, and this is a key factor for biomaterial thrombogenicity. Patra et al. [*Nano Lett* 2011] demonstrated that europium hydroxide nanorods (inorganic nanorods) with a diameter of 35 nm to 50 nm and a length of 200 nm to 300 nm cause an increase in proangiogenic cytokines, such as vascular endothelial growth factor-A and basic fibroblast growth factor.

Various nanoscale technologies are being applied to the field of stem cell therapy for the treatment of cardiovascular diseases. Other promising applications include the prevention, imaging, and treatment of atherosclerosis [Psarros C et al. *Nanomedicine* 2012] and the use of copolymer-stabilized micro- and nanobubbles as vectors for the anticancer drug doxorubicin [Rapoport N et al. *J Natl Cancer Inst* 2007]. Valenzuela and Simon [*Nanomedicine* 2012] describe a micellar estradiol formulation that serves as an alternative transdermal delivery system for hormone replacement therapy. According to Dr. Misra, nanotechnologies have far reaching implications for the practice of medicine in a wide range of fields.

Next-Generation Ventricular Assist Devices

Mark S. Slaughter, MD, University of Louisville, Louisville, Kentucky, USA, presented information on next-generation ventricular assist devices (VADs), heart valves, and other devices. All of the products he discussed are in various stages of development, and none are FDA-approved.

As VAD technology evolves it is increasingly being applied as destination therapy rather than exclusively as a bridge to transplant. Kirklin et al. [*J Thorac Cardiovasc Surg* 2012] reported that the average 2-year survival after cardiac transplantation is ~80%. However, evolution from pulsatile to continuous flow technology has dramatically improved 1- and 2-year survival, and important subsets of patients with continuous flow destination therapy now enjoy survival that is comparable with heart transplantation out to 2 years. After discussing a breakthrough technology that delivers nitric oxide from a novel liquid source, he said that new VAD technology should reduce operative trauma, thus reducing overall adverse events.

Peer-Reviewed Highlights from

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Next-Generation Valves and Devices

Next-generation valve companies are making use of the small intestine submucosa-extracellular matrix (SIS-ECM) to improve their products and potentially improve postoperative outcomes. CorMatrix Cardiovascular is testing tissue-engineered ECM for pericardial repair; the product comes from porcine-derived SIS.

SIS-ECM is obtained from the submucosa of the small intestine of pigs and consists of a complex matrix of collagen; the submucose is found between the mucosal and muscular layers of the small intestine. It provides strength to the intestine and also serves as a reservoir for cytokines that support the growth and differentiation of intestinal epithelial cells.

Transapical aortic valve implantation has evolved as a treatment option for high-risk patients who have severe aortic stenosis. While much of the focus has been on improving valves and the delivery systems, issues of vascular access and safe closure remain important and of great interest.

Dr. Slaughter reported that a first-in-human clinical trial [NCT01721642] of the Apica ASC transapical access and closure device had successful access and closure, with no device-related complications to date.

Dr. Slaughter said that natural scaffolds that repopulate with native cells might fix the problem of durability of bioprosthetic valves; that safe, reliable, and near bloodless access to the LV apex could improve outcomes and approach to both aortic and mitral valve replacements; that the ability to deliver a predetermined dose of cells/matrix to a specific area could improve clinical efficacy of regenerative medicine; and that new delivery systems for nitric oxide could allow chronic treatment in patients who are not candidates for other therapies.

Drug-Coated Balloons and Bioabsorbable Stents

Bruno Scheller, MD, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany, focused on drug-coated balloons and bioabsorbable stents—vascular restoration therapy, ie, the fourth revolution in interventional cardiology, according to Wykrzykowska et al [*EuroIntervention* 2009].

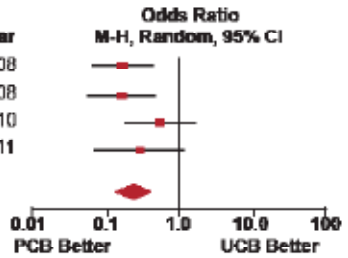
Long-term (>10 years) clinical outcomes of a first-in-human study of a fully biodegradable poly-l-lactic acid coronary stent found rates free of all-cause death, cardiac death, and major adverse cardiac events at 10 years of 87%, 98%, and 50%, respectively [Nishio S et al. *Circulation* 2012]. Intravascular ultrasound data suggest that the stent struts mostly disappear within 3 years. The external elastic membrane area and stent area did not change.

ABSORB Clinical Investigation, Cohort B [ABSORB B; NCT00856856], a multicenter, single-arm trial, assessed the safety and performance of an everolimus-eluting bioresorbable vascular scaffold [Ormiston JA et al. *Circ Cardiovasc Interv* 2012]. Forty-five patients underwent serial invasive imaging at 6 and 24 months of follow-up. Struts still recognizable on optical coherence tomography at 2 years showed 99% neointimal coverage with optical and ultrasonic signs of bioresorption accompanied by an increase in mean scaffold area compared with baseline. The 2-year major cardiac event rate was 6.8% without any scaffold thrombosis, confirming the medium-term safety and efficacy of the new device. However, randomized controlled clinical trials are missing for bioabsorbable stents.

Drug-coated balloon catheters have been studied in a variety of randomized studies and large registries, especially paclitaxel-iopromide- and paclitaxel-urea coated balloons. For patients with peripheral artery disease, a meta-analysis of randomized trials compared target lesion revascularization using paclitaxel-coated balloon angioplasty versus conventional uncoated balloon angioplasty showed superior antirestenotic efficacy compared with uncoated balloon angioplasty (Table 1) [Cassese S et al. *Circ Cardiovasc Interv* 2012]. Other studies in coronary arteries have had similar findings in the treatment of in-stent restenosis and de novo lesions [Unverdorben M et al. *Circulation* 2009; Wöhrle J et al. *J Am Coll Cardiol* 2012]. Dr. Scheller said that drug-coated balloons are not a replacement for drug-eluting stents, but a new option in endovascular and coronary interventions and potentially useful in areas of the leg where stenting is typically avoided due to joint motion. Both drug-coated balloons and bioabsorbable stents represent the technology for a new age of vascular therapy that leaves no permanent implants behind.

Table 1. Target Lesion Revascularization.

Study or Subgroup	PCB Events	PCB Total	UCB Events	UCB Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
THUNDER	7	48	28	54	32.1%	0.16 (0.60–0.42)	2008
FemPac	6	45	21	42	27.3%	0.15 (0.05–0.44)	2008
LEVANT I	6	47	10	45	24.1%	0.51 (0.17–1.55)	2010
PACIFIER	3	40	9	39	16.0%	0.27 (0.07–1.09)	2011
Total (95% CI)		180		180	100.0%	0.23 (0.13–1.40)	
Total Events	22		68				



Heterogeneity: Tau²=0.02; Chi²=3.19, df=3 (p=0.36); I²=6%; Test for overall effect: Z=5.09 (p<0.00001)
Heterogeneity$_{(Mantel)}$: Chi²=3.26, df=3 (p=0.35); Test for overall effect$_{(Mantel)}$: p<0.00001

PCB=paclitaxel-coated balloon; UCB=uncoated balloon.
Adapted from Cassesse S et al. Paclitaxel-Coated Versus Uncoated Balloon Angioplasty Reduces Target Lesion Revascularization in Patients With Femoropopliteal Arterial Disease: A Meta-Analysis of Randomized Trials, *Circ Cardiovasc Interv* 2012;5(4): 582-589.